Clinical Development

PDR001 (Spartalizumab)

Oncology Clinical Protocol CPDR001E2201 / NCT02955069

An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), that have progressed on prior treatment

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final Amendment 1

Release date: 18-Sep-2018

Number of pages: 53

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
06-Feb-2017	Prior to DB lock	Creation of final version	N/A - First version	NA
12-Jan-2018	Prior to DB lock	Creation of Amendment 1	Modifications required due to protocol amendment and changes in study design and population with addition of patients with poorly-differentiated GEP-NEC	Various sections impacted due to protocol amendment
			Further details on Immunogenicity analyses added	Section 2.10.1
18-Sep-2018	Prior to DB lock	Creation of Amendment 2	Modifications required to protocol amendment	Various sections impacted due to protocol amendment

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BIRC	Blinded Independent Review Committee
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CPDR001E2201, a single arm phase II, open-label study of PDR001 for the treatment of patients with advanced or metastatic well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), that have progressed on prior treatment.

The content of this SAP is based on protocol CPDR001E2201, version 03. The primary rationale for protocol amendment 3 is to remove the possibility to expand the study to Part 2 when at least 20% overall response rate (ORR) per RECIST 1.1 by central radiology review is observed in any of the cohorts of the well-differentiated NET group. Based on the results of the interim analysis (IA), there was a change in the clinical development strategy for PDR001, which will no longer be developed as a single agent immunotherapy in NET, and the study will not be expanded into Part 2.

All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a single arm Phase II , open-label, multi-center study evaluating safety and efficacy of PDR001 in patients with advanced or metastatic well-differentiated, non-functional neuroendocrine tumors of pancreatic, GI, or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma, that have progressed on prior treatment.

The study will enroll approximately 90 patients in the well-differentiated NET group (approximately 30 patients in each of the three cohorts of pancreatic, GI, and thoracic origins) and approximately 20 patients in the GEP-NEC group for a total of approximately 110 patients.

Overall response rate (ORR) in well-differentiated NET and poorly-differentiated GEP-NEC groups, as assessed by Blinded Indepdent Review Committee (BIRC) review of tumor response and using RECIST 1.1 criteria, is the primary endpoint in this study. Duration of response (DoR) is the key secondary endpoint.

One interim analysis is planned after at least 30 patients in the well-differentiated NET group have undergone the first 3 radiological assessments (expected around week 24) or have shown disease progression or have discontinued efficacy follow-up for any other reason. All available efficacy and safety data from well-differentiated NET and poorly differentiated GEP-NEC groups up to the cut-off date will be used for the IA

Cut-off date for the primary analysis will be 1 year after Last Patient First Treatment (LPFT) in the initially enrolled well-differentiated NET group.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To estimate the antitumor activity of PDR001 as a single agent in in the well-differentiated NET and poorly-differentiated GEP-NEC groups	ORR (confirmed PR and CR) according to blinded independent review committee (BIRC) radiological assessment by RECIST 1.1
Key secondary	
To estimate efficacy of PDR001 in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Duration of Response (DoR) by RECIST 1.1 and as per BIRC
Other secondary	
To assess the safety and tolerability of PDR001 in each group and in the overall study population	Frequency and severity of adverse events Other safety data as considered appropriate
To evaluate additional efficacy parameters in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Disease Control Rate (DCR), Time to Response (TTR), PFS by RECIST 1.1 and as per BIRC Immune Response Criteria by irRECIST and as per BIRC (irORR, irDoR, irTTR, irDCR, irPFS) 1-year and 2-year overall survival (OS) rate
To evaluate biochemical response to treatment (based on CgA and NSE) in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Changes from baseline in CgA and NSE
To characterize the pharmacokinetics of PDR001 with 400 mg flat dose Q4W in the well-differentiated NET and poorly-differentiated GEP-NEC groups	PK parameters (e.g. Ctrough)
To characterize patient's health-related quality of life with PDR001 in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Global health status/QOL score of the EORTC QLQ-C30 and the index score of the EQ-5D-5L
To evaluate the prevalence and incidence of immunogenicity in the well-differentiated NET and poorly-differentiated GEP-NEC groups	Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The interim and final analyses will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

There are 1 interim and a primary analysis planned for the primary efficacy endpoint.

The analysis cut-off date for the interim analysis will be established after 30 enrolled patients have completed 3 radiological assessments (approximately after 24 weeks of treatment) or have shown disease progression or have discontinued efficacy follow-up for any other reason. The analysis cut-off date for the primary analysis of study data will be 1 year after LPFT in the initially enrolled well-differentiated NET group. The primary analysis data will be summarized in the clinical study report (CSR).

For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event

and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

All analyses will be performed separately for the two groups of well-differentiated NET and poorly-differentiated GEP-NEC unless otherwise specified.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

In this single-arm study evaluating efficacy and safety of spartalizumab (PDR001) as monotherapy, ***investigational drug or investigational treatment***, will refer to the PDR001.

The term investigational treatment may also be referred to as ***study treatment*** which is used throughout this document.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is the same as the date of first administration of investigational drug or control drug.

Date of last administration of study treatment

The date of last administration of study treatment is the same as the date of last administration of investigational drug or control drug.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, PK, PRO, etc) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

Additional summaries will be displayed to report deaths, all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of PDR001.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RECIST/irRECIST) assessment date	Evaluation is marked as 'done'.
Verification for treatment beyond RECIST 1.1 PD	At least one non-missing parameter value
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received one dose of any study treatment (i.e. at least one dose of PDR001 (including incomplete infusion)).

Patients will be analyzed according to the treatment they have been assigned to.

Safety

The Safety Set is defined in the same way as the FAS and includes all patients who received at least one dose of study treatment (i.e. at least one dose of the PDR001 (including incomplete infusion).

Pharmacokinetic analysis set (PAS)

The Pharmacokinetic analysis set (PAS) includes all patients who provide at least one evaluable PDR001 PK concentration. For a concentration to be evaluable, patients are required to:

- receive one of the planned treatments of PDR001 prior to sampling
- for pre-dose samples, have the sample collected before the next dose administration
- for end-of-infusion samples, have the sample collected within 2 hours post end of infusion

Immunogenicity (IG) analysis sets

The Immunogenicity prevalence set includes all subjects in the Full analysis set with a determinant baseline IG sample or at least one determinant post-baseline IG sample.

The Immunogenicity incidence set includes all subjects in the Immunogenicity prevalence set with a determinant baseline IG sample and at least one determinant post-baseline IG sample.

See Section 2.9.1.1 for the definition of determinant.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-3.

Table 2-2 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	No dose of study medication
Safety set	No written inform consent	No dose of study medication
PK Analysis Set	No written inform consent	No evaluable concentration
Immunogenicity prevalence set	No written inform consent	No determinant baseline or post-baseline IG samlpe

Immunogenicity incidence set	No written inform consent	No determinant baseline and post-baseline IG sample

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

[redacted]

2.2.1 Subgroup of interest

Subgroup analyses will be only performed in well-differentiated NET group.

Efficacy

The overall response rate will be summarized by the following subgroups to examine the homogeneity of treatment effect provided that the study meets the pre-specified criteria for primary efficacy based on the FAS:

- Cohort
- Sex
- Race
- PD-L1 expression with analyses for the following thresholds:
  - <1% vs ≥ 1%
  - <5% vs ≥ 5%
  - <10% vs ≥ 10%
  - <50% vs ≥ 50%
- Age category (< 65 years, ≥65 years)
- Tumor grade
- ECOG PS
- Occurrence of at least one immune-related AE (yes, no)

Summary tables will only be produced if sufficient number of patients is present in each subgroup. Only the point estimate of the overall response rate and 95%-confidence intervals will be provided (see Sections 2.5 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Safety subgroup analyses will use the same method as for the analysis in the overall analysis set. Key safety analyses (deaths, SAEs, AESIs, AEs leading to discontinuations) will be repeated on safety set in the following subgroups:

- Cohort
- Age group (< 65 years, ≥ 65 years)
- Sex
- Race
- Ethnicity

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

Summary tables will only be produced if sufficient number of patients is present in each subgroup. Some grouping of classes will be considered for race and ethnicity.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. sex, age groups: <65 and ≥ 65 years, race, ethnicity, ECOG performance status, PD-L1 status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body surface area, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to start of study treatment (in months), stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved.

Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e) CRF will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline, including child bearing potential [redacted] will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients. The number (%) of treated patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Phase' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Phase' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post-treatment follow-up page');
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post-treatment follow-up page');
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study specification document) for all patients. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized for PDR001. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to PDR001:

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the planned end date of the last cycle in which the last non-zero dose of PDR001 was last administered (i.e last date of administration + 27 day)). If the patient died or was lost to follow-up before the derived last date, the last date of exposure is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff.

Summary of duration of exposure of PDR001 will include categorical summaries based on 28 days interval and using descriptive statistics (mean, standard deviation etc).

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for PDR001.

The **planned cumulative dose** for PDR001 refers to the total planned dose as per the protocol up to the last date of the administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

The actual cumulative dose will be defined based on the days when the subject is assumed to have taken a non-zerodose during dosing periods.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg / week) = Actual Cumulative dose (mg / week) / Duration of exposure to study treatment (mg / week).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (mg / week) = Planned Cumulative dose (mg / week) / Duration of exposure (mg / week).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg / week) / PDI (mg / week).

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations, administration stopped/paused during the infusion or interruptions, and the reasons, will be summarized.

'Dose interrupted', "Was drug administration stopped or paused" and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, administration stopped/paused and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted', 'Reason for administration stopped or paused' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive dose administrations with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive dose administrations, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level, where the regimen schedule is modified (less frequent administration of drug compared to previous regimen) or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Treatment beyond RECIST1.1 progression

The number of patients who continue treatment beyond RECIST1.1 progression according to BIRC assessment will be summarized. It includes all patients who received at least one dose of PDR001 (including incomplete infusion) after BIRC RECIST1.1 progression.

2.4.2 Prior, concomitant and post therapies

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized for all

patients. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy, immune-oncology therapy etc.), setting (e.g. adjuvant, metastatic, etc.) and also by lowest ATC class and preferred term. Summaries will include total number of regimens, best response and time from last treatment to progression for the last therapy. The medication therapy type of any combination therapy will be classified based on the following order: immune-oncology therapy, chemotherapy, biologic therapy (other than immune-oncologic therapy), targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and hormonal therapy will be classified as 'chemotherapy'. For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class and preferred term, by means of frequency counts and percentages using FAS.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Additional summaries will be provided to report medications starting between 31 days after last dose of study PDR001 and 150 days after last dose of PDR001.

The safety set will be used for all concomitant medication tables.

Duration of exposure to concomitant medication with immunosuppressive intent (days) = (last date of exposure to concomitant medication with immunosuppressive intent) – (date of first administration of concomitant medication with immunosuppressive intent) + 1

Duration of exposure to concomitant medication with immunosuppressive intent will be summarized if relevant. In addition, the duration of exposure for the subset of subjects who experienced events of interest (i.e. AESIs, patients treated with concomitant medication with immunosuppressive intent) may be summarized. Descriptive statistics such as median, min, max will be presented.

Time to initiation of concomitant medication with immunosuppressive intent is the time from start of treatment with PDR001 to first administration of concomitant medication with immunosuppressive intent. Patients who did not receive concomitant medication with immunosuppressive intent will be censored .The censoring date will be the earliest of the following dates:

- death date,
- new anticancer antineoplastic therapy start date,
- end date of on-treatment period,
- data cut-off date,
- withdrawal of informed consent date.

Time to initiation of concomitant medication with immunosuppressive intent will be summarized if relevant. Kaplan-Meier curves will be displayed as well as median and 95% confidence intervals for each treatment arm. In addition, time to occurrence for the subset of subjects who experienced events of interest (i.e. AESIs, patients treated with concomitant medication with immunosuppressive intent) may be summarized. Descripive statistics such as median, min, max will be presented.

2.5 Analysis of the primary objective

The primary objective is to estimate the antitumor activity of PDR001 as a single agent in well-differentiated NET and poorly-differentiated GEP-NEC groups.

2.5.1 Primary endpoint

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 1 of the study protocol). ORR will be calculated within each group based on the FAS using BIRC review of tumor assessment data. Patients with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if a complete response was observed. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. Limited-field palliative radiotherapy administered as concomitant therapy per protocol will not

be considered as new antineoplastic therapy. Localized radiotherapy and treatment with bisphosphonates for pre-existing, painful bone/liver metastases is permitted.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed on the FAS. ORR will be summarized using descriptive statistics (N,%) along with 2-sided exact 95% confidence interval (CI) [Clopper and Pearson 1934].

Group 1: Well-differentiated NET

In the absence of historical comparator in this setting, response rates reported in placebo arms of previous randomized phase III studies in earlier lines of treatment can be considered as a valid historical reference for ORR (see Table 1-1 in the protocol). Based on it, the response rate for placebo is expected to be ca. 3% and it is desired to ensure that the observed response rate for PDR001 is significantly higher than expected placebo response rate. Furthermore, a response rate of 10% is considered clinically meaningful among patients with advanced NET of GI, pancreatic or thoracic origin.

Therefore, the results in this group will be considered a success if both of the following conditions are met:

1. a clinically relevant response rate of at least 10% is observed
2. the two-sided exact 95% CI excludes the value 3%.

With 90 patients in the FAS, these criteria correspond correspond to at least 9 responders observed (i.e. a response rate of 10% with 95% CI: [4.7; 18.1]).

Group 2: Poorly-differentiated GEP-NEC group

This group will enroll approximately 20 patients. Estimates of the ORR along with 95% two-sided CI will be presented. Additionally, the interval probabilities for the true ORR lying within the intervals stated below will be computed.

- 0 - <3% unacceptable efficacy
- 3% - <10% limited efficacy
- 10% - <20% moderate efficacy
- ≥20% clinically relevant efficacy

For this analysis a prior distribution for the parameter of interest, ORR, must be specified. For the current study, the prior clinical assumption for PDR001 in the selected patient population is used in order to derive a minimally informative unimodal Beta prior distribution that reflects the level of uncertainty around ORR before starting the current trial (Neuenschwander et al 2008). The prior mean ORR is set to be equal to 15% and the parameters of the minimally informative Beta prior distribution of ORR have been set up as follows:

- $a/(a+b) = 0.15$
- $a = 0.176$

- b = 1.0

At the primary analysis, this prior distribution will be updated with observed ORR data and probabilities that the true ORR lies within the above intervals will be reported.

2.5.3 Handling of missing values/censoring/discontinuations

For the computation of ORR, all confirmed responses (CR or PR) reported up to the analysis cut-off will be included. Patients with no valid radiological assessment or unconfirmed responses will be considered as non-responders. In particular, patients with CR or PR at the last radiological assessment prior to cut-off and no response at the previous assessment are by definition unconfirmed and will be considered as non-responders for the primary analysis.

Patients with unknown or missing best overall response (BOR) will be counted as non-responders. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'non-responders'.

2.5.4 Supportive analyses

A sensitivity analysis considering patients with unconfirmed PR or CR (i.e. with PR or CR at the last assessment prior to the cutoff and ongoing in efficacy follow-up) as responders may be performed if large delayed treatment effect is observed.

The analysis of ORR will be repeated based on local review.

Concordance analysis of BOR

An assessment of the concordance between BIRC assessment and local assessment of the Best Overall Response for each subject will be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both Independent Reviewer and Investigator Assessments):

Percent Agreement = (Number of matched responders + Number of matched non-responders) / total number of subjects assessed.

Subgroup analyses for the primary endpoint

If both criteria for the primary efficacy analysis are met, the primary endpoint of ORR will be summarized for the subgroups specified in Section 2.2.1 based on the primary analysis source (i.e. BIRC) and the same conventions as for the primary analysis.

For each of the subgroups, the following analyses will be performed:

- Proportion of patients with objective response
- two-sided exact 95% CI

Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of treatment effect.

Reasons for "Unknown" BOR

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD or non-CR/non-PD too early
- PD too late

Note 1: A SD or Non-CR/Non-PD is considered as "SD too early"' if the SD or Non-CR/Non-PD is documented within first 6 weeks after treatment start date.

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 12 weeks after treatment start date with no qualifying CR, PR or SD or Non-CR/Non-PD in between.

Note 3: Special (and rare) cases where BOR is "unknown" due to both too early SD and too late PD will be classified as "SD too early".

Waterfall plot to depict anti-tumor activity

Waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, such assessments will not be considered for display as bars in the graph, since the percentage change in the sum of diameters of target lesions reflects the non-PD target lesion response, but the overall lesion response is PD. A patient with only such assessments will be represented by a special symbol (e.g. □) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be excluded from the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-4.

Table 2-3 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?

1	CR/PR/SD	PD	Yes but as ‘ only	PD	any
2	CR/PR/SD	PD	Yes but as ‘ only	any	Yes
3	UNK	UNK or PD	No	any	any
4	CR/PR/SD	UNK	No	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Percentage change from baseline in the sum of diameters of all target lesions over the time will be displayed for individual patients.

2.6 Analysis of the key secondary objective

The key secondary objective in this study is to estimate efficacy of PDR001 using the duration of response per RECIST 1.1 and based on tumor response data per BIRC.

2.6.1 Key secondary endpoint

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on BIRC review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer.

2.6.2 Statistical hypothesis, model, and method of analysis

DOR will be listed and summarized for all patients in the FAS with confirmed BOR of CR or PR. The duration of response will be presented graphically along with the duration of on-study follow-up and information about responses. The distribution of duration of response will be estimated using the Kaplan-Meier method and the median duration of response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case.

2.6.3 Handling of missing values/censoring/discontinuations

For DOR analysis patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using the censoring rule described for PFS analysis.

2.7 Analysis of secondary efficacy objective(s)

All secondary efficacy endpoints according to RECIST 1.1 or irRECIST will be based on tumor assessments as per BIRC. The local radiology assessments will be used as supportive analysis.

Antitumor activity (assessed by ORR and DoR per RECIST 1.1 and BIRC) in each of the three well-differentiated NET cohorts (pancreatic, GI, thoracic) will also be evaluated as secondary endpoint.

2.7.1 Secondary endpoints

Disease control rate (DCR)

DCR is defined as the proportion of patients with best overall response of CR, PR or SD according to RECIST 1.1 criteria and as per central review. DCR will be calculated using FAS and based on the BIRC tumor assessments.

Time to response

Time to response (CR or PR) is the time from date of treatment start to first documented response of CR or PR (which must be confirmed subsequently) using BIRC review of tumor assessment data and according to RECIST 1.1. All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

Progression-free survival (PFS)

PFS is defined as the time from the date of first dose to the date of the first documented radiological progression or death due to any cause. PFS will be assessed via central review according to RECIST 1.1. PFS will be censored if no PFS event is observed before the analysis cut-off date.

If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered provided tumor assessments continue after initiation of new cancer therapy. Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation.

Efficacy endpoints according to irRECIST

Immune related overall response rate (irORR) is the proportion of patients with a best overall response of irCR or irPR based on BIRC review of tumor assessment data.

The best immune related overall response for each patient is determined from the sequence of immune related overall responses according to rules described in the irRECIST appendix of the protocol.

Immune related duration of overall response (irDOR): For patients with a confirmed irCR or irPR based on BIRC review of tumor assessment data. The start date is the date of first documented confirmed response and the end date and censoring is defined the same as that for time to progression.

Date of confirmed response is derived as followed: Response (irPR or irCR) should be confirmed by a second assessment no less than 4 weeks after the first assessment showing response. Date of response is then the date of the first of these two assessments. For confirmation of irCR the two assessments must be consecutive (intervening assessments of irUNK are permissable). For confirmation of irPR the two assessments do not need to be consecutive, but must not be separated by a pseudo-progression event.

Immune related time to overall response (irTTR) is the time between date of start of treatment until first documented response (confirmed irCR or irPR).

Immune related disease control rate (irDCR) is the proportion of patients with a best overall response of irCR or irPR or irSD. Patients with BOR of irNCRNPD will also be included in DCR if patients with non-measurable disease at baseline are in analysis set.

Immune related progression-free survival (irPFS) is the time from date of start of treatment to the date of event defined as the first documented assessment of irPD that was then confirmed or death due to any cause. Unconfirmed irPD without further adequate tumor assessments will be considered as a confirmed irPD. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment. An adequate tumor assessment is a tumor assessment with overall response other than irUNK.

Immune related confirmed irPD is derived as described in section 5.5.

Overall survival rate at 1 year and 2 years

OS is defined as the time from date of start of treatment to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

2.7.2 Statistical hypothesis, model, and method of analysis

Disease control rate

DCR will be calculated based on the FAS. DCR and its 95% confidence interval will be presented.

Time to response

TTR will be listed and summarized for all patients. The distribution of time to response will be estimated using the Kaplan-Meier method only if a sufficient number of responses is observed.

Progression-free survival (PFS)

PFS based on RECIST 1.1 will be analyzed in the FAS population. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for all patients.

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided based on the following reasons:

1: Ongoing without event

2: Lost to follow-up

3: Withdrew consent

4: Adequate assessment no longer available

5: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate tumor assessment (TA) date and the earliest of the following dates is smaller or equal to interval of 2 missing TAs:

1. Analysis cut-off date,
2. Date of consent withdrawal,
3. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. 'Ongoing',
2. 'Withdrew consent',
3. 'Lost to follow-up',

If the time interval is larger than the interval of 2 missing TAs with no event observed. then the PFS censoring reason will always default to 'Adequate assessment no longer available'. If the time interval between the last adequate TA date and the PFS event date is larger than the interval of 2 missing TA then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'. Further details on the definition of last adequate assessment and two missing TAs are provided in Section 2.7.3.

Efficacy endpoints according to irRECIST

The following irRECIST endpoints will be analyzed in a similar way to the corresponding RECIST endpoints:

- irORR
- irDoR
- irTTR
- irDCR
- irPFS.

Overall Survival

The survival distribution of OS distribution will be estimated using the Kaplan-Meier method and Kaplan-Meier curves.

Survival estimates at 1 year and at 2 years will be computed with 95% confidence interval [Brookmeyer and Crowley 1982].

2.7.3 Handling of missing values/censoring/discontinuations

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD or non-CR/non-PD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the start date of treatment will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

As per protocol, tumor assessments are expected to be performed every 8 weeks for the first 12 months and every 12 weeks thereafter.

Therefore:

- if the last adequate tumor assessment is performed before end of week 36 (i.e. from study day 1 to study day 36*7=252) then the interval of 2 missing tumor asssessments is given as 2*8+2=18 weeks (126 days);
- if the last adequate tumor assessment is performed from end of week 36 up to end of week 44 (i.e. from study day 253 to study day 44*7=308) then the interval of 2 missing tumor asssessments is given as 8+12+2=22 weeks (154 days);
- otherwise, when the last adequate tumor assessment is performed after end of week 44 (i.e. from study day 44*7+1=309 onward), then the interval of 2 missing tumor asssessments is given as 2*12+2=26 weeks (182 days).

These summaries on censoring reasons will be produced for PFS by investigator and BIRC.

Refer to Table 2-5 for censoring and event date options and outcomes for PFS.

Table 2-4 Outcome and event/censor date for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of treatment	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed

Situation	Date	Outcome
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Progressed

2.8 Safety analyses

All safety analyses will be based on the safety set. All listings and tables will be presented separately for the well-differentiated NET and the poorly-differentiated GEP-NEC groups. In addition, pooled safety analyses based on all patients will be produced.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. Additional summaries will be displayed to report all AEs, AEs related to study treatment, all SAEs and SAEs related to study treatment collected up to 150 days after last administration of PDR001. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational arm.

The following adverse event summaries will be produced using the safety set; overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, requiring immunosuppressive medication and leading to fatal outcome. In

addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound PDR001. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, requiring immunosuppressive medication etc.). Additional summaries will be provided to report all AESIs, AESIs related to study treatment, all serious AESIs and serious AESIs related to study treatment collected during the on-treatment period and up to 150 days after last administratio n of PDR001.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by system organ class and preferred term. Additional summary will be displayed to report all deaths up to 150 days after last administration of PDR001.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later then 150 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listing will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN

- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

12-lead ECGs including PR, QRS, QT, QTcF and RR intervals will be obtained central/local for each subject during the study. ECG data will be read and interpreted locally.

The number and percentage of subjects with notable ECG values will be presented.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg)

Data handling

Vital signs collected on treatment will be summarized.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-6 below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented.

2.9 Pharmacokinetic endpoints

PK Concentrations

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for PDR001 concentrations will be presented at each scheduled time point for the Pharmacokinetic analysis set. For PDR001, pre-dose concentrations collected before dose administration on Day 1 of Cycle 2+ are Ctrough.

All individual PDR001 concentration data will be listed for the Safety set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (i.e. <0.25 ng/mL) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PD and PK/PD analyses

2.10.1 Immunogenicity

2.10.1.1 Sample ADA Status

Each IG sample is assessed in a three tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb). Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of the ADA response
- Presence of Nab (for positive samples, if NAb assay results are available): yes or no
- Drug tolerance level: highest drug concentration that does not interfere in the ADA detection method
- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Sample ADA status is determined based on the following definitions:

- *ADA-inconclusive sample*: Sample where assay is ADA negative and P*DR001* PK concentration at the time of IG sample collection is greater than or equal to the drug tolerance level or missing.
- *Unevaluable sample*: Sample where assay is not available.
- *Determinant sample:* Sample that is neither ADA-inconclusive nor unevaluable.

The following definitions apply only to determinant samples:

  - *ADA-negative sample*: Determinant sample where assay is ADA negative and *PDR001* PK concentration at the time of IG sample collection is less than the drug tolerance level.
  - *ADA-positive sample*: Determinant sample where assay is ADA positive.
    - *ADA-positive NAb sample*: Determinant sample where assay is ADA positive and presence of NAb = yes.

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as *treatment-boosted* or *treatment-unaffected*, both the post-baseline and baseline titer must be non-missing:

- *treatment-induced ADA-positive sample:* ADA-positive sample post-baseline with ADA-negative sample at baseline.
- *treatment-boosted ADA-positive sample:* ADA-positive sample post-baseline with titer that is at least the fold titer change greater than the ADA-positive baseline titer.
- *treatment-unaffected ADA-positive sample*: ADA-positive sample post-baseline with titer that is less than the fold titer change greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

The following summaries of ADA sample status (n and %) will be provided using *Immunogenicity prevalence set*:

- ADA-positive samples (i.e. ADA prevalence) and ADA-positive NAb samples, both overall and by time point (including baseline). For summaries by time point, the denominator is the number of subjects at that time point with a determinant sample.

Listings will be provided of sample ADA status (including titer for positive samples).

2.11 Patient-reported outcomes

The EORTC QLQ-C30 questionnaire and the EQ-5D-5L will be used to collect patient's QoL data. The FAS will be used for analyzing PRO data. The global health status/QoL scale score of the QLQ-C30 and the health status index score of the EQ-5D-5L are identified as the primary patient-reported outcome variables of interest. Physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30, and overall health status of the EQ-5D-5L are identified as secondary patient-reported QoL variables of interest.

High scores in the EORTC QLQ-C30 correspond to a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. Higher scores in the EQ-5D-5L correspond to better health states or overall health status.

Established estimates for the minimal important differences (MID) for each measure will be used to interpret change from baseline scores. For the EORTC QLQ-C30 a change of ≥10 will be defined as the MID [Osoba 1998]. For the EQ-5D-5L, a change in the index score of ≥0.08 and a changes in the VAS of ≥7 will be defined as the MID [Pickard 2007].

EORTC QLQ-C30 subscale scores will be calculated by first obtaining the raw scores through adding up the item responses on the questions which make up each domain and then applying the linear transformation to the raw scores in accordance with the respective scoring manual provided by the developer (Fayers 2001). No imputation procedures will be applied for missing items or missing assessments.

For EQ-5D-5L health states will be converted to index value, during data analysis stage, based on the EQ-5D crosswalk value set for the UK using the time trade-off method (van Hout 2015). If any one of the five items is missing, the index value will be set to missing. In addition, the visual analog scale (ranging from 0 to 100) from the EQ-5D-5L will be evaluated for patient's rating of their overall health status.

The PRO instruments are planned to be administered during screening and every *8* weeks after first day of treatment during the first 12 months, and every 12 weeks thereafter until the end of treatment. PRO assessments will continue to be collected during the efficacy follow-up after the end of treatment.

The baseline is defined as the last PRO assessment on or before the first day of treatment.

Descriptive statistics will be used to summarize the PRO scores and change from baseline for scales of the EORTC QLQ-C30 and health states, overall health status, and index values of the EQ-5D-5L at each scheduled assessment time point by cohort. Data obtained after the end of treatment will be summarized separately. Additionally, analysis by responder/non-responder may be performed if sufficient number of responders is observed.

2.12 CgA and NSE

The biochemical response will be assessed using the change from baseline for CgA and NSE levels.

Change from baseline in CgA and NSE will be summarized using descriptive statistics for all patients. CgA and NSE values might be analyzed on the logarithmic scale if their observed distribution is found be right skewed.

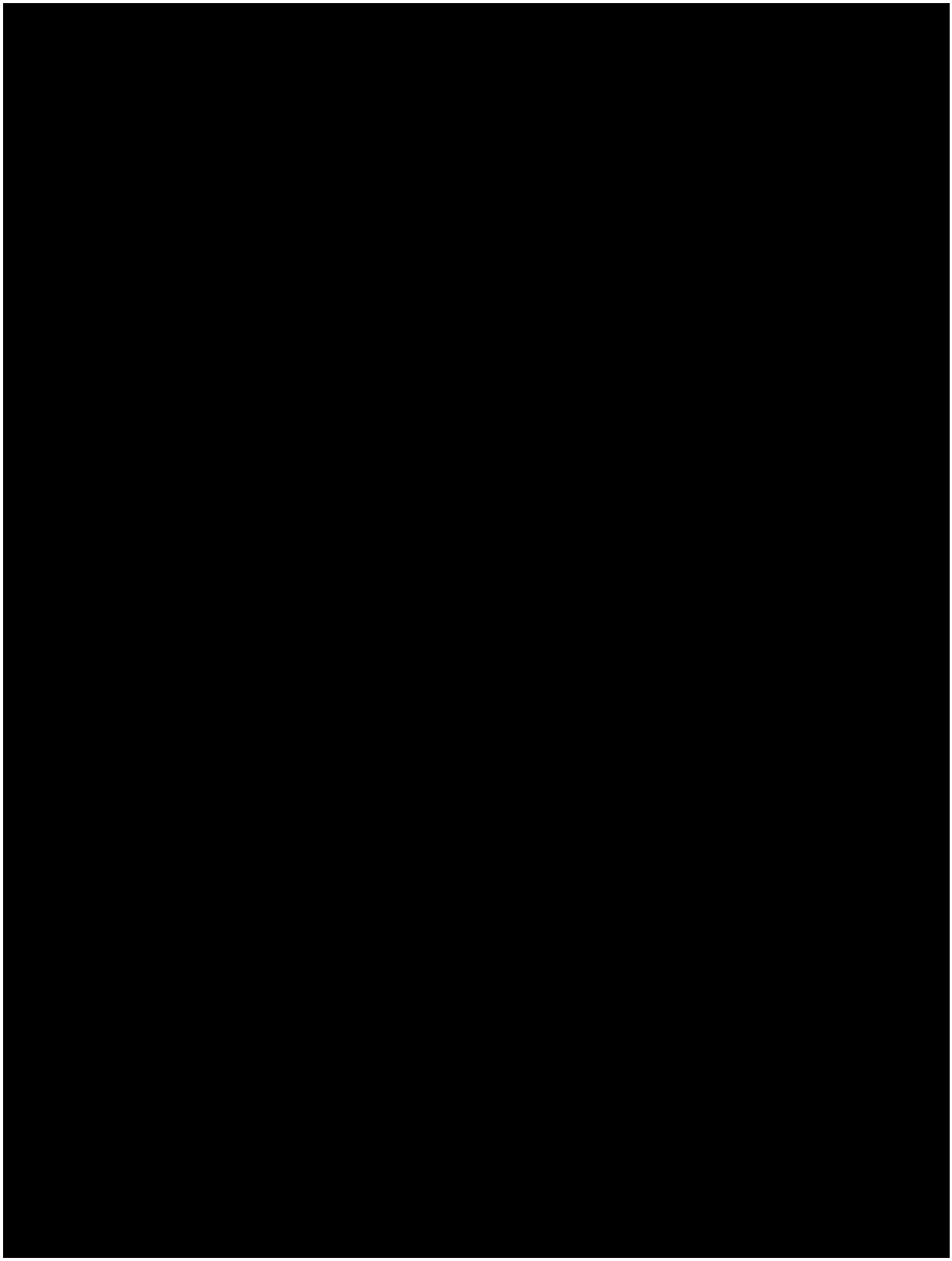
Data handling principles

The lower limit of quantification (LLOQ) values for CgA and NSE will be specified by the laboratory running the assay.

Measures below the LLOQ will be handled as follows:

- If the proportion of measures below LLOQ is below 15%, all values specified as below LLOQ will be imputed by half of the LLOQ and the standard set of summary statistics will be used.
- If the proportion of measures below LLOQ is above 15%, but below 50%, an alternative choice of summary statistics requiring no imputation such as percentiles may be used.
- Otherwise the data will be missing
- When both baseline and post baseline values are below LLOQ, change from baseline will not be imputed and reported as missing.

All available data points obtained at scheduled and unscheduled visits will be considered for the analysis.



2.14 Interim analysis

An interim analysis for preliminary assessment of PDR001 in this patient population will be conducted once at least 30 patients from the well-differentiated NET group have 3 radiological assessments (week 24) or have discontinued study for any other reason. All available efficacy and safety data from the well-differentiated NET and poorly-differentiated GEP-NEC groups up to the cut-off date will be used for IA. The study will not be stopped at the interim analysis for efficacy reasons regardless of efficacy results and will continue until mature data for all patients become available.

3 Sample size calculation

Group 1: Well-differentiated NET

In the absence of an established control treatment, ORR reported in the placebo arms of studies reported in Table 1-1 of the protocol can serve as a reference. A 3% ORR is therefore considered as a reasonable reference while an improvement up to 10% is considered as clinically meaningful in this patient population.

Total sample size of 90 patients was chosen such that with an observed 10% response rate, the corresponding 95% CI excludes the value 3%.

Approximately thirty patients will be recruited in each cohort NET cohort: pancreatic, GI and thoracic.

Operating characteristics in the well-differentiated NET group are given in Table 3-1. A sample size of 90 patients ensures an 90% probability of success if the true ORR is 15%.

Table 3-1 Operating characteristics for the full population

True response rate	Probability of observing 10% or more responders at the end of the study*
10%	0.55
11%	0.67
12%	0.77
13%	0.84
14%	0.90

15%	0.94

In addition, Table 3-2 shows the probability of observing at least 3 responders in a cohort with 30 patients under the assumption of true response rate of 10-20% in this cohort.

Table 3-2 Probability of observing at least 3 responders in a cohort with more than 10% true response rate

True response rate in a cohort	Probability of observing 3 or more responders in a cohort with 30 patients end of the study*
10%	0.59
12%	0.72
14%	0.81
16%	0.88
18%	0.93
20%	0.96

Group 2: Poorly-differentiated GEP-NEC

Approximately 20 patients will be enrolled in the poorly-differentiated GEP-NEC group. The operating characteristics are shown in Table 3-3 and Table 3-4. With the planned sample size the probability to observe at least moderate efficacy (≥10% ORR) is more than 80% if the true ORR is 15%. Posterior probability of a true ORR of at least moderate efficacy was computed for different scenarios assuming a minimally informative prior with Beta distribution and the following parameters: a=0.176, b=1. Posterior probability of a true ORR to be ≥10% ORR is more than 70% if 3 responders are observed in 20 patients.

Table 3-3 Operating characteristics for the poorly-differentiated GEP-NEC group

True response rate	Probability of observing 2 or more responders (≥10% ORR) in 20 patients	Probability of observing 3 or more responders (≥15% ORR) in 20 patients
10%	0.61	0.32
12%	0.71	0.44
15%	0.82	0.60
18%	0.90	0.73
20%	0.93	0.79

Table 3-4 Posterior probability of a true ORR in the poorly-differentiated GEP-NEC group corresponding to at least moderate efficacy (≥10% ORR)

Number of observed responders in 20 patients	Posterior probability for a true ORR ≥10%
1	15.8%
2	44.0%
3	71.4%
4	88.6%

4 Change to protocol specified analyses

5 No probabilistic evaluation of heterogeneity between three cohorts in the well-differentiated NET group will be performed. No other changes to the protocol specified analyses are included in this analysis plan. Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 150 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory

tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

Table 5-3 CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010)

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9 /L	< 3.0 – 2.0 x 10^9 /L	< 2.0 – 1.0 x 10^9 /L	< 1.0 x 10^9 /L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9 /L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils [3]↓	10^9/L	NEUT		≥2x1 0^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L

Lymphocytes [3]↓ Lymphocytes ↑	10^9/L 10^9/L	LYM LYM		≥1.5 x10^9 /L	< 1.5 - 0.8 x 10^9 /L -	< 0.8 - 0.5 x 10^9 /L > 4 - 20 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L > 20 x 10^9 /L	< 0.2 x 10^9 /L -
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/ L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/ L	CREA T	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbumine mia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-

Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol**/L or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [(2)] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L
ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range								

				CTC Grades[(1)]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[(2)] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L

Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L

Glucose [(2)] (Hypoglycemia)	mmol/L	GLUCSN/GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [(2)] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [(2)] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [(2)] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [(2)] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [(2)] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [(2)]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[(2)]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-

Fibrinogen [(4)]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.

(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.

(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9 /L (lymphocytes) and ≥ 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**

(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

LAB - CTC grades in Novartis Oncology (26Oct15)

5.4 Statistical models

5.4.1 Primary analysis

Analysis of binary data

No formal hypothesis testing will be performed. Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper and Pearson 1934].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – 0.05)) two-sided Pearson-Clopper CI.

5.4.2 Key secondary analysis

Analysis of time to events data

Kaplan-Meier estimates

An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties.

5.5 Rule of derivation for immune related criteria

Immune related confirmed irPD is derived as followed:

Confirmed progression 1 (type 1, cPD1) is declared if a patient has 2 consecutive tumor assessments at least 4 weeks (28 days) apart both showing disease progression. Assessments with an irUNK response or irPD assessments < 28 days after initial irPD, are discarded.

The first irPD is flagged as cPD1 while all subsequent irPDs are flagged as xPD1.

Sequence of assessments	Instructions

1 irPD 2 irUNK 3 irPD (Assessment 1 + 30 days)	• Assessment 3 is ≥28 days after Assessment 1 • Assessment 3 represents confirmation of irPD at assessment 1 • Assessment 1 irPD is flagged cPD1 • Assessment 3 irPD is flagged xPD1
1 irSD 2 irPD 3 irPD (Assessment 2 + 20 days) 4 irPD (Assessment 2 + 30 days)	• Assessment 3 is < 28 days after Assessment 2 • Assessment 4 is ≥ 28 days after Assessment 2 • Assessment 4 represents confirmation of irPD at assessment 2 • Assessment 2 irPD is flagged cPD1 • Assessment 3 and 4 irPDs are flagged xPD1

The date of progression is the date of the assessment flagged as cPD1.

Confirmed progression 2 (type 2, cPD2) is declared if a patient discontinues treatment following a single irPD with no subsequent assessments. Assessments with an irUNK response or irPD assessments < 4 weeks (28 days) after initial irPD, are discarded. Discontinuation of treatment is obtained from EOT case report form.

The assessment is flagged as cPD2 and subsequent irPDs (<28 days after first PD) are flagged as xPD2.

The table below shows two hypothetical data scenarios and programming instructions.

Sequence of assessments	Instructions
1 irSD 2 irPD - EOT	• Patient withdraws after initial progression (Assessment 2) without confirmation • Assessment 2 irPD is flagged as cPD2
1 irPD 2 irPD (Assessment 1 + 20 days) - EOT	• Assessment 2 irPD is <28 days after Assessment 1, so does not represent confirmation • However, patient has completed treatment • Assessment 1 irPD is flagged cPD2 • Assessment 2 irPD is flagged xPD2

The date of progression is the date of the assessment flagged as cPD2.

Unconfirmed progression. Patients with a single irPD, and no assessment of irSD or better (assessment with an irUNK response or irPD assessments < 4 weeks after initial irPD, are discarded) continuing treatment at the time of the analysis will be considered as unconfirmed (uPD).

6 Reference

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