Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS100036-0020
Title	A multicenter study with an open-label Phase Ib part followed by a randomized, placebo-controlled, double-blind, Phase II part to evaluate efficacy, safety, tolerability, and pharmacokinetics of the DNA-PK inhibitor peposertib (M3814) in combination with capecitabine and radiotherapy in participants with locally advanced rectal cancer
Study Phase	Phase Ib/II
Investigational Medicinal Product(s)	Peposertib (M3814)
Clinical Study Protocol Version	6 May 2021/Version 4.0
Integrated Analysis Plan Author	**Coordinating Author** PPD Merck PPD **Function** / **Author(s) / Data Analyst(s)** PPD / PPD PPD / PPD
Integrated Analysis Plan Date and Version	7 July 2021/ Version 3.0
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Approval Page

Integrated Analysis Plan: MS100036-0020

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Approval of the IAP by all Merck Data Analysis Responsibles has to be documented within ELDORADO via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

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2 List of Abbreviations and Definition of Terms

AE	Adverse event
ATC	Anatomical therapeutic chemical classification
AUC	Area under the concentration-time curve
$AUC_{extra, \%}$	The AUC from time t_{last} extrapolated to infinity
BSA	Body surface area
cCR	Clinical complete response
CI	Confidence interval
CL/f	Apparent total body clearance
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CR	Complete response
CRM	Circumferential margin
CRR	Complete response rate
CSP	Clinical study protocol
CSR	Clinical study report
CCI [redacted]	[redacted]
CTC	Common terminology criteria
CTMS	Clinical trial management system
CV%	Coefficient of variation
DCR	Disease control rate
DE	Dose escalation
DFS	Disease-free survival
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DNA-PK	DNA protein kinase
DRE	Digital rectal exam
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

EMVI	Extramural venous invasion
ENR	Enrolled population
EudraCT	European Clinical Trials Database
EUS	Endoscopic ultrasonography
FAS	Full analysis population
FD	Fraction day
FU	Follow up
IAP	Integrated analysis plan
ICH	International Conference on Harmonization
IR	Incomplete response
KM	Kaplan-Meier
LCL	Lower confidence limit
LLOQ	Lower limit of quantification
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MR	Metabolite to parent ratio
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
n	Sample size
nd	Not done
n/a	Not applicable
NE	Not evaluable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
pCR	Pathological complete response
PD	Progressive disease
CCI	[redacted]

PR	Partial response
PT	Preferred term
PTV	Planning target volume
PK	Pharmacokinetics
Q1	First quartile
Q3	Third quartile
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
R_{acc}	Accumulation factor
RP2D	Recommended phase 2 dose
RT	Radiotherapy
SAE	Serious adverse event
SAF	Safety analysis population
SD	Stable disease
Sd	Standard deviation
SDTM	Study data tabulation model
SMC	Safety monitoring committee
SOC	System organ class
TEAE	Treatment-emergent adverse event
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time to reach maximum observed concentration
UCL	Upper confidence limit
ULN	Upper limit of normal
UNK	Unknown
Vz/f	Apparent volume of distribution at steady state
WHO-DD	World Health Organization Drug Dictionary
λ_z	Terminal elimination rate constant

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	11 February 2020	PPD	NA
2.0	22 March 2021	PPD	- Updated author/reviewer list - Update protocol version with V3.0: • addition TNM classification, MRI-EMVI score and MRI-CRM score on Disease History description • addition TNM classification, MRI-EMVI score and MRI-CRM score on tumor evaluation • addition of prior induction therapies description) - Addition of Actual daily Dose PTV1 and PTV2 in radiotherapy cumulative dose calculation - Add analysis to assess COVID-19 impact on the study. - Removed objective “To characterize exposure response (exposure/safety and exposure/efficacy) for M3814 with respect to selected safety and efficacy endpoints” as it is planned only for Phase I and II combined - TEAE leading to a delay in dose time of RT (corresponding to AEs with action taken = “Dose time delayed”) removed from the Adverse Events Leading to Study Intervention Discontinuation description
3.0		PPD	- Update protocol version to V4.0 - Long-term Safety Follow-up period shortened to 1 year (previously 2 years) and removed Survival Follow-up. - Removed the endpoints of “overall survival” and “best overall response”.- Added endpoint of “neoadjuvant rectal score”. - Change date added on AE listing

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (IAP) is to document technical and detailed specifications for all analyses of data collected for the Phase Ib (dose escalation) protocol MS100036-0020. Results of the analyses described in this IAP will be included in the clinical study report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post hoc, or unplanned analyses performed to

provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based on Section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) guideline E9.

Separate IAPs will document technical and detailed specifications for the analyses to be provided for safety monitoring committee (SMC) meetings.

Peposertib instead of peposertib (M3814) will be used in the current document.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Primary			
To define an MTD and RP2D of peposertib in combination with capecitabine and RT	Occurrence of dose limiting toxicities (DLT)	Time from first study intervention to end of chemoradiotherapy with a final assessment at 4 weeks after surgery	15. Safety Analyses
Secondary			
To evaluate safety and tolerability of peposertib in combination with capecitabine and RT	Occurrence of TEAEs and treatment-related adverse-events according to the NCI-CTCAE version 5.0 Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, and clinically significantly abnormal ECGs including clinically important increases in QT interval (QTcF)	Time from first study intervention to final assessment at 5 years	15. Safety Analyses
To explore antitumor activity of peposertib in combination with capecitabine and RT	Composite endpoint of pCR/cCR	Pathology evaluation of specimen after surgery (pCR) and clinical evaluation 1 to 2 weeks prior to surgery (cCR)	14. Efficacy Analyses

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
	Disease-free Survival	Time from first study intervention to final assessment at 5 years	
	pCR	Pathology evaluation of specimen after surgery	
	cCR	Time from first study intervention until clinical evaluation 1 to 2 weeks prior to surgery	
	Local recurrence and/or distant metastasis	Time from surgery to final assessment at 5 years	
	Neoadjuvant rectal score	Pathology evaluation of specimen after surgery	
To assess the Pharmacokinetics (PK) of peposertib	PK profile of peposertib in terms of PK parameter estimates (eg, C_{max}, AUC, t_{max}, CL/f Vz/f, $t_{1/2}$)	Fraction Day (FD) 1 and FD9	16.1 Pharmacokinetics
CCI [redacted]			

AUC = area under the concentration time-curve ; cCR = clinical complete response; CL/f = apparent total body clearance; C_{max} = maximum observed plasma concentration; ; DLT = dose limiting toxicity; ECG = electrocardiogram; FD = fraction day; MTD = maximum tolerated dose; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events; pCR = pathological complete response; PK = pharmacokinetics; QTcF = fridericia-corrected QT interval; RP2D = recommended phase 2 dose; RT = radiotherapy; TEAE = treatment emergent adverse event; $t_{1/2}$ = apparent terminal half-life; t_{max} = time to reach maximum observed concentration; Vz/f = apparent volume of distribution at steady state.

6 Overview of Planned Analyses

6.1 Analyses for SMC meetings

During Phase Ib, to decide on dose escalation, safety and PK analyses will be provided for the purpose of SMC meetings. The cut-off for dose escalation assessments by the SMC will usually be triggered by the completion of the DLT period (or dropout) of the last participant in the respective dose escalation cohort of usually 3 participants. In addition, once a participant completed the Short-term safety follow-up period at approximately 19 weeks after starting treatment, data of the participant will be reviewed. In the event of severe toxicity, an ad-hoc SMC meeting will be scheduled to decide on potential dose adjustment.

Details of analyses for SMC meetings will be specified in the appendix of this IAP.

6.2 Interim Analysis

After the last subject has finished the DLT period and after last subject has finished short term follow-up, an analysis on key safety and efficacy endpoints will be provided to decide on further development and potentially answer HA requests.

6.3 Primary Analysis

This analysis will be the main analysis of the safety and preliminary antitumor activity data from the dose escalation phase. The cut-off will be triggered by when the last participant enrolled in dose escalation reaches the end of the Short-term safety follow-up period or dies or prematurely discontinues the study for any reason, whichever occurs first.

6.4 Further Analyses

Follow-up analyses to report further efficacy and safety data will be done once all participants have completed the 1-year follow-up period and at the end of study.

Additional analyses of safety and preliminary antitumor activity might be performed for the purpose of publication at scientific congresses.

7 Changes to the Planned Analyses in the Clinical Study Protocol

Outcome of the tumor assessment prior to surgery is reflected in the analysis of cCR. As the number of subjects in the dose escalation cohorts is low, PK exposure of peposertib versus safety and exposure will not be performed.

7.1 COVID-19 Impact

Additional listings will be generated to assess potential impacts of COVID-19 to this study including:

- listing of participants potentially affected by pandemic and with any AEs or PDs related to COVID-19
- listing of PDs related to COVID-19
- listing of AEs related to COVID-19.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations and Analysis Populations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

The following deviations will be identified and confirmed prior to or at the data review meeting, at the latest.

Important protocol deviations will be categorized into one of the following:

- Subject enrolled and dosed on the study who did not satisfy enrolment criteria
- Subject fulfills withdrawal criteria whilst on the study but is not withdrawn

- Subject is administered the wrong study intervention or an incorrect dose
- Subject is administered or takes concomitant medication excluded by the clinical study protocol (CSP)
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviations from good clinical practice (e.g. deviations related to informed consent of study participants)
- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being

All important protocol deviations are listed in a separate document. In addition, all important protocol deviations are documented in study data tabulation model (SDTM) datasets whether identified through site monitoring, medical review or programming.

8.2 Definition of Analysis Populations and Subgroups

The analysis populations are specified below:

Table 1 Description of Analysis Sets

Population	Description
Enrolled	All participants who sign informed consent
Dose escalation (DE)	The DE Analysis Set will include all participants treated in dose escalation cohorts, who receive at least 80% of peposertib, 50% of capecitabine, and 80% of RT planned dose and complete the DLT period (5 or 5.5 weeks after start of treatment or for the entire duration of the treatment). The DE set will also include participants treated in dose escalation cohorts who experience a DLT during the DLT period regardless of the amount of each study intervention received/completion of the DLT period.
Full analysis set (FAS)	The FAS will include all participants who are enrolled in the study and received at least 1 dose of study intervention.
Safety (SAF)	The SAF analysis set will include all participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the actual treatment they receive. In case of differenct doses received the dose whith high number of administrations will be used as actual treatment.
Pharmacokinetics (PK)	The PK analysis set is defined as all participants who receive at least 1 dose of peposertib and have sufficient peposertib plasma concentration data to enable the calculation of at least 1 PK parameter. Sufficient concentration data is defined as at least 3 valid, post dose, concentration points in the PK profile to obtain any PK parameter.

DE=dose escalation, DLT=dose limiting toxicity, FAS=full analysis set, PK=pharmacokinetic, RT=radiotherapy, SAF=safety

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Table 2 Summary of Analyses and associated Analysis Set

Analyses	ENR	SAF	FAS	DE	PK
Disposition	✓				
Baseline assessments		✓			
Past and concomitant therapies		✓			
Compliance and exposure		✓			
Primary endpoint: DLTs				✓	
Efficacy			✓		
Safety and tolerability		✓			
CCI					
Pharmacokinetics					✓
CCI					

DE=dose escalation, ENR=enrolled, FAS=full analysis set, PK=pharmacokinetic, SAF=safety

9 General Specifications for Data Analyses

Study intervention groups

Unless otherwise indicated all analyses will be presented separately for each dose level, and overall.

Data handling after cut-off date

Data after cut-off do not undergo the cleaning process, will not be included in SDTMs, and will not be displayed in any listings or used for statistical analyses or imputation.

Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

Significance level

All statistical tests mentioned in this IAP are to be regarded as exploratory. All statistical tests comparing study intervention groups will be performed two-sided. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in the corresponding section of this IAP.

Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics, i.e.

- number of participants, number of participants with non-missing values,

- mean, standard deviation,
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of participants in the analysis population of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

For summaries by visits, only visits where all subsequent visits have 3 or more participants will be displayed. In case the analysis refers only to certain visits, percentages will be based on the number of participants in the corresponding analysis set.

Presentation of PK concentration data

Peposertib, its metabolite (if available), capecitabine, and its metabolite (if available) concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (Sd), coefficient of variation (CV%), minimum (Min), median (Median), and maximum (Max). If $n \leq 2$, only n, Min, and Max will be reported.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max: 3 significant digits

Sd: 4 significant digits

CV%: 1 decimal place

Presentation of PK parameter data

Pharmacokinetic parameter data will be descriptively summarized using: n, Mean, Sd, CV%, Min, Median, Max, geometric mean (GeoMean), and the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCL 95% GM, UCL 95% GM). For time to reach maximum observed concentration (t_{max}), only n, Min, Median, and Max will be reported.

If $n \leq 2$, only n, Min, and Max will be reported.

The PK parameter maximum observed plasma concentration (C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the SDTM and ADaM PP domain, PK parameters will be provided with full precision, and will not be rounded. Descriptive statistics of PK parameter data will be calculated using full precision values and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
Sd:	4 significant digits
CV%, GeoCV%:	1 decimal place

Study day

Study day (also called treatment day) is defined relative to the date of start of treatment (first administration of peposertib, RT, or capecitabine, whatever is earliest). Study day 1 defines the day of first treatment, the day before is defined as study day –1 (no study day 0 is defined).

Definition of baseline

The last measurement prior to first administration of trial treatment (either peposertib, RT or capecitabine) will be used as the baseline measurement. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Definition of change from baseline (per visit)

Change from baseline: visit value – baseline value

Percent change from baseline: 100 * (visit value – baseline value) / baseline value

Definition of on treatment period:

On treatment period is defined as the time from the first administration of study intervention to the last administration of study treatment + 30 days, or the clinical cut-off date (if the treatment is still ongoing), or death, whichever occurs first.

Date of last known to be alive

The date of last known to be alive will be derived for participants not known to be dead at the analysis cut-off using the latest complete date among the following:

- All subject assessment dates:

- Laboratory assessments using information from "Hematology", "Biochemistry", "Coagulation", "Urinalysis", "Pregnancy test" and "Creatinine Clearance" eCRF pages (LBDTC variable from LB SDTM domain to be used)
- Vital signs using information from "Vital signs" eCRF page (VSDTC variable from VS SDTM domain to be used)
- Performance status using "ECOG Performance status" eCRF page (QSDTC variable from QS SDTM domain to be used)
- ECG, using information from both local and central ECGS (EGDTC variable from EG SDTM domain to be used)
- Tumor assessments using "Tumor assessments" eCRF pages (TRDTC/TUDTC variable from TR/TU SDTM domain to be used)
- Surgery information using "Rectal Surgery at week 15", "Rectal Surgery after Week 15", "Surgery after discontinuation" eCRF pages
- Anti-cancer treatment after discontinuation start and end date from "Anti-Cancer treatment after discontinuation" eCRF page.
- Start dates of concomitant medications or anti-cancer therapies administered after study treatment termination using "Concomitant medications", "Anti-cancer treatment after discontinuation details" eCRF pages (CMSTDTC variable from CM SDTM domain to be used)
- AE start dates from "Adverse events details" eCRF page (AESTDTC variable from AE SDTM domain to be used)
- Study treatment administration dates using "M3814 (PEPOSERTIB)/PLACEBO Administration Details", "RT Administration" and "Capecitabine Administration" eCRF pages (EXSTDTC variable from EX SDTM domain to be used)
- Last known to be alive date using "Survival Follow-up page" (SSDTC variable from SS SDTM domain where SSCAT="SURVIVAL FOLLOW-UP"), where status is "Alive".

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status (such as the date a blood sample was processed) will not be used. Assessment dates after the cut-off date will not be considered for derivation of last date known to be alive.

Definition of duration/ time since an event

Duration will be calculated by the difference of start and stop date + 1 (e.g., survival time [days] = date of death – date of Study day 1 + 1), if not otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as date of event – Study day 1 +1.

Conversion factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data

Unless otherwise specified, missing data will not be replaced.

In all participant data listings imputed values will be presented, and the imputed information will be flagged (if not specified otherwise).

Missing statistics, e.g., when they cannot be calculated, should be presented as "nd" (not done). For example, if n=1, the measure of variability (Sd) cannot be computed and should be presented as "nd".

Adverse events

For identification of AE treatment emergence, incomplete dates will be handled as follows:

- In case the onset date is completely missing, or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of trial treatment then the onset date will be replaced either by the start of trial treatment date or the AE resolution date, whichever is the earliest.
- In all other cases, the missing onset day or onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

Previous/Concomitant medication

For identification of previous or concomitant medications/procedures, no formal imputation will be performed on missing or incomplete dates. Table 3 indicates whether a treatment is considered to be stopped before or after start of treatment. Rules presented in Table 4 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

Table 3 Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	Month	Year	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	>= Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	>= Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
>= Treatment start (complete date)			After treatment start

UNK = Unknown

Table 4 Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule (see Table 3)	Medication/ procedure
Day	Month	Year		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and <= Treatment end + 30 days (year)	After treatment start	Concomitant
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end + 30 days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and <= Treatment end + 30 days (date)			After treatment start	Concomitant

UNK = Unknown

Tumor assessments

Tumor response assessments will be based on MRI, endoscopic and digital rectal evaluation. (DRE). All investigation dates (e.g. MRI, endoscopy, DRE) must be completed with day, month and year.

If there are multiple dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple dates associated with an evaluation, the earliest of the dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date, and assessment date is calculated as the earliest of all investigation dates (e.g. MRI, endoscopy, DRE).

If all measurement dates for an evaluation have no day recorded, the first of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If the previous or the following assessment is not available, the assessment in between will not be used for any calculations.

Death date

For imputing missing day of death date, if month and year is available, the day will be imputed by 15, unless this results in a date not later as a date the participant is known to be alive. In that case the date of death will be imputed by the last date known to be alive + 1.

Start/stop date of subsequent anti-cancer therapy

Incomplete dates for start date of subsequent anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows:

- If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anti-cancer therapy is before that date. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of the anti-cancer therapy.
- If both day and month are missing, no imputation will be performed.

Incomplete subsequent anti-cancer therapy stop dates will not be imputed.

Categorization of participants for COVID-19 impact assessment

For the assessment of COVID-19 impact on this study, participants will be categorized as being potentially affected by COVID-19 based on the COVID-19 pandemic start date.

This date is defined as the minimum of the first COVID-19 death date per country and 11 March 2020 (WHO-start of world-wide pandemic). First death from COVID-19 per country is determined according to the published data by European Centre for Disease Prevention and Control (Status of 26 June 2020).

If the pandemic start is before the end of DLT period, both DLT and FUP periods for the subject will be considered as potentially affected. If it starts during the FUP period, only this period will be considered as potentially affected.

Software

All statistical analyses will be performed using SAS® Software version 9.4 or higher. Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® Version 8.0 or higher (Pharsight Corporation, a Certara Company, Princeton, New Jersey).

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

All tables and listings related to disposition of participants and discontinuations will be generated using Enrolled analysis set.

A primary table of subject disposition will provide the overall summary of the analysis sets by dose level and overall:

- Number of screened participants (will be reported in the overall column only)
- Number of participants discontinued prior to treatment start (overall and by reason) (will be reported in the overall column only)
- Number of participants who continued beyond screening
- End of treatment status for peposertib with:
    - Number of participants who did not receive peposertib ("M3814/PLACEBO ADMINISTRATION DETAILS" eCRF Page)
    - Number of participants with ongoing peposertib administration ("M3814/PLACEBO ADMINISTRATION DETAILS" and "M3814/PLACEBO TERMINATION" eCRF Page)

  - Number of participants who completed treatment with peposertib ("M3814/PLACEBO TERMINATION" eCRF Page)
  - Number of participants who discontinued from peposertib overall and by reason ("M3814/PLACEBO TERMINATION" eCRF Page)
- End of treatment status for RT with:
  - Number of participants who did not receive RT ("RADIOTHERAPY ADMINISTRATION" eCRF Page)
  - Number of participants with ongoing RT administration ("RADIOTHERAPY ADMINISTRATION" and "RADIOTHERAPY TERMINATION" eCRF Page)
  - Number of participants who completed treatment with RT overall and by reason ("RADIOTHERAPY TERMINATION" eCRF Page)
  - Number of participants who discontinued from RT overall and by reason ("RADIOTHERAPY TERMINATION" eCRF Page)
- End of treatment status for capecitabine with:
  - Number of participants who did not receive capecitabine ("CAPECITABINE ADMINISTRATION" eCRF Page)
  - Number of participants with ongoing capecitabine administration ("CAPECITABINE ADMINISTRATION" and "CAPECITABINE TERMINATION" eCRF Page)
  - Number of participants who completed treatment with capecitabine overall and by reason ("CAPECITABINE TERMINATION" eCRF Page)
  - Number of participants who discontinued from capecitabine overall and by reason ("CAPECITABINE TERMINATION" eCRF Page)
- Number of participants who underwent rectal surgery at week 15 ("RECTAL SURGERY AT WEEK 15" eCRF page)
- End of study status with:
  - Number of participants with peposertib, RT and/or capecitabine administration ongoing
  - Number of participants off all treatments and in follow-up, and for those, the number of participants last known to be alive within 3 months before the cut-off date and the number of participants last known to be alive more than 3 month prior to the cut-off date (all ADMINISTRATION and TERMINATION related eCRF pages and "STUDY TERMINATION" eCRF pages)
  - Number of participants who discontinued or completed trial overall and by reason ("STUDY TERMINATION" eCRF page)

A second summary table on analysis sets will be generated:

- Number of participants in Enrolled population (overall only)
- Number of participants in FAS analysis set
- Number of participants in SAF analysis set
- Number of participants in DE analysis set
- Number of participants in PK analysis set

A third summary table will display the number of participants overall, in each country and in each site (per analysis set).

A listing of subject disposition will include the following information (as applicable): Dose level, subject identification number, date of informed consent form (ICF), rectal surgery at 15 weeks flag and date, reason for screen failure, date of first and last dose, FAS/SAF analysis set, DE analysis set and PK analysis set.

A second listing will include the following study termination information: Dose level, subject identification number, end of trial status (completed, ongoing, discontinued), the reason for termination of the trial, the date of trial termination, time on trial (time from ICF signature to end of trial), and the date of first and last dose of peposertib, RT and capecitabine.

A third listing will include the following peposertib termination information: Dose level, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for peposertib termination, and the date of first and last dose.

A fourth listing will include the following RT termination information: Dose level, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for RT termination and the date of first and last dose.

A fifth listing will include the following capecitabine termination information: Dose level, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for capecitabine termination, and the date of first and last dose.

In addition, for the assessment of COVID-19 impact on this study, a listing will include the following information (as applicable): Formulation, dose level, subject identification number, date of first and last dose, pandemic start date in the country, if DLT or any FUP periods were potentially affected by pandemic, if any COVID-19 related AE or PD occurred during the pandemic period.

10.2 Protocol Deviations

Population: SAF analysis set

10.2.1 Important Protocol Deviations

Important protocol deviations will be summarized in a table on the safety population, by dose level and overall:

- The number of participants with at least one important protocol deviation
- The number of participants with deviation of inclusion/exclusion criteria, overall and by criteria using the information provided in "Study Entry" eCRF page
- The number of participants with deviation of post inclusion criteria, overall and by criteria.

The following listings of important protocol deviations will be provided on the safety population, including:

- Deviations from inclusion or exclusion criteria, using information provided in "Study Entry" eCRF page. This listing will include: dose level, subject identification number, inclusion/exclusion criteria not met and date of deviation.
- Important protocol deviations. This listing will include: dose level, subject identification number, date of protocol deviation, deviation category, deviation description and if the PD occurred after pandemic start.
- A subject listing of any COVID-19 related PD will also be provided.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

Participants excluded from the DE analysis set will be displayed in a listing. This listing will include: dose level, subject identification number, reason for exclusion from the DE Analysis Set. Reason for exclusion could be:

- Insufficient exposure to peposertib
- Insufficient exposure to RT
- Insufficient exposure to capecitabine
- DLT period not completed.

11 Demographics and Other Baseline Characteristics

Population: SAF analysis set

11.1 Demographics

The following demographic characteristics will be summarized using the information from the "Demographics" eCRF pages.

- Sex: male, female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not collected at this site, Other
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Age (years)
- Age categories:
    - < 65 years
        - < 50
        - 50-64
    - ≥ 65 years
        - 65-74
        - 75-84
        - ≥ 85

Specifications for computation:

Age [years]: (date of given informed consent - date of birth + 1) / 365.25

- In case of missing day for at least one date, but month and year available for both dates:

  For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
- In case of missing month for at least one date, but year available for both dates:

  For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used.

The integer part of the calculated age will be presented.

Data will also be provided in listings (see Section 11.3).

11.2 Medical History

Population: SAF analysis set

The medical history will be summarized from the "Medical History" eCRF page, using the most recent available version of MedDRA (version 21.0 or later) preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetic order.

A supportive listing of medical history data by subject will include all the relevant data fields as collected on the "Medical History" eCRF pages.

11.3 Other Baseline Characteristics

Population: SAF Analysis Set

The following baseline characteristics will be summarized using the information from the "Vital Signs" and "ECOG performance status" eCRF pages.

- Height (cm)
- Weight (kg)
- BSA (m^2) = ([Height(cm) × Weight(kg)]/3600)½ (Mosteller,1987)
- ECOG Performance status

A listing of baseline characteristics will include the following information (as applicable): Dose level, subject identification number, date of birth, age (years), sex, race, height (cm), weight (kg), BSA (m^2), ECOG performance status and result from pregnancy test (serum β-HCG).

Disease history will be summarized by dose level and overall, in a frequency table including the following information from the 'DISEASE HISTORY' eCRF page:

- Disease stage at diagnosis, by stage
- Disease stage at study entry, by stage
- Histopathological classification, by classification.
- TNM classification: each T, N, M category and the TNM classification will be described (TX, T0, N1, etc.)
- MRI-EMVI score
- MRI-CRM score

In addition, a supportive listing of disease history will be provided including the following information from the 'DISEASE HISTORY' eCRF page: Dose level, subject identification

number, site of primary tumor, sub site of primary tumor, date of initial cancer diagnosis, histopathological classification, stage at initial diagnosis, stage at study entry, TNM at initial diagnosis and at study entry, MRI-EMVI socre at initial diagnosis and at study entry and MRI-CRM score at initial diagnosis and at study entry.

Prior induction therapy details will be displayed in a listing including the following information from the 'PRIOR INDUCTION THERAPIES' and 'PRIOR INDUCTION THERAPY DETAILS' eCRF pages: Dose level, subject identification number, prior induction therapy (Yes/No), regimen name, overall response, documented progression disease date, Drug(s) given as part of the therapy, start and end dates.

Finally, a listing of the pharmacogenomics findings will include the following information regarding the molecular diagnosis for each participant: Dose level, subject identification number and all relevant information from the "Molecular Diagnosis" section of the "Disease History" eCRF page.

12 Previous or Concomitant Medications/Procedures

Population: SAF analysis set

12.1 Prior Anti-Cancer Treatments and Procedures

The prior anti-cancer treatments and procedures are collected under the "Prior anti-cancer drug therapies", "Prior anti-cancer surgeries", and "Prior anti-cancer radiotherapy" eCRF pages.

The listings of prior anti-cancer treatments and procedures will be provided:

- Listing of prior anticancer drug therapies,
- Listing of prior anticancer surgeries,
- Listing of prior anticancer RT.

These will include the subject identification number, dose level and all the relevant collected data-fields on the corresponding eCRF pages.

In addition, a summary table will be provided by dose level and overall, with;

- The number of participants having received prior anti-cancer drug therapies, overall and by type of therapy
- The number of participants having received prior anti-cancer surgeries, overall and by intent (curative intent or not)
- The number of participants having received prior anti-cancer RT.

12.2 Previous and Concomitant Medications

Concomitant medications are medications other than study medications and premedications for study drug, which started prior to first dose date of study treatment and continued during the on treatment period as well as those started during the on treatment period. Previous medications are medications, other than study medications and pre medications for study drug, which started before first dose date of study treatment. A medication may be classified as both concomitant and previous.

In case the date values will not allow unequivocal allocation of a medication to previous/concomitant medication, the medication will be considered as both, previous and concomitant medication (see Section 0 for incomplete or missing dates).

Previous and concomitant medications will be summarized separately based on the "Relevant previous medications" and "Concomitant medications" eCRF pages. The anatomical therapeutic chemical (ATC)-second level and PT will be tabulated as given from the World Health Organization Drug Dictionary (most recent available version of WHO-DD). If multiple ATC can be assigned to a drug, all ATCs will be reported.

Previous and concomitant medications will also be listed. The listings will include: dose level, subject identification number and all corresponding collected data-fields on the corresponding eCRF page.

12.3 Concomitant Procedures

Concomitant procedures are procedures other than study medications and pre medications for study drug, which started prior to first dose date of study treatment and continued during the on treatment period as well as those started during the on treatment period. These will be listed according to the CRF page "Concomitant Procedures". Procedures started after the on treatment period will be presented and flagged in listing.

In case the date values will not allow unequivocal allocation of a procedure to concomitant procedure, the procedure will be considered as concomitant procedure (see Section 0 for incomplete or missing dates).

The listing will include: dose level, subject identification number and all collected data-fields on the corresponding eCRF page.

12.4 Subsequent Anti-cancer Treatment

Subsequent anti-cancer treatments will be listed according to eCRF pages "Anti-cancer treatment after discontinuation", "Surgery after discontinuation" and "Anti-cancer radiotherapies after discontinuation". The listings will include: dose level, subject identification number and all collected data-fields on the corresponding eCRF pages. Name of the anti-cancer RT will be tabulated as given from the most recent available version of WHO-DD .

In addition, participants who underwent rectal surgery after Week 15 will be listed according to eCRF page "Rectal surgery after Week 15 details". This listing will include: dose level, subject identification number and all collected data fields on the corresponding eCRF page.

13 Treatment Compliance and Exposure

Population: SAF analysis set

Treatment compliance and exposure will be listed and summarized by dose level and overall using the SAF analysis set.

All dosing calculations and summaries will be based on "M3814 (PEPOSERTIB)/PLACEBO Administration", "Radiotherapy Administration" and "Capecitabine Administration" eCRF pages.

In the Phase Ib part, participants will be assigned peposertib given in combination with capecitabine 825 mg/m^2 twice daily 5 days/week. The starting dose of peposertib for the first cohort will be 50 mg once daily 5 days/week. The planned dose of RT to the tumor area is

- 50 Gy with a schedule of 25 days and
- 50.4 Gy with a schedule of 28 days

For the calculations, only doses > 0 will be taken into account if not otherwise specified.

Treatment duration

The duration of peposertib treatment (in weeks) during the study is defined as :

$$\text{duration} = \left(\frac{\text{date of last dose of peposertib} - \text{date of first dose of peposertib} + 1}{7} \right).$$

The durations of RT and capecitabine treatments (in weeks) are derived correspondingly.

Cumulative dose

Cumulative doses will be calculated based on the actual doses received by the participants as filled in the relevant administration eCRF pages.

The cumulative dose (mg) of peposertib will be calculated as the sum of all actual doses that the subject received.

The cumulative dose (Gy) of RT will be calculated as the sum of all actual doses that the subject received (Actual daily Dose PTV1).

The cumulative dose (mg/m^2) of capecitabine will be calculated as the sum of the total daily doses that the subject received.

The total daily dose (mg/m²) of capecitabine per subject is the sum of the total dose that the subject received at each fraction day. At a given fraction day, the total daily dose (mg/m²) received is derived as:

Total daily dose = [Actual morning dose administered (mg) + Actual evening dose administered (mg)] / BSA (m²)

The BSA measured at baseline will be used for all visits, unless the measured weight for a participant varies more than 10% from baseline The recalculated BSA is derived based on formula described in Section **Error! Reference source not found.**, using weight measured at the corresponding visit. In case the weight measurement is missing, the weight measurement closest to the administration date will be used. If there are two measurements that are equal distance away from the missing measurement, the earliest measurement will be used.

Dose intensity

Dose intensity will be based on the planned dose as defined in the CTP and defined as:

- For peposertib:

$$\text{Dose intensity (mg/weeks)} = \left(\frac{\text{cumulative dose (mg)}}{\text{duration (weeks)}}\right)$$

- For RT:

$$\text{Dose intensity (Gy/weeks)} = \left(\frac{\text{cumulative dose (Gy)}}{\text{duration (weeks)}}\right)$$

- For capecitabine:

$$\text{Dose intensity (mg/m}^2\text{/weeks)} = \left(\frac{\text{cumulative dose (mg/m}^2\text{)}}{\text{duration (weeks)}}\right)$$

Relative dose intensity

Relative dose intensity will be based on the planned dose as defined in the CSP. The relative dose intensity is defined as:

- For peposertib:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{cumulative dose (mg)}}{\text{x} * \text{dose level (mg)}} * 100\right)$$

- For RT:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{cumulative dose (Gy)}}{\text{x} * \text{planned daily dose (Gy)}} * 100\right)$$

- For capecitabine:

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{cumulative dose (mg/m}^2\text{)}}{\text{x} * \text{ planned daily dose (mg/m}^2\text{)}} * 100\right)$$

Where planned daily dose (mg/m²) is the sum of planned doses per day . Each fraction day, the planned daily dose (mg/m²) is derived as:

Planned daily dose = Planned morning dose (mg/m²) + Planned evening dose (mg/m²)

For all 3 relative intensity formula above, x = 25 or 28, depending on the number of fraction doses the participant received.

The relative dose intensity will be displayed using the following categories:

- > 110%
- [80% - 110%]
- [65% - 80%[
- [50% - 65%[
- < 50%

Statistical outputs

The treatment exposure and compliance will be summarized in 4 tables including informations for each study treatment (peposertib /RT/capecitabine).

The first table will summarize the duration in weeks of each treatment (peposertib /RT/Capecitabine), by displaying the number of participants by dose level in each of the following categories:

- < 2 weeks
- [2 - 4 weeks[
- [4 - 6 weeks[

- ≥ 6 weeks

The table will also display summary statistics of the duration in weeks of each treatment.

The second table will summarize the number of total administrations of each treatment (peposertib /RT/capecitabine), by displaying the number of participants by dose level in each of the following categories:

- < 10 administrations/fraction days (peposertib /RT)
-]10 -20 administrations/fraction days] (peposertib /RT)
-]20 - 25 administrations/fraction days] (peposertib /RT)
-]25 - 28 administrations/fraction days] (peposertib /RT)
- > 28 administrations/fraction days (peposertib /RT)

The categories to display for cisplatin are:

- <=20 administrations
-]20 - 40 administrations]
-]40 - 56 administrations]
- > 56 administrations.

The third table will summarize the cumulative dose, dose intensity and relative dose intensity for each treatment.

The fourth table will summarize dose reductions by dose level, with for each treatment (peposertib /RT/capecitabine):

- Number of participants without any dose reduction
- Number of participants with at least one dose reduction
- Number of participants who did not receive this study intervention
- Number of participants with a minimum of 90%, 70-90%, 50-70%, and < 50% level of the planned dose.

The listing of exposure data (including e.g. start date and time of administration, planned and actual doses, frequency, change in dose and meal time before dose) will be provided by subject as recorded from the related eCRF pages and for each peposertib, RT and capecitabine administration.

In addition, a summary listing will be provided with the treatment duration in weeks, the total number of treatment administrations/fraction days received, the cumulative dose, and the relative dose intensity for each subject and treatment.

In addition, a listing of all participants receiving peposertib will be displayed to address accountability for peposertib according to page "peposertib/Placebo accountability" of eCRF. This listing will include the subject identification number, and all collected fields of the corresponding eCRF Page.

14 Efficacy Analyses

No primary efficacy endpoints are planned in Phase Ib of this study. Secondary efficacy endpoints include the composite endpoint of pathological complete response / clinical complete response (pCR/cCR), disease-free survival (DFS) time, pCR according to local review, cCR and time to local/distant recurrence.

In the context of efficacy analyses when using 'surgery', the rectal surgery at Week 15 is meant. Consequently, delayed rectal surgeries, or surgeries other than the one planned at Week 15 are not considered.

14.1 Secondary Endpoints: pCR, cCR, and pCR/cCR

Population: FAS analysis set

Pathological complete response

Only subjects who undergo surgery at Week 15 can be considered as pathological complete responders. Subjects with pCR will be identified based on the "Histological response" item on the "RECTAL SURGERY AT WEEK 15 DETAILS" eCRF page.

Clinical complete response

Clinical complete response will be assessed according to the tumor evaluation charter. Participants with cCR will be identified based on the "Overall response" item on the "Tumor Assessement (According to NCCN) after RT in ETT/ Week 14" eCRF page .

Composite endpoint of pathological complete response/clinical complete response

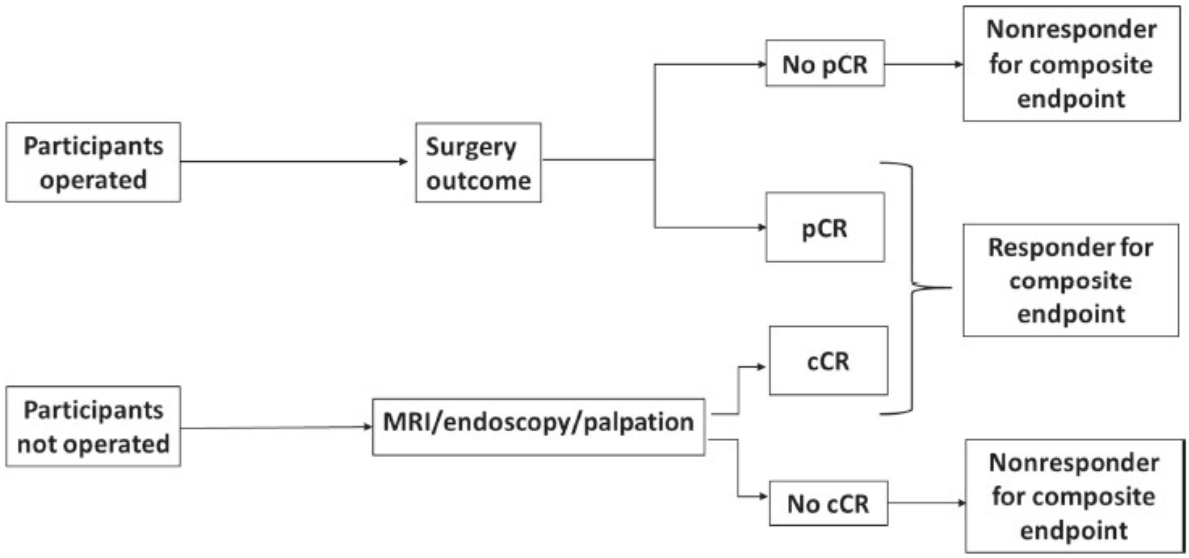
Participants are considered as responders to the composite endpoint pCR/cCR if 1 of the following 2 criteria is fulfilled (Figure 1):

- Participant had surgery and has pCR (Histological response on "Rectal surgery at week 15 Details" eCRF page is 'Pathological Complete response (pCR)')

- Participant did not undergo surgery but has cCR (defined above; Overall Status on "Tumor Assessement (According to NCCN) after RT in ETT/ Week 14" eCRF page is 'Clinical Response').

Participants who are not operated and do not undergo the procedures to define cCR or have histological response and pathological response not 'Complete response' will be regarded as non-responders for the composite endpoint.

Figure 1 Derivation of Composite Endpoint



cCR=Clinical complete response, MRI=Magnetic Resonance Imaging, pCR=Pathological complete response.

Analysis Methods

Table 5 Summary of analyses performed on the composite endpoint of pCR/cCR, pCR and cCR

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing Data Handling
Secondary endpoint: Composite endpoint of pCR/cCR			
Primary (FAS)	Derivation of the pCR/cCR composite endpoint (pCR based on local review) is described in Section 14.1.	The proportion of participants with pCR/cCR is indicated together with the 95%-Clopper-Pearson CI (Clopper & Pearson, 1934).	Participants who are not operated and do not undergo the procedures to define cCR as per tumor assessment charter or participants who have no pCR and no cCR will be regarded as non-responders
Secondary endpoint: pCR			
Primary (FAS)	The definition of pCR is provided in Section 14.1. pCR will be analyzed once on the local review of the histology slides	The proportion of participants with pCR will be reported together with the corresponding 95% Cis (Clopper & Pearson, 1934)	Participants who are not operated or have Pathological Response = 'No pathological complete response' will be regarded as non-responders
Secondary endpoint: cCR			
Primary (FAS)	The definition of cCR is provided in Section 14.1.	The proportion of participants with cCR will be reported together with the corresponding 95% CIs (Clopper & Pearson, 1934)	Participants who do not undergo the procedures to define cCR per tumor assessment charter, or have clinical response = 'No clinical complete response' will be regarded as non-responders

cCR = clinical Complete Response; CI = Confidence Interval; FAS = Full Analysis Set; pCR = pathological Complete Response

Proportion of responders with the 95%-Clopper-Pearson CI for pCR/cCR as well as for each component of the composite endpoint (subjects with surgery and pCR, subjects without surgery and cCR and subjects with cCR regardless of surgery), will be displayed in a table by dose level and overall. For pCR, a dedicated table will summarize the proportion of participants who had surgery at week 15, as well as the outcome of surgery, and the proportion and 95% Clopper Pearson CI of participants who had pCR. For cCR, a dedicated table will summarize the number who had at least one procedure (Endoscopy, DRE, EUS and/or MRI) performed during the tumor assessment at ETT/Week 14, as well as the overall status of the tumor assessment performed at week 14, the proportion and 95% Clopper Pearson CI of participants with "Complete response" and the results by tumor assessment method.

Additionally all information available on the "TUMOR EVALUATION - WEEK 14" and "TUMOR EVALUATION - WEEK 15" eCRF pages will be described in a table with the following variables:

- MRI-EMVI score
- MRI-CRM score
- ypTNM score
- Surgical-CRM score
- Modified Ryan scheme

All tumor assessments will be displayed in two listings. Tumor assessments at Screening and at Week 14/ETT will be sorted by dose level and subject identification number and listed with the following variables:

- Dose level
- Visit
- Subject identification number
- Method of tumor assessment
- Date of tumor assessment
- Outcome of the tumor assessment

Tumor assessments during the long-term safety and survival follow-up period will be sorted by dose level, subject identification number and assessment visit and listed with the following variables:

- Dose level
- Subject identification number
- Assessment visit
- Date of imaging
- Assessment method
- Overall status.

Finally, all information available on the "RECTAL SURGERY AT WEEK 15" eCRF page will be listed. The listing will be sorted by dose level, subject identification number and date of surgery and will display the following variables:

- Dose level

- Subject identification number
- Date of surgery
- Surgery procedure
- Outcome of surgery
- Histological response.

14.2 Secondary Endpoint: Disease-Free Survival

Population: FAS analysis set

Disease-free survival (DFS) time is defined as the time from the first treatment day to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first. DFS data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death) or for participants with an event after two or more subsequent missing tumor assessments (i.e. 2 times the scheduled time interval between two subsequent response assessments). Participants who do not have a baseline tumor assessment or who do not have any post baseline tumor assessments will be censored at the start of first trial treatment unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

The last adequate tumor assessment is defined as the last tumor assessment result that is not "NE" or "NA".

Disease-free survival in months is calculated as follows:

DFS (months) = [date of event or censoring– treatment start date +1]/30.4375

Table 6 Date of event / censoring for DFS analysis

Status		Censoring	Date of event / censoring
Progressed or died	No consecutive missing tumor assessments	Event	Minimum (Date of PD, Date of death)
	After two or more subsequent missing tumor assessments (i.e. 2 times the scheduled time interval between two subsequent response assessments)	Censored	Date of last tumor assessment with outcome CR, Nearly-CR or IR or treatment day 1, whatever is later

Neither progressed nor died and no missed tumor assessment	Censored	Date of last tumor assessment with outcome CR, Nearly-CR or IR or treatment day 1 whatever is later
No baseline or no post-baseline tumor assessment and no death within 147 days (21 weeks) of study intervention start	Censored	Treatment day 1
No baseline or no post baseline tumor assessment and death within 147 days (21 weeks) of study intervention start	Event	Date of death

CR = Complete response; IR = Incomplete response; PD = Progressive disease

If more than one condition is met for censoring, the earliest one is considered.

14.2.1 Secondary Objective: Analysis of Disease-Free Survival

Table 7 Summary of analysis of the Disease-Free Survival

Analysis Population	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Disease-Free Survival			
FAS	Disease-free Survival time, defined as the time from first treatment day to the date of the first documentation of objective PD or death due to any cause, whichever occurs first.	Kaplan-Meier estimates will be presented overall, together with a summary of associated statistics (median survival time and survival rate estimates) including the corresponding 2-sided 95% CIs. Confidence intervals for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer & Crowley, 1982) and CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch& RL, 1980): conftype=loglog default option in SAS Proc LIFETEST. The estimate of the standard error will be computed using Greenwood's formula	Model based

CI = Confidence interval; FAS = Full analysis set; PD = Progressive disease

14.3 Secondary Endpoint: Local Recurrence and/or Distant Metastasis

Population: FAS analysis set (participants with surgery only)

Time from surgery to local recurrence will be defined as time from day of surgery to the date of the first documentation of progression of disease, flagged as 'local recurrence' or 'local recurrence and distant metastasis'('TUMOR ASSESSMENT(ACCORDING TO NCCN) DURING LONG-TERM SAFETY AND SURVIVAL FOLLOW-UP' eCRF page).

Time from surgery to distant metastasis will be defined as time from day of surgery to the date of the first documentation of progression of disease, flagged as 'distant metastasis' or 'local recurrence and distant metastasis' ('TUMOR ASSESSMENT(ACCORDING TO NCCN) DURING LONG-TERM SAFETY AND SURVIVAL FOLLOW-UP' eCRF page). Only subjects who undergo rectal surgery (week 15) will be included in this analysis.

Table 8 Date of event / censoring definition for Local/Distant recurrence Analysis

Status		Censoring	Date of event / censoring
Time to local recurrence: PD flagged as 'Local recurrence' or 'Local recurrence and distant metastasis'	No consecutive missing tumor assessments	Event	Date of progression
	After two or more subsequent missing tumor assessments (i.e. 2 times the scheduled time interval between two subsequent response assessments)	Censored	Date of last tumor assessment with outcome CR or date of surgery, whatever is later
Time to distant metastasis: PD flagged as 'Distant metastasis' or 'Local recurrence and distant metastasis'	**Time to local recurrence:** No consecutive missing tumor assessments and PD flagged as ‚Distant metastasis' **Time to distant metastasis:** No consecutive missing tumor assessments and PD flagged as ‚Local recurrence'	Censored	Date of progression
No PD flagged as 'Local recurrence', 'Distant metastasis' or 'Local Recurrence and Distant metastasis' and no missed tumor assessment		Censored	Date of last tumor assessment with outcome CR or date of surgery, whatever is later

CR = Complete response; PD = Progressive disease

14.3.1 Secondary Objective: Analysis of Local Recurrence and/or Distant Metastasis

Table 9 Summary of the analysis of the local recurrence and/or distant metastasis

Analysis Population	Derivation	Statistical Analysis Methods	Missing data handling
FAS	The following analyses will be performed: • Time from surgery to local recurrence • Time from surgery to distant metastasis.	Kaplan-Meier estimates will be presented overall, together with a summary of associated statistics (median survival time and survival rate estimates) including the corresponding 2-sided 95% CIs. Confidence intervals for the median will be calculated according to Brookmeyer and Crowley (Brookmeyer & Crowley, 1982) and CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch & RL, 1980): conftype=loglog default option in SAS Proc LIFETEST. The estimate of the standard error will be computed using Greenwood's formula	Model based

CI = Confidence interval; FAS = Full analysis set

The listing of tumor assessments prior Surgery (including Screening tumor assessments) and all relevant informations as recorded on the 'TUMOR ASSESSEMENT (ACCORDING TO NCCN) AFTER RADIOTHERAPY in ETT/WEEK14' and 'TUMOR ASSESSEMENT (ACCORDING TO NCCN) DURING LONG-TERM SAFETY and SURVIVAL FOLLOW-UP' eCRF pages,will be provided by subject.
A swimmer plot displaying some key radiological milestones as well as surgery will be produced, sorted by follow-up time. For the purpose of CSR, a version of the swimmer plot without subject id will be provided. For each subject, the time from treatment start until end of follow-up will be represented (from treatment start to last date known to be alive or date of death). In addition, the following information will be displayed: time of first occurrence of CR, Nearly-CR, IR, and PD , time of surgery, pCR achievement and status at the end of the follow-up (alive or dead).

In addition, a listing will be provided summarizing all of the efficacy endpoints (as defined above) for each participant. This listing will include dose level, subject identification number, date of first dose, date of last evaluable tumor assessment, efficacy endpoint, and event. In addition, for DFS, and local/distant recurrence, event/censor date, censor flag, and the time-to-event/censoring will be included.

Finally, all tumor assessments performed during the long-term safety and survival follow-up period will be listed. This listing will include dose level, subject identification number, assessment

visit, imaging date, assessment method and the overall status. This listing will be sorted by dose level, subject identification number and Imaging date.

14.4 Secondary Endpoint: Neoadjuvant Rectal Score

Population: FAS analysis set

The neoadjuvant rectal score (NAR) was developed by George and colleagues to serve as a short term clinical study surrogate endpoint (George 2015). The Valentini nomograms (Valentini 2011) to predict overall survival in rectal cancer patients after neoadjuvant treatment are the basis of the NAR score. Its score ranges from 0 to 100, whereas a score close to 100 is indicative of a poorer prognosis.

14.4.1 Secondary Objective: Analysis of NAR score

Table 10 Summary of the analysis of the NAR score

Analysis Population	Derivation	Statistical Analysis Methods	Missing data handling
FAS	See NAR formula below.	The neoadjuvant rectal score will be presented in terms of summary statistics (such as mean, median, standard deviation, and quartiles) and graphically using a boxplot by dose level.	Participants with at least one item of the NAR score missing will be considered as having a missing NAR score.

FAS = Full analysis set

The Neoadjuvant Rectal Score (NAR) will be calculated using a formula that includes the clinical tumor (cT) stage, pathologic tumor (pT), and node (pN) stage according to the tumor, node, metastasis classification system for colorectal cancers. The NAR score is calculated as follows:

$$NAR = \frac{[5pN - 3(cT - pT) + 12]^2}{9.61}$$

Where cT is an element of the set {1, 2, 3, 4}, pT is in {0, 1, 2, 3, 4}, and pN is in {0, 1, 2}.

cT is collected on the "DISEASE HISTORY" eCRF page, from the "TNM classification at study entry" item, as follows:

- Numeric part of the T stage = cT

pN and pT are collected on the "TUMOR EVALUATION – WEEK 15" eCRF page, from the "ypTNM score", as follows:

- Numeric part of the N stage = pN
- Numeric part of the T stage = pT

The listing of NAR socre and all relevant informations for calculation pN and cT from 'DISEASE HISTORY' eCRF page and PT from 'TUMOR EVALUATION – WEEK 15' eCRF page,will be provided by subject.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical studies such as AE, laboratory tests and vital signs.

The primary endpoint of the Phase Ib is the occurrence of DLTs during the DLT observation period (5.5 weeks after the start of treatment). Based on the data observed, a recommendation of the next dose level is based on a Bayesian dose escalation design using a two-parametric logistic regression model. More details about the analysis to be provided to SMC members are presented in a dedicated IAP.

15.1 DLT (Primary Endpoint)

Population: DE analysis set

The DLT information will be based on "Adverse Events" eCRF page with "Is the adverse event a dose limiting toxicity?" = Yes or with "Is the adverse event a dose limiting toxicity upon SMC review" = Yes.

A summary table of DLTs during the DLT period will be provided for each dose level and overall with:

- Number of participants with at least one DLT as per SMC decision

The listing of DLTs will also be provided.

15.2 Adverse Events

Definitions

Treatment-emergent adverse events: those events with onset dates occurring within the on treatment period.

Counting rules and observation periods for AEs during the on treatment period (TEAEs):

- If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated.

- Adverse events related to trial treatment are those events with relationship missing, unknown or related to at least one treatment (peposertib, RT or capecitabine).
- Adverse events related to peposertib are those events related to peposertib, regardless of relationship with RT and/or capecitabine
- Adverse events related to RT are those events related to RT, regardless of relationship with peposertib and/or capecitabine
- Adverse events related to capecitabine are those events related to capecitabine, regardless of relationship with peposertib and/or RT
- In case a subject has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

For identification of AE treatment emergence, incomplete dates will be handled using the rules presented in Section 0.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

Missing data handling

Incomplete AE-related dates will be handled using the rules presented in Section 0. In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

15.2.1 All Adverse Events

Population: SAF Analysis Set

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per subject, using the most recent available MedDRA version (21.1 or higher) PT as event category and primary SOC body term as Body System category.

Frequency tables for AEs captured on the "Adverse Events" eCRF pages will be based on TEAEs as defined above.

A first overview table of adverse events will be provided by dose level and overall by summarizing the number and percentage of participants with any:

- TEAE
- TEAEs related to trial treatment, (i.e. peposertib, RT, or capecitabine)

- TEAEs related to peposertib
- TEAEs related to RT
- TEAEs related to capecitabine
- Serious TEAE
- Serious TEAE related to trial treatment (i.e. peposertib, RT, or capecitabine)
- Serious TEAEs related to peposertib
- Serious TEAEs related to RT
- Serious TEAEs related to capecitabine
- TEAEs with grade ≥ 3
- TEAEs with grade ≥ 4
- TEAEs with grade ≥ 3 related to trial treatment (i.e. peposertib, RT or capecitabine)
- TEAEs with grade ≥ 4 related to trial treatment (i.e. peposertib, RT or capecitabine)
- TEAEs with grade ≥ 3 related to peposertib
- TEAEs with grade ≥ 4 related to peposertib
- TEAEs with grade ≥ 3 related to RT
- TEAEs with grade ≥ 4 related to RT
- TEAEs with grade ≥ 3 related to capecitabine
- TEAEs with grade ≥ 4 related to capecitabine
- TEAEs leading to dose modification of any trial treatment (i.e. peposertib, RT or capecitabine)
- TEAEs leading to dose modification of peposertib
- TEAEs leading to dose modification of RT
- TEAEs leading to dose modification of capecitabine
- TEAE leading to death
- TEAE leading to death related to trial treatment, peposertib, RT or capecitabine
- TEAE leading to death related to peposertib
- TEAE leading to death related to RT
- TEAE leading to death related to capecitabine
- TEAE leading to trial discontinuation

- TEAE leading to temporary discontinuation of at least one trial treatment
- TEAE leading to temporary discontinuation of all trial treatments
- TEAE leading to temporary discontinuation of M3814
- TEAE leading to temporary discontinuation of RT
- TEAE leading to temporary discontinuation of Capecitabine
- TEAE leading to permanent discontinuation of at least one trial treatment
- TEAE leading to permanent discontinuation of all trial treatments
- TEAE leading to permanent discontinuation of M3814
- TEAE leading to permanent discontinuation of RT
- TEAE leading to permanent discontinuation of Capecitabine

Frequency tables summarizing events in the following categories will be prepared by dose level and overall, sorted by alphabetical order of SOC and PT:

- TEAEs
- TEAEs related to trial treatment (i.e. peposertib, RT, or capecitabine)
- TEAEs related to peposertib
- TEAEs related to RT
- TEAEs related to capecitabine
- Serious TEAEs
- TEAEs excluding SAEs, with overall frequency ≥ 5% by SOC and PT (threshold will be applied on PT)
- Serious TEAEs related to trial treatment
- Serious TEAEs related to peposertib
- TEAEs by worst CTCAE grade: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs related to trial treatment by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs related to peposertib by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs related to RT by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5

- TEAE related to capecitabine by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs leading to death

In addition, all TEAEs and TEAEs related to peposertib with at least 2 participants will be summarized in two tables sorted by frequency (descending order) and PT.

The following listings will be produced based on the "Adverse Events" eCRF page:

- All AEs (whether treatment-emergent or not)
- Serious TEAEs related to any trial treatment
- TEAEs within 6 weeks after surgery and delayed surgery

These listings will include the following items:

- Dose level
- Subject identification number
- Age
- Sex
- Race
- First and last dose date for peposertib, RT and capecitabine
- Reported Term with SOC and PT
- Start, change and end date with their corresponding treatment day
- Treatment Emergent Adverse Events flag (N/Y; only for the listing of all AEs)
- Timing related to treatment (if same day of treatment administration)
- TEAE related to peposertib flag (N/Y)
- TEAE related to RT flag (N/Y)
- TEAE related to capecitabine flag (N/Y)
- Serious Adverse Events flag (N/Y; only for the listing of all AEs)
- DLT flag (Y/N)
- CTCAE Grade
- Action taken with peposertib, with RT and with capecitabine
- Outcome of AE
- AE occurred after COVID-19 pandemic start (Y/N).

Evaluation of COVID-19 effects on AEs

The direct effect of COVID-19 for AEs will be assessed via listing of COVID-19 related AEs. The following listing will be generated using the 'COVID-19 related terms MedDRA 23.0 update Spreadsheet', considering all 'search terms for COVID-19-related' ='Y'. Same information as for the listing of all AEs will be provided.

15.2.2 Adverse Events Leading to Study Intervention Discontinuation

Population: SAF analysis set

An overview table of adverse events leading to discontinuation or dose reduction will be provided, by dose level and overall, summarizing the number and percentage of participants with any:

- TEAE leading to temporary discontinuation of at least one trial treatment, all trial treatments, peposertib (regardless of other trial treatments status), RT (regardless of other trial treatments status), capecitabine (regardless of other trial treatments status) (corresponding to AEs with action taken = "Drug interrupted" for peposertib, RT or capecitabine)
- TEAE leading to permanent discontinuation of at least one study intervention, all trial treatments, peposertib (regardless of other trial treatments status), RT (regardless of other trial treatments status) or capecitabine (regardless of other trial treatment) (corresponding to AEs with action taken = "Drug withdrawn" for peposertib, RT or capecitabine respectively)

The following frequency tables will be produced for each dose level and overall, by SOC and PT in alphabetical order:

- TEAEs leading to temporary discontinuation of at least one trial treatment
- TEAEs leading to temporary discontinuation of peposertib (regardless of other trial treatments status)
- TEAEs leading to temporary discontinuation of RT (regardless of other trial treatments status)
- TEAEs leading to temporary discontinuation of capecitabine (regardless of other trial treatments status)
- TEAEs leading to permanent discontinuation of at least one trial treatment

- TEAEs leading to permanent discontinuation of peposertib (regardless of other trial treatments status)
- TEAEs leading to permanent discontinuation of RT (regardless of other trial treatments status)
- TEAEs leading to permanent discontinuation of capecitabine (regardless of other trial treatments status)
- TEAEs leading to a delay in dose time of RT

15.2.3 Late Toxicities

A number of outputs will be produced for late adverse events. An adverse event is defined as a late toxicity if it starts after the on-treatment period, and it meets one of the following criteria:

- It is the first occurrence of adverse event for this participant on MedDRA preferred term level
- It is a recurring adverse event but there is gap between the end date of the previous occurrence and the start date of the re-occurrence (start date of re-occurrence – end date of previous occurrence > 0)
- It is a recurring adverse event and there is no gap between the end date of the previous occurrence and the start date of the re-occurrence, and the grade has worsened.

The following outputs will be produced for late toxicities:

- Table of all late toxicities by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- Listing of all late toxicities related to any trial treatment
- Listing of all late toxicities grade ≥ 3

15.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.3.1 Deaths

Population: SAF analysis set

All deaths, deaths within 60 days after first dose of trial treatment, and deaths within 30 days and within 90 days after last dose of trial treatment, as well as reasons for deaths (disease progression, adverse event related to study treatment, adverse event not related to study treatment, other, unknown), will be tabulated based on all relevant information available in the eCRF:

- Number of deaths

- Number of deaths within 60 days after first dose of trial treatment
- Number of deaths within 30 days after last dose of trial treatment
- Number of deaths within 90 days after last dose of trial treatment
- Primary reason of death

In addition, the date (non-imputed) and cause of death will be provided in individual subject data listings together with selected dosing information (date of first/last administration of peposertib, RT and capecitabine, dose level and number of fraction days/duration).

Subject listing of deaths includes columns for:

- Subject identification
- Age
- Sex
- Race
- AEs with fatal outcome (list PTs of AEs with outcome=fatal),
- Flag for death within 60 days after first dose of peposertib
- Flag for death within 60 days after first dose of RT
- Flag for death within 60 days after first dose of capecitabine
- Flags for death within 30, 90 days after last dose of peposertib
- Flags for death within 30, 90 days after last dose of RT
- Flags for death within 30, 90 days after last dose of capecitabine

Finally, all treatment related TEAEs (i.e. peposertib, RT or capecitabine) leading to death, will be listed in a separate listing, displaying:

- Dose level
- Subject identification number
- Age
- Sex
- Race
- First and last dose date for peposertib, RT and capecitabine
- Reported Term with SOC and PT
- Start and end date with their corresponding treatment day
- Treatment Emergent Adverse Events flag (N/Y)

- Timing related to treatment (if same day of treatment administration)
- TEAE related to peposertib flag (N/Y)
- TEAE related to RT flag (N/Y)
- TEAE related to capecitabine flag (N/Y)
- Serious Adverse Events flag (N/Y)
- DLT flag (Y/N)
- CTCAE Grade
- Action taken with peposertib, with RT and with capecitabine
- Outcome of AE
- Date of death with the corresponding treatment day

15.3.2 Serious Adverse Events

Population: SAF analysis set

SAEs will be summarized for each dose level and overall, by SOC, and PT in alphabetical order (please refer to Section 15.2.1 for items to be listed).

In addition, subject listings of SAEs will be provided.

15.4 Clinical Laboratory Evaluation

Population: SAF analysis set

Listings and summaries by visit will include all assessments, whereas shift tables and summaries of worst on-treatment values will not consider assessments after the on-treatment period.

Local laboratory values (including corresponding normal ranges) will be presented in summary statistics, shift tables and boxplots. In addition, liver toxicity will be assessed with Hy's Law analysis.
Laboratory results will be classified according to the NCI-CTCAE version 5.0. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges).

Common Terminology Criteria (CTC) gradable parameters

In this trial, Common Terminology Criteria (CTC) gradable parameters are the following:

Table 11 Common Terminology Criteria (CTC) gradable parameters

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC version 5.0	Direction of abnormality
	Clinical Chemistry			
Electrolytes	Calcium	CA	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Magnesium	MG	Hypomagnesemia/Hypermagnesemia	Low/High
Electrolytes	Potassium	K	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	SODIUM	Hyponatremia/Hypernatremia	Low/High
Enzymes/cardial	Creatine phosphokinase (CPK)	CK	CPK increased	High
Enzymes/liver	Alanine aminotransferase	ALT	Alanine aminotransferase increased	High
Enzymes/liver	Alkaline phosphatase	ALP	Alkaline phosphatase increased	High
Enzymes/liver	Aspartate aminotransferase	AST	Aspartate aminotransferase increased	High
Enzymes/liver	Total bilirubin	TBILI	Blood bilirubin increased	High
Metabolism	Glucose	GLUC	Hypoglycemia	Low
Metabolism	Uric acid(1)	URATE	Hyperuricemia	High
Plasma proteins	Albumin	ALB	Hypoalbuminemia	Low
Renal/kidney	Creatinine	CREAT	Creatinine increased	High
Renal/kidney	Creatinine clearance	CREATCLR	Chronic kidney disease	Low
Enzymes/cardial	Lactate dehydrogenase	LDH	Lactate dehydrogenase increased	High
Coagulation	Activated partial thromboplastin time	APTT	Activated partial thromboplastin time prolonged	High
Coagulation	International normalized ratio (INR)	INR	INR increased	High

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC version 5.0	Direction of abnormality
	Hematology			
Platelets	Platelets count	PLAT	Platelet count decreased	Low
Red blood cells	Hemoglobin	HGB	Anemia/Hemoglobin increased	Low/High
White blood cells/differential	White blood cell count	WBC	White blood cell decreased/Leukocytosis	Low/High
White blood cells/differential	Absolute lymphocytes count	LYM	Lymphocyte count decreased/increased	Low/High
White blood cells/differential	Absolute neutrophils nount	NEUT	Neutrophil count decreased	Low/High
White blood cells/differential	Eosinophils	EOS	Eosinophilia	High

(1) According to CTCAE grade, if uric acid value is greater that ULN it should be graded as follows:
o Grade 1 >ULN without physiologic consequences
o Grade 3 >ULN with physiologic consequences
As information on physiologic consequences of laboratory parameters are not available, values > ULN will all be graded as Grade 1 (if any physiologic consequences are observed, it should be completed as an adverse event).

For all CTC gradable parameters, shift tables from baseline to worst grade on-treatment will be produced. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and on-treatment will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa.

Non-CTC gradable parameters

In this trial, non-CTC gradable parameters are displayed in table below

Table 12 Non-CTC gradable parameters

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Direction of abnormality
	Clinical chemistry		
Electrolytes	Phosphorus (phosphate)	PHOS	Low/High
Electrolytes	Chloride	CHLO	Low/High
Plasma proteins	Total protein	PROT	Low
	Hematology		
Red blood cells	Hematocrit	HCT	High/Low
Red blood cells	Mean corpuscular hemoglobin	MCH	High/Low
Red blood cells	Mean corpuscular volume	MCV	High/Low
Red blood cells	Reticulocytes	RETI	High/Low
White blood cells/differential	Basophils	BASOLE	High
White blood cells/differential	Monocytes	MONOLE	High/Low

Direct bilirubin (DBIL), Blood urea nitrogen (BUN) and Red blood cells (RBC) parameters will only be presented in listings

Shift tables based on the normal range from baseline to lowest and highest on-treatment value will be produced with the following categories for all hematology and blood chemistry parameters (CTC gradable and non-CTC gradable):

- Baseline: Low/Normal/Missing/Overall for low parameters;
  Normal/High/Missing/Overall for high parameters
- Lowest On treatment: Low/Normal/Missing/Overall
- Highest On trial: Normal/High/Missing/Overall
- Normal category includes low values for high parameters and high values for low parameters.

Boxplots will be produced for all quantitative hematology and biochemistry parameters, to display:

- Values by time point
- Difference from baseline to highest deviation on treatment by cohort

All CTC gradable and non-CTC gradable parameters will be listed for each measurement (pre treatment, on treatment and post treatment). Parameters will be grouped by category.

Listings will include at least the following items:

- Dose level
- Subject identification number
- First / last dosing date for peposertib, RT and capecitabine
- Parameters
- Visit
- Date (Treatment day)
- Analysis value
- SI unit
- Change from baseline
- Reference range status (Low, Normal, High)
- CTC grade (with associated CTC name)
- Baseline flag (Yes/No)
- Worst value on-treatment flag (Yes/No)
- On treatment flag (pre/on/post)

Gradable parameters with at least one value with Grade ≥ 3, will be considered clinically significant laboratory values. For hematology and biochemistry, a listing displaying clinically significant laboratory values will be provided. For each participant, only parameters where at least one value has Grade ≥ 3 will be displayed (all visits for the corresponding parameter will be displayed). The listing will be sorted by dose level, subject ID, parameter name, and datetime.

Coagulation parameters

All coagulation parameters will be listed for each measurement (pre treatment, on treatment and post treatment).

Urinalysis

A listing of urinalysis and microscopic analysis will be provided.

Liver toxicity

On-treatment liver function tests will be summarized in a table presenting the number and percentage of participants, by dose level and overall:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- Total Bilirubin ≥ 2×ULN
- (ALT or AST) ≥ 3×ULN and Total Bilirubin ≥ 2×ULN (Hy's Law case)

Categories will be cumulative, i.e., a participant with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created by graphically displaying:

- peak serum ALT(/ULN) vs simultaneous Total Bilirubin (/ULN) including reference lines at ALT > 3ULN and bilirubin > 2ULN.
- peak serum AST(/ULN) vs simultaneous Total Bilirubin (/ULN) including reference lines at AST > 3ULN and bilirubin > 2ULN.

Participants under the Hy law's case (right upper corner) will be flaged with their subject identifier.

In addition, a listing of all TBILI, ALT, AST and ALP values for subjects with an on-treatment TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

15.5 Vital Signs

Population: SAF Analysis Set

Body temperature, SBP, DBP, respiratory rate and heart rate will be analyzed with shift tables of maximum CFB of on-treatment assessments using the categories defined below:

Table 13 Vital signs categories

Parameter	Unit	Shift	Baseline categories	On-treatment categories (absolute change)
Temperature	°C	Increase	< 37 / ≥ 37 - < 38 / ≥ 38 - < 39 /≥ 39 - < 40 / ≥ 40	< 1[a] / ≥ 1 - < 2 /≥ 2 - < 3 / ≥ 3
Heart rate	Bpm	Increase and decrease	< 100 / ≥ 100	≤ 20[a] / > 20 - ≤ 40 / > 40
SBP	mmHg	Increase and decrease	< 140 / ≥ 140	≤ 20[a] / > 20 - ≤ 40 / > 40
DBP	mmHg	Increase and decrease	< 90 / ≥ 9≥ 90	≤ 20[a] / > 20 - ≤ 40 / > 40
Respiratory rate	breaths/min	Increase and decrease	< 20 / ≥ 20	≤ 5[a] / > 5 - ≤ 10 / > 10

a This category will include the subjects with no changes or decrease/increase in the increase/decrease part of the table, respectively.

Line plots per dose level and overall will be produced for systolic blood pressure, diastolic blood pressure, heart rate, temperature and weight. These will be presented by visit.

Maximum change from baseline will also be listed for each parameter and participant and will include: Dose level, subject ID, parameter, visit, date, unit, baseline value and maximum change from Baseline for each participant. This listing will be sorted by dose level, subject ID, parameter and visit.

Finally, all vital signs data from “Vital Signs” eCRF pages will be listed.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECOG Performance Status

Population: SAF analysis set

The listing will include all the data from the “ECOG Performance Status” eCRF section.

Additionally, one spaghetti plot per dose level will be produced, using different colors/line types per participant.

15.6.2 ECG and QT/QTc Evaluations

Population: SAF analysis set

Electrocardiogram values based on the "Electrocardiogram" eCRF section will be used for summary statistics and shift tables.

ECG parameters (Heart Rate, R-R duration, PQ/PR duration, QT duration, QR duration, QTcF) will be summarized by dose level and visit, using descriptive statistics (see Section 9) for absolute values and absolute change from baseline.

The number of participants with normal ECGs at baseline and abnormal ECGs post baseline will be calculated by visit and summarized in a frequency table by dose level and overall. In addition, ECG parameters on treatment will be presented by the following frequency table (by dose level and overall):

- Shift from normal baseline result to the worst on-treatment value
- Worst mean absolute QTcF interval on treatment
    - <= 450 ms
    - > 450 ms and ≤ 480 ms
    - > 480 ms and ≤ 500 ms
    - > 500 ms
- Worst on treatment mean QTcF increase from baseline
    - <= 30 ms
    - > 30 ms and ≤ 60 ms
    - > 60 ms

If duplicate/triplicate measurements are performed at any time point, the following will apply:

- For quantitative parameters, the mean of the triplicate measurement will be used as summary
- For results interpretation, the worst Overall conclusion will be retained.

Visits and time points to be displayed in summary tables are all scheduled visits where ECG assessments are performed.

Two listings will display all the results as presented in "ECG" eCRF page, one on qualitative results and another one on quantitative results. All visits, time points, flag for pre /on /post treatment, and, in case of triplicates, mean for quantitative results and worst overall conclusion for qualitative results, will be included in listings.

15.6.3 Pregnancy Test

Pregnancy testing (serum β-HCG) will be performed at screening and 30 days post treatment. A listing will display all the results as presented in "Pregnancy Test" eCRF page.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Population: PK Analysis Set

Pharmacokinetic parameters will be calculated by the Clinical PK/Pd Group of QP, Merck, Darmstadt, Germany, or by a clinical research organization selected by the sponsor, using standard non-compartmental methods and the actual administered dose. Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 15 significant digits or the SAS format Best12. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.".

PK concentrations which are erroneous due to a protocol violation (as defined in the CSP), sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis, if agreed by the sponsor. In this case the rationale for exclusion must be provided in the CSR. Any other PK concentrations that appear implausible to the clinical pharmacologist/clinical PK/Pd scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

The following PK parameters will be calculated from peposertib and peposertib metabolite (M467) plasma concentrations for fraction day (FD) FD1 and/or FD9 as indicated. Appropriate adjustments will be made for differences in molecular weight (MW) (peposertib MW = 481.92 $gmol^{-1}$; *metabolite* M467 MW = 467.12 $gmol^{-1}$).

C_{max}	Maximum observed concentration
C_{max}/Dose	The dose-normalized C_{max}. Normalized using the formula C_{max}/Dose.
t_{max}	The time to reach C_{max} during a dosing interval (unless otherwise defined, the first occurrence is taken if multiple/identical C_{max} values)
AUC_{0-t}	The area under the curve (AUC) from time 0 (dosing time) to the last sampling time at which the concentration is at or above the lower limit of quantification (LLOQ). Calculated using the mixed log linear trapezoidal rule (linear up, log down)
AUC_{0-24}	The AUC from time 0 (dosing time) to 24 hours postdose. AUC_{0-24} will be based on the estimated concentration at 24 hours, and not the concentration at the actual observation time. Calculated using the mixed log linear trapezoidal rule (linear up, log down)
$AUC_{0-\infty}$	The AUC from time 0 (dosing time) to infinity based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination for FD1. Calculated using the mixed log linear trapezoidal rule (linear up, log down). $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda_z$
AUC_{0-t}/Dose	The dose-normalized AUC_{0-t}. Normalized using the formula AUC_{0-t}/Dose.
AUC_{0-24}/Dose	The dose-normalized AUC_{0-24}. Normalized using the formula AUC_{0-24}/Dose.
$AUC_{0-\infty}$/Dose	The dose-normalized $AUC_{0-\infty}$. Normalized using the formula $AUC_{0-\infty}$/Dose.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$, $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100 for FD1
$t_{½}$	Apparent terminal half-life, $t_{½} = \ln 2/\lambda_z$
CL/f	Apparent total body clearance of drug, calculated as Dose/$AUC_{0-\infty}$ (predicted) for FD1 for peposertib only
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration for peposertib only. V_z/f = Dose/($AUC_{0-\infty}$*λ_z) for FD1 and V_z/f = Dose/(AUC_{0-24}*λ_z) for FD9

CLss/f	The apparent total body clearance at steady state following extravascular administration, taking into account the faction of dose absorbed. Calculated by Dose/AUC_{0-24} for FD9 for peposertib only
$R_{acc}(C_{max})$	The accumulation factor to assess the increase in maximum concentration from FD1 to FD9 $R_{acc}(C_{max})$ = (C_{max} FD9)/(C_{max} FD1) for peposertib and M467
$R_{acc}(AUC_{0-24})$	The accumulation factor to assess the increase in exposure from FD1 to FD9 during time 0 to 24 hours. $R_{acc}(AUC_{0-24})$ = (AUC_{0-24} FD9)/(AUC_{0-24} FD1) for peposertib and M467
MR_{AUC0-t}	Metabolic ratio of AUC_{0-t}. AUC_{0-t} for M467 divided by the AUC_{0-t} of peposertib corrected for MW: MR_{AUC0-t}*481.92/467.12
$MR_{AUC0-24}$	Metabolic ratio of AUC_{0-24}. AUC_{0-24} for M467 divided by the AUC_{0-24} of peposertib corrected for MW: $MR_{AUC0-24}$*481.92/467.12
$MR_{AUC0-\infty}$	Metabolic ratio of $AUC_{0-\infty}$ for FD1 only. $AUC_{0-\infty}$ for M467 divided by the $AUC_{0-\infty}$ of peposertib corrected for MW: $MR_{AUC0-\infty}$*481.92/467.12
MR_{Cmax}	Metabolic ratio of C_{max}. C_{max} for M467 divided by the C_{max} of peposertib corrected for MW: MR_{Cmax}*481.92/467.12

The following PK parameters will be calculated from capecitabine and its metabolite (5-fluorouracil) plasma concentrations for FD1 and/or FD9 as indicated.

C_{max}	Maximum observed concentration
t_{max}	The time to reach C_{max} during a dosing interval (unless otherwise defined, the first occurrence is taken if multiple/identical C_{max} values)
t_{last}	The time at which last quantifiable concentration occurs.
AUC_{0-t}	The area under the curve (AUC) from time 0 (dosing time) to the last sampling time at which the concentration is at or above the LLOQ. Calculated using the mixed log linear trapezoidal rule (linear up, log down)
$AUC_{0-\infty}$	The AUC from time 0 (dosing time) to infinity based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination for FD1. Calculated using the mixed log linear trapezoidal rule (linear up, log down). $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda_z$

$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$, $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100 for FD1
$t_{½}$	Apparent terminal half-life, $t_{½} = \ln 2/\lambda_z$
CL/f	Apparent total body clearance of drug, calculated as Dose/$AUC_{0-\infty}$ (predicted) for FD1 for capecitabine only
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration. V_z/f = Dose/($AUC_{0-\infty}$*λ_z) for FD1 for capecitabine only

The following PK parameters will be calculated for diagnostic purposes and listed:

- Apparent terminal rate constant (λ_z).
- First (λz low) and last (λz upp) time point of the time interval of the log-linear regression to determine λz.
- Number of data points (N) included in the log-linear regression analysis to determine λz.
- Goodness-of-fit statistic (Rsq,adj) for calculation of λz.

Concentrations below the LLOQ at any point in the profile will be taken as zero for calculating the AUC. Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study drug administration. The same applies to predose samples during multiple dosing.

The regression analysis for λ_z will contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin best fit methodology will be used as standard. However, in some cases, further adjustment may be made by the pharmacokineticist, if warranted, and reviewed by the Sponsor. The last quantifiable concentration will always be included in the regression analysis, while the concentration at t_{max} and any concentrations below the LLOQ which occur after the last quantifiable data point will not be used.

If AUCextra%> 20% and/or the coefficient of correlation (Rsq,adj) is <0.800 and/or the observation period over which the regression line is less than two-fold the resulting $t_{½}$ itself, rate constants and all derived parameters will be listed, flagged and included in the parameter outputs and descriptive statistics regardless of whether or not these criteria are met.

Partial area, AUC_{0-24} should be calculated using the scheduled dosing interval, as defined in the protocol. The actual interval calculated from CRF time data should not be used.

CCI [redacted]

- Scatter plot of individual dose-normalized AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} versus dose on a linear scale. A linear regression may also be overlaid.

The following listings, figures, and summary statistics of peposertib, its metabolite (*0*-demethylated product M467), and capecitabine and its metabolite (5-fluorouracil) PK concentration and parameter data will be provided:

- Listing of individual PK concentration data by scheduled time point, dose level, and fraction day
- Listing of individual PK parameters by dose level and fraction day
- Descriptive summary table of PK concentration data by scheduled time point, dose level, and fraction day
- Descriptive summary table of PK parameter data by dose level and fraction day
- Individual peposertib , M467, and capecitabine and 5-fluorouracil concentration-time profiles (linear and semi-logarithmic scales) will be plotted by dose level for each fraction day as spaghetti plots, using actual time points (where available).
- Arithmetic mean concentrations will be plotted on both linear (±Sd) and semi-logarithmic scales using scheduled time points – with all dose levels overlaid per fraction day, and with all fraction days overlaid per formulation dose level. Additional mean plots will be produced (on both linear [±(Sd] and semi-log scale) to show the mean concentration-time data per dose level over the entire-time course. PK concentrations excluded form summary statistics will not be included in mean figures. Mean plots will only contain averages when n> 2.

All descriptive summaries of PK data will be performed using the PK analysis set.

Any PK concentrations or PK parameters excluded from PK evaluation or summary statistics will be included in subject listings and flagged; a reason for exclusion will detailed in a footnote. Any flags should be included in the study specific SDTM and ADaM data sets**.** The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

CCI [redacted]

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16.4 Patient Reported Outcome

Not applicable for Phase Ib.

17 References

Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.

Kalbfleisch JD and Prentice RL. The statistical analysis of failure time data, New York: John Wiley & Sons 1980.

Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-44.

Mosteller RD. Simplified calculation of body-surface area. N Eng J Med 1987;317:1098.

18 Appendices

18.1 SMC SAP

Refer to : ctp-ms100036-0020-smc-iap-v1-26apr2019

18.2 Clavien-Dindo classification

Refer to : Peposertib-Clavien_Dindo-Terms-v23_1.xlsx

ELECTRONIC SIGNATURES

Document: ctp-ms100036-0020-iap-v3

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PPD	Task Completed (Approval eSign): Approved	Technical Approval	08-Jul-2021 09:32
PPD	Task Completed (Approval eSign): Approved	Business Approval	08-Jul-2021 18:30