Clinical Study Protocol

Title Page

Clinical Study Protocol 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 Number:	MS100036-0020
Protocol Version:	06 May 2021/Version 4.0
Merck Compound:	M3814
Merck Registered Compound Name in Japan:	Not applicable
Short Title:	Phase Ib/II study of peposertib in combination with capecitabine and radiotherapy in rectal cancer
Coordinating Investigator:	PPD PPD
Sponsor Name and Legal Registered Address:	For all countries except the US and Canada: **Merck KGaA** Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: **EMD Serono Research & Development Institute, Inc.** An affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike, Billerica, MA 01821-3936, USA
Regulatory Agency Identifying Numbers:	US FDA IND CCI EudraCT: 2018-002275-18

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	09 Aug 2018
2.0	Global Protocol Amendment	17 April 2019
3.0	Global Protocol Amendment	11 May 2020
4.0	Global Protocol Amendment	06 May 2021

Protocol Version 4.0 (06 May 2021)

Overall Rationale for the Amendment

This protocol amendment is being issued to document the premature discontinuation of study MS100036-0020.

As of 06 May 2021, in the Phase Ib dose escalation part, 19 participants have been treated with doses ranging from 50 to 250 mg peposertib once daily in combination with standard of care (SoC) capecitabine and radiotherapy (RT). CCI [redacted]

Since the benefit/risk ratio of peposertib plus chemoradiotherapy as compared to SoC in locally advanced rectal cancer is impaired, the Sponsor decided to prematurely discontinue the dose escalation in the Phase Ib portion of the study after the Cohort 5 of 150 mg and to not proceed with Phase II.

In Phase Ib, no further participants will be screened or enrolled, and all participants have completed the treatment. Participants currently in the study will continue to perform the study procedures and assessments until they complete 1-year follow-up after start of study intervention. This will be a sufficient timeframe to address any possible late toxicities due to RT that normally develop in the first year after treatment and is in line with clinical practice.

Participants who have already been followed up for more than 1 year (Long-term Safety or Survival Follow-up) will be discontinued from the study after the approval of protocol amendment version 4.0 by the respective Health Authority and Ethics Boards. Participants will be informed of the discontinuation by the Investigator via a phone call. No further study visits or assessments are planned.

Section # and Name	Description of Change	Brief Rationale
Title Page	Removed the details of Medical Responsible and Medical Monitor. Removed the row for protocol previous version.	Required and/or recommended changes per Merck Protocol Template version 15.
Section 5 Study Population Appendix 2 Study Governance	Included mandatory text regarding participant's legal representative. Removed the definition of "legally authorized representative" from Appendix 2.	
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities Section 2.3 Benefit/Risk Assessment Section 3 Objectives and Endpoints Section 3.1 Definitions of Pathological Complete Response and Clinical Complete Response, and Derivation of the Composite Endpoint Section 4.1 Overall Design Section 4.1.2 Treatment Period Section 4.1.3 Follow-up Periods Section 4.2 Scientific Rationale for Study Design Section 5.4 Screen Failures Section 6.1 Study Intervention(s) Administration Section 6.3.1 Study Intervention Assignment Section 6.3.2 Blinding Section 6.3.3 Emergency Unblinding (Section removed) Section 6.6 Dose Selection and Modification Section 6.6.2 Dosing Instructions (and subsections) Section 8 Study Assessments and Procedures Section 8.1.1 Pathological Complete Response Section 8.1.2 Tumor Evaluation Methods and Response Assessment Section 8.1.3 Quality of Life (Section removed) Section 8.2.3 Electrocardiograms Section 8.5 Pharmacokinetics CCI [redacted] Section 9.3 Population for Analyses Section 9.4 Statistical Analyses Section 9.4.1 Efficacy Analyses Section 9.4.2 Safety Analyses Section 9.4.3 Other Analyses Section 9.4.4 Sequence of Analyses Appendix 2 Study Governance	Appropriate details of Phase II part of the study removed from the protocol in the respective sections.	Study will be prematurely discontinued. Participants in Phase Ib will only be followed for 1 year, Phase II will not be started (see overall rationale above).

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 4.1 Overall Design Section 4.1.3 Follow-up Periods Section 6.5 Concomitant Therapy Section 8.1.2 Tumor Evaluation Methods and Response Assessment Section 8.1.2.2 Tumor Response Evaluation Section 8.2 Safety Assessments and Procedures Section 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information Section 8.3.3 Follow-up of Adverse Events and Serious Adverse Events Appendix 5 Tumor Response Criteria	Long-term Safety Follow-up period shortened to 1 year (previously 2 years) and removed Survival Follow-up.	Safety Follow-up is reduced to 1 year since this will provide a sufficient timeframe to address any possible late toxicities due to radiotherapy that normally develop in the first year after treatment.
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9.4.1 Efficacy Analyses	Removed the endpoints of “overall survival” and “best overall response”.	Overall survival removed as the Safety Follow-up period is reduced to 1 year.
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9.4.1 Efficacy Analyses	Added endpoint of “neoadjuvant rectal score”.	Due to discontinuation of Phase II, data on the neoadjuvant rectal score of Phase Ib will be analyzed to obtain more comprehensive data on antitumor activity.
Section 6.1 Study Intervention(s) Administration	Added that “for Spain, capecitabine will be provided by local vendor”.	To clarify the Supplier details of capecitabine in Spain.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol 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.

Short Title: Phase Ib/II study of peposertib in combination with capecitabine and radiotherapy in rectal cancer.

CCI [redacted]

Phase II of this study will not be performed and was therefore deleted from this protocol.

Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To define a maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) of peposertib in combination with capecitabine and RT	Occurrence of dose limiting toxicities (DLTs)	Time from first study intervention to the end of chemoradiotherapy with a final assessment at 4 weeks after surgery
Secondary		
To evaluate safety and tolerability of peposertib in combination with capecitabine and RT	• Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events according to the National Cancer Institute (NCI)-Common Terminology Criteria of Adverse Events (CTCAE) version 5.0 • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, and clinically significantly abnormal electrocardiograms (ECGs) including clinically important increases in QT interval (QTcF)	Time from first study intervention to final assessment at 1 year

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
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)
	• Disease-free Survival	• Time from first study intervention to final assessment at 1 year
	• 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 1 year
	• Neoadjuvant rectal score	• Pathology evaluation of specimen after surgery
To assess the pharmacokinetics (PK) of peposertib	Pharmacokinetic profile of peposertib in terms of PK parameter estimates (e.g. C_{max}, AUC_{0-t}, t_{max}, CL/f, Vz/f, and $t_{1/2}$)	Fraction day (FD)1 and FD9

Overall Design: This is a multicenter, open-label, single arm, dose escalation study in participants with locally advanced rectal cancer.

The study will consist of a Screening period of 4 weeks, a Treatment period of 5 to 5.5 weeks (25 or 28 FD) (DLT period), a Short-term Safety Follow-up period of 13.5 weeks (including 30 days after surgery), a Long-term Safety Follow-up period until 1 year after the start of study intervention/randomization.

Number of Participants: The planned cohort size is 3 participants. The total sample size will depend on the number of cohorts to be evaluated. It is anticipated that 18 to 30 evaluable participants will be required.

Study Intervention Groups and Duration: Participants will be assigned to peposertib given in combination with capecitabine 825 mg/m^2 twice daily 5 days/week and RT of 50 to 50.4 Gy to the tumor area and 45 Gy to the electively irradiated tissues in 25 or 28 fractions (corresponding to 5 to 5.5 weeks). The starting dose of peposertib for the first cohort will be 50 mg once daily 5 days/week. The peposertib dose for the next cohorts will be determined by the Safety Monitoring Committee (SMC) guided by a Bayesian 2-parameter logistic regression model with overdose control.

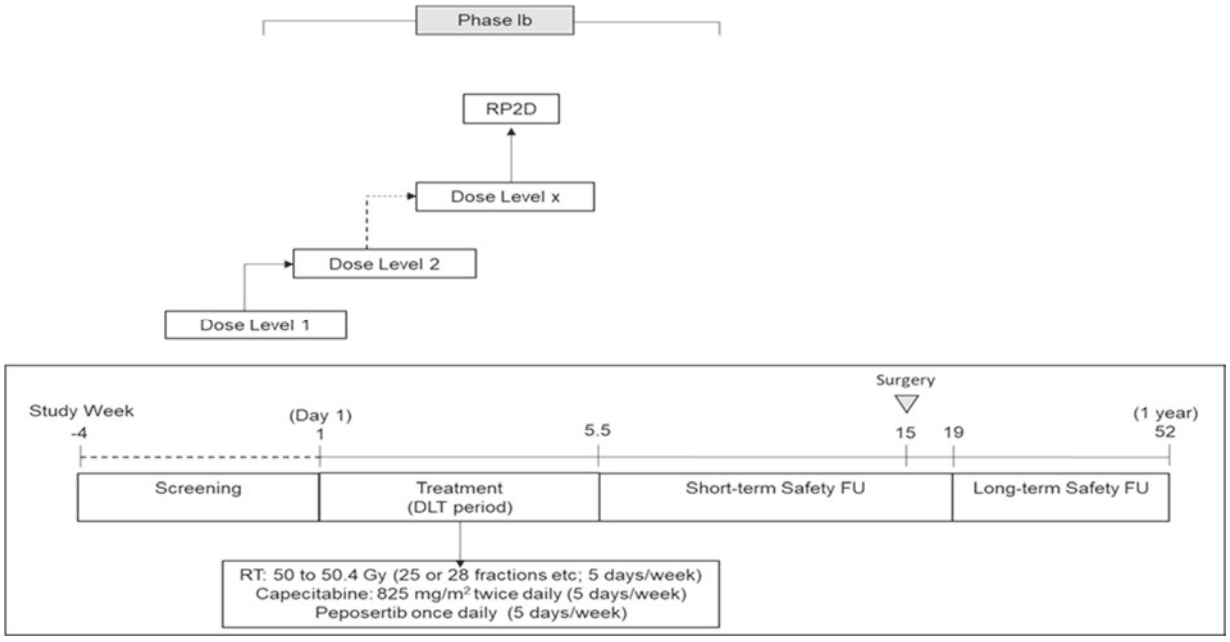
Premature Discontinuation: As of 06 May 2021, in the Phase Ib dose escalation part, 19 participants have been treated with doses ranging from 50 to 250 mg peposertib once daily plus capecitabine and RT. Preliminary clinical data from 16 participants that have finished the study up to Week 19 as well as changing treatment landscape in locally advanced rectal cancer indicate that the ability to generate a meaningful proof of concept under the current protocol is low. Therefore, the dose escalation in the Phase Ib part will be prematurely discontinued after completing the Cohort 5 of 150 mg, and the Phase II part of the study will not be initiated.

Involvement of Special Committee(s): Yes

1.2 Schema

Figure 1 shows a schematic overview of the study design.

Figure 1 Study Design Diagram



DLT=dose limiting toxicity, Gy=Gray, FU=follow-up, RP2D=recommended Phase II dose, RT=radiotherapy.

1.3 Schedule of Activities

The treatment period will include 25 or 28 RT fractions, depending on local practice.

- The Schedule of Activities (SoA) is provided in Table 1.
- The SoA for the Long-term Safety Follow-up is provided in Table 2.
- CCI [redacted]
- The PK sampling schedule is provided in Table 4.
- CCI [redacted]

Table 1 Schedules of Activities – 25 or 28 Fraction Days

		Evaluation Period											Notes
Study Period	**Screening**	**Treatment Period/DLT Period (peposertib + capecitabine + RT)**								**Short-term Safety FU**			Capecitabine given within 30 min after meal (AM and PM dosing), peposertib given 1 h after meal, RT given 1.5 h (± 30 min) after M3814 dosing. See Table 7 and Section 6.6.2.4.
Study Day	**Day -28 to -1**	**FD1 to 25 or 28 Visits: on all FD (FD1 to FD25 or 28), FD25 or 28 is last RT day**											
Peposertib Capecitabine RT		**X: Peposertib qd 5 d/wk (only on FD) X: Capecitabine 825 mg/m^2 bid 5 d/wk (only on FD) X: RT 1.8 Gy/fraction, 5 FD/wk, integrated concomitant boost (total daily dose 2 Gy) is allowed**									**Surgery**		
Visit Week	**-4 to -1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**5 or 6**	**7 to 14**	**15**	**19**	
Visit Day	**-28 to -1**	**FD1**	**FD2**	**FD6**	**FD9**	**FD11**	**FD16**	**FD21**	**FD25 or FD28/ ETT**	**In case of acute toxicities one visit/wk until recovery[a,b]**	**One visit / wk**		If premature discontinuation during treatment, the SoA for FD25/FD28 should be performed. In such cases, this visit will be considered the ETT visit. [a]Where recovery means until the toxicity reduces to Grade 1 or to baseline Wk 14 visit is mandatory. [b]In case of a pandemic, it is per Investigator's discretion if these visits can be done via a phone call. Wk 14 visit remains a clinic visit.
Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
Signed ICF	X												
Inclusion/ Exclusion Criteria	X	X											
Demography	X												
Medical History	X												

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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
Serum β-HCG Pregnancy	X									Wk 14 only			If applicable.
Vital Signs	X	X		X		X	X	X	X	X		X	Pulse rate, DBP, SBP, and body temperature. Vital signs during treatment are to be done on a weekly basis, not necessarily on the specified FD

		Evaluation Period											Notes
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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
Physical Examination	X	X		X		X	X	X	X	X		X	Physical examination (including body weight) will report findings in the irradiated area during Short- and Long-term FU periods. Height at Screening only. Physical examination during treatment is to be done on a weekly basis, not necessarily on the specified FD.
ECOG PS	X					X			X	X		X	

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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
AE Assessment	X	X	X	X	X	X	X	X	X	X		X	AEs collected from FD1 to FD25/FD28 will guide dose escalation for next cohort. During the Wk 19 visit all AEs since the last visit including any AEs during the surgical and postsurgical periods will be collected.
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X		X	

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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
Hematology	X	X		X		X	X	X	X	X		X	Hematology at FD1 has a visit window of up to -3 days; during treatment hematology is to be done on a weekly basis, not necessarily on the specified FD
Serum Chemistry	X	X		X		X	X	X	X	X		X	Serum chemistry at FD1 has a visit window of up to -3 days; during treatment serum chemistry is to be done on a weekly basis, not necessarily on the specified FD.

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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
Coagulation	X								X	Wk 14 only		X	Coagulation during treatment: coagulation is to be done on a weekly basis, not necessarily on the specified FD.
Urinalysis	X					X			X	Wk 14 only		X	Routine urinalysis followed by microscopic examination if abnormal results. Urinalysis during treatment urinalysis is to be done on a weekly basis, not necessarily on the specified FD

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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
12-Lead ECG	X	X				X			X				Triplicate. On FD1 pre peposertib dose (± 30 min) and 2 h (± 30 min) post peposertib dose. On other FDs only taken 2 h (± 30 min) post peposertib dose.
MRI	X									Wk 14 only			T_2 weighted and diffusion weighted.

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Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
DRE and endoscopy (and EUS if indicated or if performed)	X									Wk 14 only			Assessment at Screening only for participants who received induction chemotherapy prior to start of the study. Photograph of mucosa at endoscopy, and biopsy, if required.
Study Intervention		X	X	X	X	X	X	X	X				Administration of study intervention is described above. A patient diary will be used to record compliance.

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Study Period	**Screening**	**Treatment Period/DLT Period (peposertib + capecitabine + RT)**								**Short-term Safety FU**			Capecitabine given within 30 min after meal (AM and PM dosing), peposertib given 1 h after meal, RT given 1.5 h (± 30 min) after M3814 dosing. See Table 7 and Section 6.6.2.4.
Study Day	**Day -28 to -1**	**FD1 to 25 or 28 Visits: on all FD (FD1 to FD25 or 28), FD25 or 28 is last RT day**											
Peposertib Capecitabine RT		**X: Peposertib qd 5 d/wk (only on FD) X: Capecitabine 825 mg/m^2 bid 5 d/wk (only on FD) X: RT 1.8 Gy/fraction, 5 FD/wk, integrated concomitant boost (total daily dose 2 Gy) is allowed**									**Surgery**		
Visit Week	**-4 to -1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**5 or 6**	**7 to 14**	**15**	**19**	
Visit Day	**-28 to -1**	**FD1**	**FD2**	**FD6**	**FD9**	**FD11**	**FD16**	**FD21**	**FD25 or FD28/ ETT**	**In case of acute toxicities one visit/wk until recovery[a,b]**	**One visit / wk**		If premature discontinuation during treatment, the SoA for FD25/FD28 should be performed. In such cases, this visit will be considered the ETT visit. [a]Where recovery means until the toxicity reduces to Grade 1 or to baseline Wk 14 visit is mandatory. [b]In case of a pandemic, it is per Investigator's discretion if these visits can be done via a phone call. Wk 14 visit remains a clinic visit.
Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
PK Blood Samples		X	X		X								PK blood sample collection also on FD10 (predose). See Table 4 for details.
Archival FFPE Tumor	X												If no archival material is available, then a fresh biopsy will be taken.
CCI [redacted]													

		Evaluation Period											Notes
Study Period	**Screening**	**Treatment Period/DLT Period (peposertib + capecitabine + RT)**								**Short-term Safety FU**			Capecitabine given within 30 min after meal (AM and PM dosing), peposertib given 1 h after meal, RT given 1.5 h (± 30 min) after M3814 dosing. See Table 7 and Section 6.6.2.4.
Study Day	**Day -28 to -1**	**FD1 to 25 or 28 Visits: on all FD (FD1 to FD25 or 28), FD25 or 28 is last RT day**											
Peposertib Capecitabine RT		**X: Peposertib qd 5 d/wk (only on FD) X: Capecitabine 825 mg/m^2 bid 5 d/wk (only on FD) X: RT 1.8 Gy/fraction, 5 FD/wk, integrated concomitant boost (total daily dose 2 Gy) is allowed**									**Surgery**		
Visit Week	**-4 to -1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**5 or 6**	**7 to 14**	**15**	**19**	
Visit Day	**-28 to -1**	**FD1**	**FD2**	**FD6**	**FD9**	**FD11**	**FD16**	**FD21**	**FD25 or FD28/ ETT**	**In case of acute toxicities one visit/wk until recovery[a,b]**	**One visit / wk**		If premature discontinuation during treatment, the SoA for FD25/FD28 should be performed. In such cases, this visit will be considered the ETT visit. [a]Where recovery means until the toxicity reduces to Grade 1 or to baseline Wk 14 visit is mandatory. [b]In case of a pandemic, it is per Investigator's discretion if these visits can be done via a phone call. Wk 14 visit remains a clinic visit.
Visit Window (Days)										**± 7 for Wk 14 only/± 2 for other visits**	**± 14**	**± 14**	
Assessments and Procedures													
CCI													
Plasma Sample		X					X			Wk 14 only			Predose plasma sampling for ctDNA. A sample will also be taken at progression.
Surgery											X		Followed by histological evaluation. Mandatory tumor tissue sample from surgical specimen if there is any tumor left.

AE=adverse event, ctDNA=circulating tumor DNA, DBP=diastolic blood pressure, DLT=dose limiting toxicity, DRE=digital rectal examination, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, ETT=End of Trial Treatment, EUS=endoscopic ultrasound, FD=fraction day, FFPE=formalin-fixed paraffin-embedded, FU=Follow-up, Gy=Gray, HCG=human chorionic gonadotropin, ICF=informed consent form, MRI=magnetic resonance imaging, CCI , CCI , PK=pharmacokinetics, RT=radiotherapy, SBP=systolic blood pressure, SoA=Schedule of Activities, Wk/wk=Week/week.

Table 2 Schedule of Activities – Long-term Safety Follow-up Period

Study Periods	Long-term Safety FU	Notes
Visit Weeks	**19 to 52**	
Visit Week	**21 and 27 wk after start of study intervention/ randomization: Wk 21 and 27; thereafter every 3 mo in Yr 1: Wk 39 and 52**	Participants followed-up until 1 year after start of study intervention/randomization, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g. if new treatment is started, study discontinued, withdrawal of consent). Adjuvant chemotherapy is allowed as per local standards (see Section 6.5). Participants receiving adjuvant chemotherapy will continue to follow the schedule of activities as per protocol. If adjuvant chemotherapy is given any additional safety evaluations/laboratory tests will be as per local practice. Reason for early discontinuation should be captured in source documents. If EOT occurs before Wk 52, all assessments must be done as planned for Wk 52.
Visit Windows (Week)	**± 1 for Wk 21; ± 2 for other visits**	
Participants who have already been followed up for more than 1 year (Long-term Safety or Survival Follow-up) will be discontinued from the study after the approval of protocol amendment version 4.0 by the respective Health Authority and Ethics Boards. Participants will be informed of the discontinuation by the Investigator via a phone call. No further study visits or assessments are planned.		
Assessment and Procedures		
Vital Signs	X	Pulse rate, DBP, SBP, body temperature, and body weight.
Physical Examination	X	Physical examination (including body weight) will report findings in the irradiated area during Short- and Long-Term FU periods.
ECOG PS	X	
Adverse Event Assessment	X	Evaluation of ongoing or new AEs assessed as related to study intervention until resolution or permanent outcome. New SAE assessed as unrelated to study intervention only up to Wk 27.
Concomitant Therapy	X	
Adjuvant Chemotherapy	X	Adjuvant chemotherapy if given, according to local guidelines, must start between 1 and 3 mo after surgery.
Hematology	X	
Serum Chemistry and Coagulation	X	

Study Periods	Long-term Safety FU	Notes
Visit Weeks	**19 to 52**	
Visit Week	**21 and 27 wk after start of study intervention/ randomization: Wk 21 and 27; thereafter every 3 mo in Yr 1: Wk 39 and 52**	Participants followed-up until 1 year after start of study intervention/randomization, or earlier due to any reason whereby tumor assessments are no longer applicable (e.g. if new treatment is started, study discontinued, withdrawal of consent). Adjuvant chemotherapy is allowed as per local standards (see Section 6.5). Participants receiving adjuvant chemotherapy will continue to follow the schedule of activities as per protocol. If adjuvant chemotherapy is given any additional safety evaluations/laboratory tests will be as per local practice. Reason for early discontinuation should be captured in source documents. If EOT occurs before Wk 52, all assessments must be done as planned for Wk 52.
Visit Windows (Week)	**± 1 for Wk 21;** **± 2 for other visits**	
Participants who have already been followed up for more than 1 year (Long-term Safety or Survival Follow-up) will be discontinued from the study after the approval of protocol amendment version 4.0 by the respective Health Authority and Ethics Boards. Participants will be informed of the discontinuation by the Investigator via a phone call. No further study visits or assessments are planned.		
Assessment and Procedures		
Carcinoembryonic Antigen	X	
CCI [redacted]		
MRI/CT	X (starting Wk 27)	T_2 weighted and diffusion weighted, without gadolinium. No MRI/CT at Wk 21.

AE=adverse event, CT=computerized tomography, ctDNA=circulating tumor DNA, DBP=diastolic blood pressure, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EOT=End of Trial, FU=Follow-up, MRI=magnetic resonance imaging, SAE=serious adverse event, SBP=systolic blood pressure.


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Table 4 Pharmacokinetic Sampling Schedule of Peposertib and Capecitabine

Study Day	Sampling Time Point (Peposertib)	Sampling Window	Phase Ib	Notes
FD1	Predose	Within 60 min prior to peposertib administration	X	Predose samples should be taken before capecitabine and peposertib administration. All other sampling times are related to peposertib administration; sampling for capecitabine/metabolite PK is done at the same time as the blood is drawn for peposertib PK analysis
	1 h	± 10 min	X	
	2 h	± 10 min	X	
	3 h	± 20 min	X	
	4 h	± 20 min	X	
	6 h	± 30 min	X	
FD2	Predose	Within 60 min prior to peposertib administration	X	Predose samples should be taken before capecitabine and peposertib administration.
FD9	Predose	Within 60 min prior to peposertib administration	X	Predose samples should be taken before capecitabine and peposertib administration. All other sampling times are related to peposertib administration; sampling for capecitabine/metabolite PK is done at the same time as the blood is drawn for peposertib PK analysis
	1 h	± 10 min	X	
	2 h	± 10 min	X	
	3 h	± 20 min	X	
	4 h	± 20 min	X	
	6 h	± 30 min	X	
FD10	Predose	Within 60 min prior to peposertib administration	X	Predose samples should be taken before capecitabine and peposertib administration.

FD=fraction day, PK=pharmacokinetics.

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2 Introduction

M3814, here-in after referred to as peposertib (International Nonproprietary Name), is a potent and selective, adenosine triphosphate (ATP)-competitive inhibitor of DNA-protein kinase (DNA-PK) that targets tumor cell growth and survival by inhibiting the critical DNA damage repair mechanism in solid and hematological malignancies. The present study evaluates the safety, tolerability, pharmacokinetics (PK), and efficacy of the neoadjuvant treatment combination of peposertib, capecitabine, and radiotherapy (RT) in participants with locally advanced rectal cancer.

Complete information on the chemistry, pharmacology, efficacy, and safety of peposertib is in the Investigator's Brochure.

CCI [redacted]

2.2 Background

Peposertib is a novel, potent, and selective ATP-competitive inhibitor of DNA-PK that targets tumor cell growth and survival by inhibiting the critical DNA damage repair mechanism in solid and hematological malignancies. DNA-protein kinase with its protein subunits, kilo units 70 and 80, regulates one of the major pathways responsible for repair of DSBs in DNA caused by RT or chemotherapeutic agents (Curtin 2012). The activity of DNA-PK is critical for successful DSB repair via the nonhomologous end joining mechanism.

The antitumor effect of peposertib is dependent on the functionality of DNA repair and checkpoint signaling in cancer cells, which have a lowered ability to cope with DSBs in their DNA and frequently undergo apoptotic cell death (Furgason 2013). Hence, one rationale of DNA-PK inhibition is to potentiate the effect of DNA damage generated by RT.

CCI [redacted]

The clinical development of peposertib comprises 3 studies using the capsule formulation. The first-in-man study (EMR100036-001) initiated in participants with advanced solid tumors

completed the single dose escalation part where 31 participants were treated with dose levels between 100 mg once daily and 400 mg twice daily. The maximum tolerated dose (MTD) was not reached at 400 mg twice daily; however, further dose escalation was not done, per Safety Monitoring Committee (SMC) decision. There were no dose limiting toxicities (DLTs) reported at the 400 mg twice daily dose level. The recommended Phase II dose (RP2D) for peposertib monotherapy was established as 400 mg twice daily and confirmed in an additional 6 aspirin-naïve participants (aspirin-naïve participants were included to test for alterations in platelet aggregation). The efficacy data did not support further development of peposertib in monotherapy due to the lack of clear clinical activity in this setting.

The second study with peposertib (EMR100036-002) is currently ongoing and is a combined Phase Ia/Ib, open label, dose escalation and dose-expansion study designed to explore the safety, tolerability, PK, CCI and clinical activity of peposertib in combination with RT/chemoradiotherapy (CRT), and to determine the MTD and a RP2D for peposertib in combination with RT/CRT.

- The Arm A-Phase Ia part of the study includes previously treated participants with locally advanced disease (any tumor or metastases including lymphomas) localized in the head and neck region or thorax that is not amenable to surgical therapy or with standard systemic therapy with an indication for palliative RT (30 Gy in 10 fractions) over 2 weeks.
- The Arm B-Phase Ia part includes treatment naïve SCCHN participants who are eligible for fractionated RT (66 to 70 Gy in 33 to 35 fractions) with concurrent cisplatin.
- In ancillary clinical proof-of-principle part of the study, participants with at least 2 cutaneous/subcutaneous tumors/metastasis are included to evaluate alterations in phosphorylated-DNA-PK expression induced by RT (Lesion 1), as compared with expression induced by RT after administration of peposertib (Lesion 2).

A third study (MS100036-0022) investigated peposertib in combination with etoposide and cisplatin in participants with treatment naïve extensive disease SCLC. Two participants were treated with peposertib (capsule and tablet formulation). One participant received a single dose of the tablet, and the capsule for the remainder of the study. No DLTs or deaths were reported, and none of the participants discontinued due to an adverse event (AE). Enrollment in the study was prematurely terminated due to recruitment challenges and not due to concerns of safety for the subjects.

The Investigator's Brochure provides a more detailed overview of the nonclinical and clinical information on peposertib.

Rectal cancer is a subset of colorectal cancer, which is the third most common diagnosed cancer. An estimated 40,000 new cases of rectal cancer were diagnosed in 2017 in the USA with an increase in incidence rates in the younger population (Siegel 2017). In the European Union the incidence of rectal cancer is 15 to 25 cases/100,000 population per year resulting in approximately 125,000 new cases per year, and mortality is 4-10/100,000 population per year (Glynne-Jones 2017). Rectal cancer is a distal large bowel adenocarcinoma tumor located at or below the peritoneal reflection. The standard of care (SoC) for locally advanced rectal cancers is neoadjuvant CRT, with or without sequential chemotherapy followed by surgical intervention (e.g.

total mesorectal excision [TME]), with the aim to remove the irradiated tumor and decrease the risk of local recurrence and mortality (National Comprehensive Cancer Network® [NCCN] Guidelines for Patients® Rectal Cancer 2019; Glynne-Jones 2017). This methodology has resulted in a decrease in local recurrence and an improvement in mortality rates (Shahab 2017). However, one-third of patients with locally advanced rectal cancer will later develop distant metastases and will subsequently die from the disease. In addition, most survivors experience significant impairment in their QoL, due primarily to removal of the rectum. Consequently, the current challenges in the treatment of locally advanced rectal cancer are how to improve survival by reducing the risk of distant metastases, and how to improve QoL in surviving patients by preserving the rectum. There is an unmet need to improve long-term outcomes and QoL and so the development of new therapeutic strategies to further increase these aspects is of key importance.

2.3 Benefit/Risk Assessment

The benefit-risk relationship has been carefully considered in the planning of this study. Nonclinical data show that peposertib potently and selectively inhibits DNA DSB repair induced by IR and other DNA damaging agents.

As of 18 December 2019 (Investigator's Brochure, Version 8.0), the important potential risks with peposertib identified for the purpose of the study based on nonclinical studies are as follows:

- Lymphoid depletion with risk of infection
- Stomatitis, mucositis
- Rash
- Increased radiation dermatitis
- Reproductive toxicity
- Increase in liver enzymes: aspartate aminotransferase, alanine aminotransferase and glutamate dehydrogenase
- Drug-drug interactions

Further, the following not important potential risks have been identified:

- Vomiting
- Diarrhea

There are no other important potential risks from completed/ongoing studies that are considered relevant for this rectal study population.

Recommendations for the clinical use of peposertib include the monitoring of adverse effects in the digestive tract and radiation side effects, as well as monitoring of hematological parameters and liver enzymes. In addition, precautionary measures to mitigate the risks of other treatments and treatment recommendations of known adverse reactions, need to be respected when given in combination with peposertib.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of peposertib may be found in Section 4.2 (Scientific Rationale for Study Design)

and the Investigator's Brochure, Participant Information Leaflet, or Development Safety Update Report.

The purpose of this study is to determine whether peposertib can be safely administered in combination with the current neoadjuvant SoC for rectal cancer, capecitabine in combination with RT, and whether the combination with peposertib shows a relevant antitumor efficacy advantage compared with SoC. Improved rates of clinical complete response (cCR) should translate into higher rates of organ preservation in patients with locally advanced rectal cancer. It is hypothesized that this will improve long-term QoL outcomes.

In this study, appropriate precautionary measures to mitigate the potential risks are implemented. The safety will be monitored on an ongoing basis by the SMC. The study will be discontinued in the event of any new findings that indicate a relevant deterioration of the benefit-risk balance for the participants, which would render continuation of the study unjustifiable.

The SoC CRT has a known and well-established toxicity profile. Nausea, vomiting, diarrhea, mucositis, hand-foot syndrome, radiation dermatitis, and decreases in hemoglobin, leucocytes, and platelets, are the most frequently reported Grade 3 AEs in clinical studies with capecitabine and RT (Liu 2016). These potential toxicities can be readily monitored with clinical laboratory, AE, and clinical assessments.

It is known that RT can cause acute toxicities in the form of, e.g. radiation dermatitis and mucositis. Late toxicities arising 3 months or later after the end of RT can be seen in the form of, e.g. mucositis, fibrosis, and bowel perforation. This must be evaluated by appropriate means including physical examination, imaging and endoscopy when indicated. Potentially, acute and late toxicities can be more severe when RT is given in combination with peposertib. This will be evaluated on an ongoing basis.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

The starting dose of 50 mg once daily peposertib in combination with RT and capecitabine is considered appropriate to mitigate possible AEs by overlapping or unexpected toxicities of the combination, and possible higher formulation-dependent fraction absorbed.

Peposertib has a nonclinical safety profile adequate for the treatment of patients with life-threatening advanced malignancies, and the safety profile does not raise concerns about further investigation of peposertib in participants with cancer. In addition, the available clinical safety data for peposertib when given as a single agent forms a basis for the clinical study in combination with RT, as well as chemotherapy, and supports the investigation also in the neoadjuvant setting.

In conclusion, emerging clinical safety data from studies EMR100036-001 and EMR100036-002, and supportive results of a comprehensive series of nonclinical safety pharmacology, PK, and toxicology studies, as well as primary and secondary PD findings support continued clinical development of peposertib in combination with RT, and/or chemotherapy.

3 Objectives and Endpoints

Study objectives and endpoints are provided in Table 6. Statistical analysis of the endpoints is described in Section 9.4.

Table 6 Study Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe
Primary		
To define an MTD and RP2D of peposertib in combination with capecitabine and RT	Occurrence of dose limiting toxicities	Time from first study intervention to the end of CRT with a final assessment at 4 weeks after surgery
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 1 year
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)
	• Disease-free Survival	• Time from first study intervention to final assessment at 1 year
	• 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 1 year
	• Neoadjuvant rectal score	• Pathology evaluation of specimen after surgery
To assess the PK of peposertib	PK profile of peposertib in terms of PK parameter estimates (e.g. C_{max}, AUC_{0-t}, t_{max}, CL/f, Vz/f, $t_{1/2}$)	FD1 and FD9

cCR=Clinical Complete Response, CRT=chemoradiotherapy, CCI [redacted] ECG=electrocardiogram, FD=fraction day, MTD=maximum tolerated dose, NCI-CTCAE=National Cancer Institute Common Terminology Criteria of Adverse Events, CCI [redacted], pCR=Pathological Complete Response, PK=pharmacokinetic(s), RP2D=recommended Phase II dose, RT=radiotherapy, TEAE=treatment-emergent adverse event.

The definition of pathological complete response (pCR) and cCR, and derivation of the pCR/cCR composite endpoint are described in Section 3.1. Statistical aspects of other endpoints are described in Section 9.4.

3.1 Definitions of Pathological Complete Response and Clinical Complete Response, and Derivation of the Composite Endpoint

Pathological Complete Response

Participants are considered to have a pCR if they undergo surgery and no residual cancer is found on histological examination of the removed specimen (ypT_0N_0).

The assessment of pCR will be based on local review of the histology slides.

Clinical Complete Response

Participants are considered to have a cCR if all the criteria below are fulfilled:

- Absence of any residual tumor in the primary site and draining lymph nodes on imaging with magnetic resonance imaging (MRI; T_2 weighted and diffusion weighted) as defined in the Appendix 5, which is based on a modification of tumor evaluation as described by Maas 2015.
- No visible lesion at endoscopy except a flat scar, telangiectasia, and/or whitening of the mucosa (documented by photography)
- Absence of any palpable tumor or irregularity on digital rectal examination (DRE) and endoscopic ultrasonography (EUS) (if indicated or if performed)
- If a biopsy is taken, it must be negative.

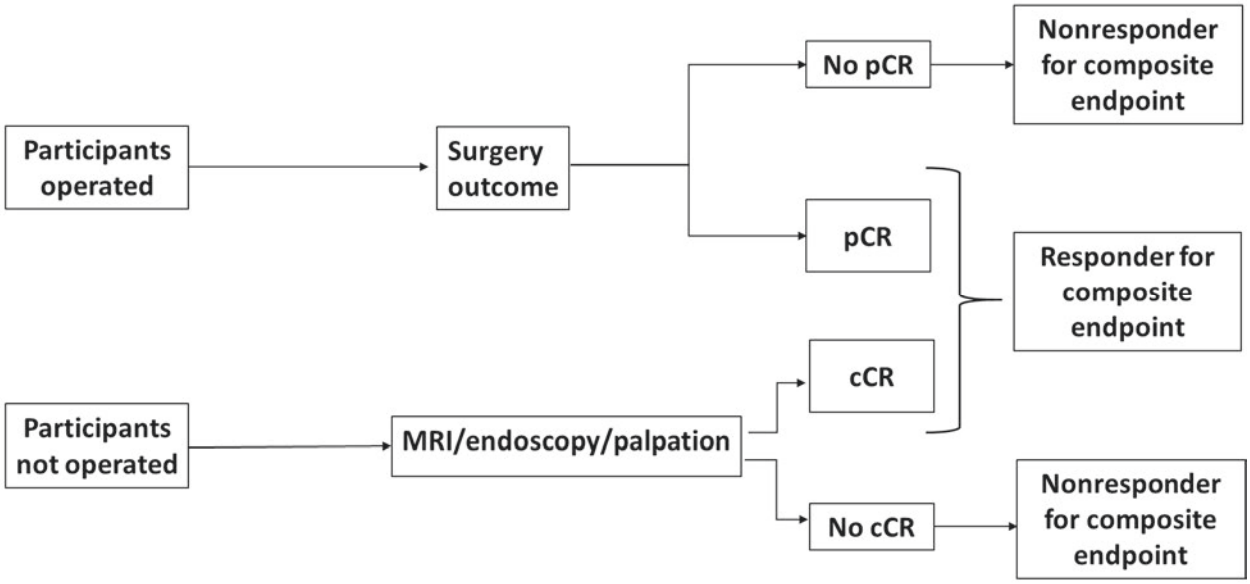
Composite Endpoint of Pathological Complete Response/Clinical Complete Response

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

- Participant had surgery and has pCR
- Participant did not undergo surgery but has cCR (defined above).

Participants who are not operated on and do not undergo the procedures to define cCR will be regarded as nonresponders.

Figure 2 Derivation of Composite Endpoint



cCR=Clinical Complete Response, CR=Complete Response, pCR=Pathological Complete Response, MRI=Magnetic Resonance Imaging. See Section 9.4 for the statistical aspects of the endpoints.

4 Study Design

4.1 Overall Design

This is a multicenter open-label, single arm, dose escalation study in participants with locally advanced rectal cancer.

The study will consist of a Screening period of 4 weeks, a Treatment period of 5 to 5.5 weeks (25 or 28 fraction days [FDs]) (DLT period, see Section 6.6.1), a Short-term Safety Follow-up period of 13.5 weeks including 30 days after surgery, a Long-term Safety Follow-up period until 1 year after the start of study intervention/randomization.

A schematic overview of the study is shown in Section 1.2. A detailed SoA is provided in Section 1.3.

4.1.1 Screening Period

Screening will be performed within 4 weeks prior to FD1 and first day of study intervention administration. Participants will be assessed for eligibility to participate in the study, and will undergo clinical evaluations to ensure compliance with the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively). Details of tumor evaluation methods at Screening are provided in Section 8.1.2. Details of rescreening are provided in Section 5.4. For participants who received induction chemotherapy prior to the study, a DRE and endoscopy (and EUS if indicated or if performed per local practice) will need to be done to determine current stage before starting CRT, in compliance with the inclusion criteria (Section 5.1).

4.1.2 Treatment Period

The starting dose of peposertib for the first cohort will be 50 mg once daily (Section 4.3). Participants for next cohorts will be assigned to an peposertib dose determined by the SMC. The SMC dose recommendations will be guided by a Bayesian 2-parameter logistic regression model with overdose control (Appendix 10). The planned cohort size is 3 participants. Peposertib will be given in combination with capecitabine at a dose of 825 mg/m^2 twice daily and RT of 50 to 50.4 Gy to the tumor area and 45 Gy to the electively irradiated tissues in 25 or 28 fractions (corresponding to 5 to 5.5 weeks). Full details of the dosing regimens are provided in Section 6.6.2.

After each cohort has completed the 5 to 5.5-week treatment period (DLT period), the SMC will review safety, including DLT data, tolerability, and PK data if available, and will recommend the peposertib dose for the next cohort. In addition, any toxicities observed during the Short-term Safety Follow-up will be reviewed and considered by the SMC for the overall evaluation of the safety and proposal of dose escalation of peposertib. Dose limiting toxicities are defined in Section 6.6.1. If the SMC decides to escalate the dose for the next cohort, it is in exceptional cases at discretion of the study team (medical lead and safety lead with input from statistician) to include up to 3 further participants in parallel, on a dose level that has already been tested in a previous cohort.

Participants will receive CRT until treatment completion after 25 or 28 RT fractions or disease progression, unacceptable toxicity or participant refusal to continue.

4.1.3 Follow-up Periods

The study follow-up will include:

- **Short-term Safety Follow-up:** the duration of the Short-term Safety Follow-up is approximately 13.5 to 14 weeks after treatment completion, including 30 days after surgery, with an optional 1 visit per week from Week 7 to Week 14 in case of acute toxicities until recovery to Grade 1 or to baseline. For all participants, a mandatory visit will be performed at Week 14, approximately 1 to 2 weeks prior to surgery, including a tumor assessment with MRI (T_2 weighted and diffusion weighted) needed for restaging and evaluation. Additional details on tumor evaluation methods and response assessments are provided in Section 8.1.2.
- Surgical intervention must be performed 15 weeks (± 14 days) after start of study intervention/randomization (i.e. approximately 9.5 weeks after stopping RT), unless there are contraindications for surgery, or if the participant refuses. The last Short-term Safety Follow-up visit is scheduled for Week 19, approximately 4 to 6 weeks after surgical intervention/imaging/biopsy, as per SoC. During this visit, all safety information since the last visit, including surgical and/or biopsy morbidities/toxicities will be collected.
- **Long-term Safety Follow-up:** participants will be followed-up at 21 and 27 weeks after start of study intervention/randomization; every 3 months until 1 year after start of study intervention/randomization. Details on tumor evaluation methods and response assessments are provided in Section 8.1.2. Adjuvant chemotherapy is allowed as per local standards (see Section 6.5). Participants receiving adjuvant chemotherapy will continue to follow the schedule of activities (SoA) as per protocol. If adjuvant chemotherapy is given, any additional safety evaluations/laboratory tests will be as per local practice.
- Participants who have already been followed up for more than 1 year (Long-term Safety or Survival Follow-up) will be discontinued from the study after the approval of protocol amendment version 4.0 by the respective Health Authority and Ethics Boards. Participants will be informed of the discontinuation by the Investigator via a phone call. No further study visits or assessments are planned.

4.2 Scientific Rationale for Study Design

Study Interventions:

- In this study, peposertib will be used in combination with capecitabine and RT. Peposertib is a potent and selective, ATP-competitive inhibitor of DNA-PK and blocks a major DSB repair pathway (nonhomologous end joining pathway). Inhibitors of DNA-PK are expected to synergistically enhance the therapeutic effect of DSB-inducing anticancer modalities.
- The current SoC for locally advanced rectal cancer is capecitabine, a prodrug of 5-fluorouracil (5FU), in combination with RT (NCCN 2019, Glynne-Jones 2017). The mechanism of 5FU cytotoxicity has been attributed to the mis-incorporation of fluoronucleotides into RNA and

DNA and to the inhibition of the nucleotide synthetic enzyme thymidylate synthase which is responsible for the de novo synthesis of DNA (Longley 2003).

- The combination of peposertib with RT and 5FU showed improved antitumor activity and progression-free survival compared with RT + 5FU alone, in the HCT116 colorectal cancer xenograft model (please refer to the Investigator's Brochure for further details).

Study Population:

- The inclusion and exclusion criteria (provided in Section 5.1 and Section 5.2, respectively) were chosen to maximize participant safety and possible potential benefit from peposertib in combination with capecitabine and RT.

Endpoint Selection:

- The aim of the study is to establish the MTD and RP2D of peposertib when given in combination with capecitabine and RT; therefore, the primary endpoint chosen is the occurrence of DLTs, which is a globally accepted endpoint for similar studies.

Interval to Surgery:

- Studies suggest that pCR rates when neoadjuvant CRT is administered in rectal cancer improve when the interval between the end of CRT and surgery ranges between 7 to 12 weeks (Ferrari 2015, Tulchinsky 2008, Kalady 2009, Zeng 2014, Roxburgh 2018). Therefore, in the current study, surgery is planned at approximately 9.5 to 10 weeks after the end of CRT.

4.3 Justification for Dose

The justification to use peposertib tablets for the dose escalation part of the study derives from nonclinical and clinical results obtained with peposertib with the capsule formulation (refer to the Investigator's Brochure for further details).

Owing to its formulation characteristics, dissolution and kinetic solubility of the drug substance may be enhanced in the tablet compared with the capsule formulation. CCI [redacted]

[redacted]

In the ongoing EMR100036-002 study, doses up to 200 mg once daily (capsule formulation) in combination with palliative RT (30 Gy in 10 fractions) are considered safe and well tolerated by the SMC. Considering a conservative scenario of an exposure increase of 2-fold of the tablet relative to the capsule formulation, a starting dose of 100 mg once daily can be defined; however,

as this study intervention is in the neoadjuvant setting and therefore potentially curative, the starting dose will be 50 mg to increase the probability that participants can complete the study intervention as per protocol.

Peposertib tablets will be given once daily and on RT days only. Peposertib has an apparent terminal half-life ($t_{1/2}$) of approximately 5.5 h. Therefore, once daily dosing will give adequate exposure for the timeframe in which the DSB caused by RT are repaired (Kwok 1989, Schulz 2017).

Capecitabine will be administered at a twice daily dose of 825 mg/m^2 and RT will be given at a total dose of 50 to 50.4 Gy to the tumor area and 45 Gy to the electively irradiated tissues in 25 or 28 fractions. These doses are in accordance with current medical guidelines (NCCN 2019, Glynne-Jones 2017).

See Section 6.6 for dosing instructions and the procedures for selecting and modifying each participant's dose.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study visits, interventions, and procedures, including the last scheduled activity shown in the SoA (Section 1.3). No further data will be collected from a participant after completion of the respective follow-up period (refer to Section 4.1.3).

The end of the study is defined as the date of the last scheduled activity, shown in the SoA (Section 1.3), for the last participant in the study globally.

The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason (Appendix 2).

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants who are appropriate for the study; thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2 (Study Governance).

Participants will be recruited based on referrals to study sites and local site review of participant profiles.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥ 18 years of age, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Have an Eastern Cooperative Oncology Group Performance Status ≤ 1

3. Have histologically confirmed and localized resectable rectal cancer (Stage II or Stage III at original staging). Participants who received induction chemotherapy are allowed to be enrolled to this study except if this induction is resulting in cCR or tumor progression (see Section 8.1.2 and Appendix 5). Participants who received induction chemotherapy should be evaluated by MRI, endoscopy and DRE before start of study intervention/randomization (peposertib and CRT), see Appendix 5. The following induction chemotherapies prior to screening for the current study are allowed: FOLFOX (folic acid, 5-FU, and oxaliplatin) and CAPEOX (capecitabine and oxaliplatin) as per NCCN 2019 guidance.

4. Have lower edge of the tumor located in rectum

5. Have evaluable disease in MRI

6. Have adequate hematological function: hemoglobin ≥ 9 g/dL, neutrophils ≥ 1.5×10^9/L and platelets ≥ 100×10^9/L

7. Have adequate renal function: serum creatinine ≤ 1.5 × upper limit of normal (ULN) or creatinine clearance ≥ 50 mL/min (Cockcroft 1976)

8. Have adequate liver function: aspartate aminotransferase, alanine transaminase, alkaline phosphatase ≤ 3 × ULN, and bilirubin ≤ 1.5 × ULN

Sex

9. Are male or female

- Male participants:

  Agree to the following during the study intervention period and for at least 12 weeks after the last dose of study intervention:

  - Refrain from donating sperm

  Plus, either:

  - Abstain from any activity that allows for exposure to ejaculate.

  OR

  - Use a male condom:

- When having sexual intercourse with a woman of childbearing potential, who is **not** currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.
- When engaging in any activity that allows for exposure to ejaculate.

- Female Participants:
  - Are **not** pregnant or breastfeeding, and at least one of the following conditions applies:
    - **Not** a woman of childbearing potential

    OR

    - If a woman of childbearing potential, use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
  - Before the first dose of the study intervention(s), if using hormonal contraception:
    - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

    OR

    - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

    AND

    - A barrier method, as described in Appendix 3.
  - During the intervention period
  - After the study intervention period (i.e. after the last dose of study intervention is administered) for at least 12 weeks, after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

  The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  - Have a negative serum pregnancy test, as required by local regulations, within 4 weeks before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.4.
- The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

10. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in an informed consent form (ICF) and this protocol.

Details of rescreening are provided in Section 5.4.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History of any other significant medical disease or psychiatric conditions that might in the assessment of the Investigator preclude safe participation in the study

2. History of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the study intervention

3. Unstable cardiovascular function within 6 months prior to enrollment (i.e. ischemia, symptomatic angina, congestive heart failure, Class III to IV New York Heart Association uncontrolled conduction abnormalities including a history of long QTc syndrome [QTcF > 480 ms] and/or pacemaker, or myocardial infarction)

4. Hypertension uncontrolled by medication (i.e. systolic blood pressure ≥ 150 mmHg and diastolic blood pressure ≥ 90 mmHg)

5. History of other malignant disease within the past 5 years, other than successfully treated basal carcinoma of the skin or carcinoma in situ of the cervix

6. Known human immunodeficiency virus positivity, known active viral hepatitis, current alcohol abuse, or cirrhosis

7. Ongoing active infection or treatment with a live attenuated vaccine within 4 weeks of dosing.

Prior/Concomitant Therapy

8. Previous radiation therapy to the pelvis

9. Concurrent use of other anticancer therapy

10. Major surgical intervention within 4 weeks prior to the first dose of study intervention. Biopsy(s) to establish the diagnosis for rectal cancer is permitted. Diverting ostomy is permitted

11. Concomitant or prior use of medications or herbal supplements, known to be strong inhibitors of cytochrome P450 (CYP) 3A and/or CYP2C19, unless use can be discontinued 1 week prior to receiving the first dose of study intervention. Concomitant or prior use of medications or herbal supplements, known to be strong inducers of CYP3A and/or CYP2C19, unless use can be discontinued at least 3 weeks prior to receiving study intervention. Concomitant or prior therapy use of medications or herbal supplements mainly metabolized by CYP3A with a narrow therapeutic index must be stopped at least 1 day prior to receiving study intervention

12. Concomitant use of H_2-blocker or proton pump inhibitors (PPIs) (or unable to stop at least 5 days prior to the first treatment). Note that calcium carbonate is acceptable

13. Treatment with sorivudine or its chemically related analogues, such as brivudine

Prior/Concurrent Clinical Study Experience

14. Participation in any interventional clinical study within 28 days prior to Screening or during participation in this study

Diagnostic Assessments

15. Contraindications to MRI imaging

Other Exclusions

16. Pregnant or nursing (lactating) women

17. Known dihydropyrimidine dehydrogenase deficiency

18. History of severe and unexpected reactions to fluoropyrimidine therapy

19. Hypersensitivity to capecitabine or to any of the excipients or fluorouracil.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

The timing of meals relative to dosing of study interventions and fasting requirements are detailed in the SoA (Section 1.3) and Section 6.6.2.

Participants will be instructed to refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, Seville orange marmalade, star fruit, or other products containing grapefruit, Seville oranges or star fruit from 7 days before the start of study intervention until after the final dose because its potential to interfere with the PK of peposertib.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions on caffeine, modest alcohol, or tobacco use apply during this study, with the exception of red wine (Section 5.3.1).

5.3.3 Activity

Electrocardiograms (ECG) will be obtained after the participant has been in a semi-supine position for at least 5 min (Section 8.2.3).

Participants will abstain from strenuous exercise for 2 h before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (potential participants who failed screening) may be rescreened. Rescreened participants will be assigned a new participant number. Retesting before baseline will be permitted only once, and the test for the specific abnormal value must be repeated within the timeframe of the Screening period. The last value of the previously questioned test result must meet the study criteria before start of study intervention. In the case of a rescreen and the screening CT scan is > 28 days from the previous screening scan, the screening CT must be repeated.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol. For this study, peposertib is the investigational intervention, and the study interventions include peposertib, capecitabine, and RT. Peposertib and capecitabine will be administered on an outpatient basis, except on dosing days requiring predose PK samples (Table 4, Table 7).

6.1 Study Intervention(s) Administration

Study interventions are summarized in Table 7.

Table 7 Description of Study Interventions

Study Intervention Name:	Peposertib	Capecitabine
Dose Formulation:	Film-coated tablet	Film-coated tablet
Unit Dose Strengths:	50 mg	150 mg/500 mg
Route of Administration:	Oral	Oral
Dosing Instructions:	Administered at home (except on days requiring predose PK sample), once daily and on RT days only. Take 1 h after meal, and fast 1 h post peposertib intake. On days when predose PK sample is drawn (Fraction Days 1, 2, 9, and 10), dose should be taken at the clinic after the predose PK blood draw. See Section 6.6 for dose selection	Administered at home (except for the morning dose on days requiring predose PK sample) and on RT days only. Take within 30 min after meal (breakfast/dinner). On days when predose PK sample is drawn (Fraction Days 1, 2, 9, and 10), morning dose should be taken at the clinic after the predose PK blood draw. See Section 6.6 for dose selection
CCI [redacted]		
Packaging and Labeling	Study intervention will be provided in aluminum/aluminum blisters. Each blister will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines	Study intervention will be provided as a marketed product. It will be prepared in accordance with its product labeling

PK=pharmacokinetics, RT=radiotherapy.

- Capecitabine is administered as part of the study. General guidance on the use of capecitabine is provided. However, Investigators must follow and instruct participants to follow the package insert, the Product Information, the Summary of Product Characteristics (SmPC), and their site's specific policies/instructions for the final use of capecitabine.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

- Peposertib will be supplied as formulated film-coated tablets intended for ready-to-use oral administration. The aluminum 'ALU/ALU' blisters are used as the container closure system for peposertib film-coated tablets. CCI [redacted]
- The preparation, handling and storage of capecitabine at the study site will be in accordance with its product label. Investigators or assigned staff should instruct participants on proper handling and storage.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

After completion of the study, any study intervention distributed to the site but not administered, dispensed to or taken by the participant will be destroyed at the site. Details will be agreed upon between the Sponsor and the Investigator. All unused medications will be carefully recorded and documented before destruction. The Investigator will ensure the supplied study intervention is not used for any purpose other than this study.

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Any temperature excursion during shipment or damaged receipt must be properly documented in the Interactive Voice/Web Response System (IVRS/IWRS) and the sending site must be informed.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Each study site must ensure that the study intervention(s) is not used:
    - After the expiry date, or
    - After the retest date unless the study intervention is reanalyzed and its release date extended.

  This is to be closely monitored by the study monitor.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study and prepared at the site.
    - The dose(s) each participant used during the study.
    - The disposition (including return, if applicable) of any unused study intervention(s).
    - Dates, quantities, batch numbers, kit numbers, expiry/use-by dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be redispensed to a different participant.

- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Clinical Operations Plan.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

- The IVRS/IWRS will be used to assign unique participant numbers, and study intervention to participants at each study intervention visit.
- Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site. The site will contact the IVRS/IWRS prior to starting study intervention administration for each participant. The site will record the study intervention assignment in the applicable Case Report Form (CRF).

6.3.2 Blinding

Blinding is not applicable as this is an open-label study.

6.4 Study Intervention Compliance

- Acceptable compliance for this study will be defined in the Monitoring Plan.
- Measures to monitor and document participants' compliance with study intervention will include:
    - Patient diaries used to document the dates and times of study intervention administration and to support the participant in planning the correct times to take study intervention(s)
    - Compliance will be captured in the source documents using electronic data capture, reviewed by the study monitor and documented in the Monitoring Report.
- Participants must be withdrawn from the study intervention in the event of noncompliance that is deemed by the Investigator or Sponsor to compromise participant safety or study integrity (Section 7.1 and Section 8.4).
- The following procedures will be used for increasing compliance:
    - Use of patient diaries
    - Regular review of dosing with the participant.

  Further details of procedures used for increasing compliance will be included in the Monitoring Plan.

6.5 Concomitant Therapy

- Adjuvant chemotherapy is allowed during the Long-term Safety Follow-up period if initiated within 1 to 3 months after surgery. The following adjuvant chemotherapies are allowed: FOLFOX and CAPEOX or capecitabine as per NCCN 2019 guidance.
- Drugs mainly metabolized by CYP3A with a narrow therapeutic index are to be used with caution. Examples of drugs are found on the following page: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. The Investigator may decide not to include a participant in the study, if the participant cannot withdraw the drugs that have a narrow therapeutic index and that are known to be metabolized via CYP3A; if the Investigator decides to enroll a participant who is treated with one of these drugs, close safety monitoring is advised.
- Record in the electronic Case Report Form (eCRF) all concomitant therapies (e.g. medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Prohibited Medicines

- Participants must not have received any prior anticancer therapy for locally advanced rectal cancer including experimental agents, except induction chemotherapy. Use of any investigational agent within 28 days prior to the first study intervention administration is prohibited.
- During the treatment period and up to 30 days after last study intervention administration, any other investigational agent, or any other anticancer therapy (i.e. chemotherapy, RT, biologics, other targeted therapy, or immunotherapies) are prohibited. Use of any investigational agent during the entire study duration is not permitted.
- Medications or herbal supplements known to be strong inhibitors or inducers of CYP3A or CYP2C19, are prohibited. A list is provided on the following page: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm, although this list may not be exhaustive.
- The solubility of peposertib is pH dependent; therefore, antacid drugs, H_2-blocker and PPIs might affect absorption. PPIs should be stopped 5 days prior to the first study intervention and avoided during the entire study intervention period. Antacid drugs should not be taken 1 h before and until 2 h after peposertib administration. H_2 blockers may be allowed at least at 2 h after peposertib dose and 1 h after RT dose but it should be stopped at least 4 h before the evening dose of capecitabine and 8 h before peposertib dose in the next morning.
- Capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. Concomitant use of allopurinol with capecitabine should be avoided. Caution is required with concomitant use of leucovorin with capecitabine as per standard practice.

If prohibited concomitant therapy becomes necessary during the treatment period, e.g. due to AEs, the participant should be interrupted for a safe duration of time.

6.6 Dose Selection and Modification

Physician discretion may be used if monitoring or dose modification outside of the guidelines is considered necessary.

If participants vomit after taking their dose of peposertib and/or capecitabine, they should be given an antiemetic but the dose(s) will not be replaced. Prophylactic antiemetics should then be considered prior to subsequent doses of peposertib and/or capecitabine. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

In general, each participant will stay on the peposertib, and capecitabine dose level assigned in the study unless treatment needs to be interrupted, modified or stopped. If peposertib dosing interruptions are necessary, the SMC may decide to start the next cohort at a lower dose level or at a lower dosing intensity (e.g. three times weekly or twice weekly).

If 1 study intervention must be withheld, that study intervention's dose should be skipped rather than delayed, and the other study intervention (capecitabine or peposertib) should be given alone.

If hemoglobin is < 8 g/dL then appropriate measures according to standard clinical practice must be taken prior to any further dose administration.

The SMC will be responsible for dose escalation decisions and will provide input into the selection of a RP2D. Details of SMC decision making processes are provided in Appendix 2. The DLT definition is provided in Section 6.6.1.

6.6.1 Definition of Dose Limiting Toxicity

A DLT is defined as any of the following TEAEs considered possibly related to peposertib and/or capecitabine and/or RT by the Investigator and/or the Sponsor up to completion of the assigned CRT treatment (25 FD or 28 FD) (DLT period). A DLT must be confirmed by the SMC:

1. An adverse drug reaction that, in the opinion of the SMC, is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk

2. Any occurrence of drug-induced liver injury (DILI) meeting the Hy's law criteria (i.e. defined as aminotransferases > 3 × ULN, alkaline phosphatase < 2 × ULN, total bilirubin ≥ 2 × ULN, with no other reason to account for these abnormalities)

3. Any Grade 3 toxicity, excluding:

    a) Diarrhea (< 7 days duration) despite early, adequate and optimal antidiarrhea therapy

    b) Neutropenia lasting for ≤ 5 days and not associated with fever

c) Isolated Grade 3 lymphocytopenia without clinical correlate

d) Grade 3 radiation dermatitis that resolves to Grade ≤ 2 with supportive measures within 5 weeks

e) Nausea and vomiting (< 3 days duration) with adequate and optimal therapy

f) Fatigue or headache (< 7 days duration) following initiation of adequate supportive care

g) Any other single laboratory values out of the normal range that have no clinical significance as confirmed by the Investigator, and that resolve to Grade 2 or less with adequate measures within 7 days

h) Grade 3 thrombocytopenia without bleeding

4. All Grade ≥ 4 AEs at least possibly related to study intervention, irrespective of duration, excluding:

   a) Isolated Grade 4 lymphocytopenia without clinical symptoms

   b) Neutropenia lasting for ≤ 5 days and not associated with fever

5. Any toxicity related to study intervention that causes the participant to receive less than 80% of the planned peposertib, capecitabine or RT dose

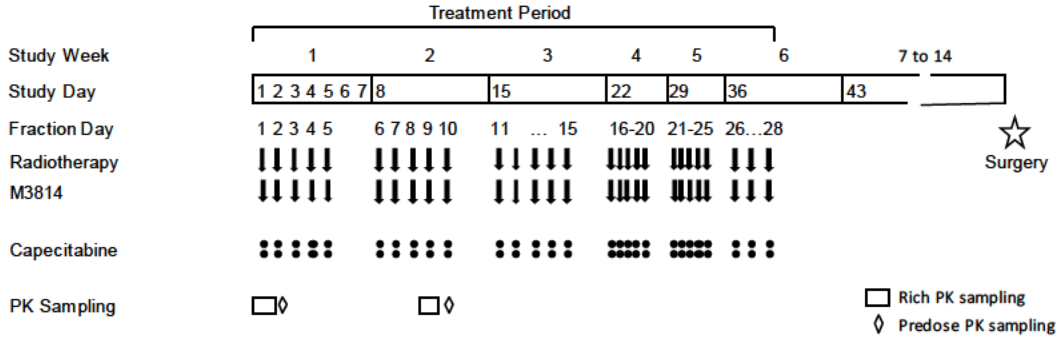
6.6.2 Dosing Instructions

See Table 7.

6.6.2.1 Peposertib

The participants will take peposertib orally once daily in the morning for 5 days a week (on all FDs) throughout the RT course in combination with capecitabine (Figure 3).

Figure 3 **Dosing Schedule for Peposertib, Capecitabine, and Radiotherapy (28 Fraction Days[a])**



PK=pharmacokinetic.
[a]Note: In case of only 25 fraction days, treatment and radiotherapy will stop after 25 fraction days/5 weeks.

Peposertib tablets will be taken orally once daily in the morning, 1.5 h (± 30 min) prior to RT, for 5 days a week (on all FDs) throughout the RT course in combination with capecitabine. Peposertib must be taken after fasting for at least 1 h. Participants must continue fasting for 1 h after administration. The dose of peposertib in the starting cohort is 50 mg. The dose in subsequent cohorts will be determined by the SMC. No intraparticipant dose escalation is permitted.

If new data related to food effect and peposertib administration become available, the SMC may decide to recommend peposertib administration with food or to relax the food intake restriction.

Participants will take their assigned dose of peposertib once daily with a full glass of water (approximately 240 mL or 8 fluid ounces).

The participants will be instructed to swallow the tablets whole.

6.6.2.2 Capecitabine

Capecitabine is to be administered as recommended per current medical guidelines (NCCN 2019, Glynne-Jones 2017) for neoadjuvant treatment of locally advanced rectal cancer. The capecitabine dose is calculated according to body surface area.

Body surface area should be calculated based on established methods, e.g. the Mosteller formula (Mosteller 1987):

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$$

Or in inches and pounds:

$$BSA\ (m^2) = \sqrt{\frac{Height\ (in) \times Weight\ (lbs)}{3131}}$$

If there is a change in body weight of at least 10% from baseline, the individual capecitabine doses should be recalculated. Otherwise the initial body surface area should be utilized for subsequent doses.

Capecitabine will be administered orally at a dose of 825 mg/m^2 twice daily 5 days a week throughout the RT course. The total daily dose, calculated in terms of mg/m^2, will be rounded to the nearest 500 mg, to allow for tablet size, and then divided into 2 doses. If this results in an uneven number of tablets (e.g. 7 tablets daily), then then the larger number will be taken with the morning dose (i.e. 4 tablets in the morning and 3 tablets in the evening). Capecitabine tablets are not to be split.

In addition, participants will be instructed to:

- Take capecitabine tablets in 2 daily doses: a morning dose and an evening dose
- Swallow capecitabine tablets with water within 30 min after a meal (breakfast and dinner).

6.6.2.3 Radiotherapy

Radiotherapy will be given at a total dose of 50 to 50.4 Gy to the tumor area and 45 Gy to the electively irradiated tissues in 25 or 28 fractions, concomitant integrated boost is allowed based on local guidelines (NCCN 2019, Glynne-Jones 2017). Radiotherapy will be given 5 days a week. Radiotherapy will be given using intensity modulated RT or volumetric modulated arc therapy, using gold standard for dose planning and rigorous constraints for organs at risk (OAR). Participants must be treated with fields that at least include the tumor, presacral nodes, mesorectal region, and internal iliac nodes. In addition, quality assurance on the delivered dose and fields will be mandated. Details are provided in Appendix 4.

6.6.2.4 Administration of the Combination Therapy

The regimen for the study consists of once daily administration of peposertib together with capecitabine and RT:

- Capecitabine should be given within 30 min after a meal in 2 daily doses (a morning dose and an evening dose)
- Peposertib should be given 1 h after a meal
- Radiotherapy should be given 1.5 h (± 30 min) after peposertib dosing.

The combination therapy follows the SoC therapy schedule, which is generally administered over 25 or 28 FDs.

6.6.3 Management of Toxicities

Participants should be reviewed at least weekly during CRT when acute toxicity assessments are performed.

The following guidance should be followed for the management of acute toxicity and dose modifications:

- AEs should be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)
- In the event of overlapping toxicities, dose modification should be based on the worst toxicity grade observed.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken in the case report and in the medical notes.
- If a participant experiences a toxicity, then dose modifications should be applied as per protocol, even if the toxicity has resolved by the time the participant is next seen.

6.6.3.1 Diarrhea

It is particularly important to assess and monitor participants who experience diarrhea during CRT. Recommendation for participants who experience diarrhea during concurrent CRT is given in the diarrhea management charter.

6.6.3.2 Capecitabine Management for Toxicities Other Than Diarrhea

Investigators must follow the package insert, the product information, the SmPC, and their site's specific policies/instructions for the final use of capecitabine.

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. Participants taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity will not be replaced.

Hematological Toxicity

Participants with baseline neutrophil counts of $< 1.5 \times 10^9$/L and/or platelet counts of $< 100 \times 10^9$/L should not be treated with capecitabine. If these counts drop during treatment, doses of capecitabine are modified as shown in Table 8.

Table 8 Dose Adjustment for Capecitabine for Absolute Neutrophil Count and/or Platelet Counts

Cell Count	Order of Occurrence	Action	Dose Resumed at (% of Starting Dose)
ANC ≥ 1.0 × 10^9/L and platelets ≥ 75 × 10^9/L		Maintain capecitabine dose	100%
ANC < 1.0 × 10^9/L and/or platelets < 75 × 10^9/L	First occurrence	Interrupt treatment until ANC ≥ 1.0 × 10^9/L and platelets ≥ 75 × 10^9/L	100%
ANC < 1.0 × 10^9/L and/or platelets< 75 × 10^9/L	Second occurrence	Interrupt treatment until ANC ≥ 1.0 × 10^9/L and platelets ≥ 75 × 10^9/L	75%
ANC < 1.0 × 10^9/L and/or platelets < 75 × 10^9/L	Third occurrence	Interrupt treatment until ANC ≥ 1.0 × 10^9/L and platelets ≥ 75 × 10^9/L	50%
ANC < 1.0 × 10^9/L and/or platelets < 75 × 10^9/L	Fourth occurrence	**Discontinue capecitabine treatment**	Not applicable

ANC=absolute neutrophil count.

Nonhematological Toxicity

For nonhematological toxicity due to capecitabine, doses are to be modified in line with Table 9.

Table 9 Dose Adjustment for Capecitabine According to Common Terminology Criteria of Adverse Events Version 5.0 – Nonhematological Toxicity

Order of Occurrence	Grade 2	Grade 3	Grade 4
First Occurrence	Interrupt treatment until resolved to Grade 0/1, then continue at 100% or original capecitabine dose	Interrupt treatment until resolved to Grade 0/1, then continue at 75% or original capecitabine dose	**Discontinue capecitabine treatment**
Second Occurrence	Interrupt treatment until resolved to Grade 0/1, then continue at 75% or original capecitabine dose	Interrupt treatment until resolved to Grade 0/1, then continue at 50% or original capecitabine dose	
Third Occurrence	Interrupt treatment until resolved to Grade 0/1, then continue at 50% or original capecitabine dose	**Discontinue capecitabine treatment**	
Fourth Occurrence	**Discontinue capecitabine treatment**		

Source: EU Summary of Product Characteristics Version 02 February 2006.

6.6.3.3 Peposertib and Radiotherapy

The criteria for peposertib and RT dose modification in the study are included in Table 10.

Table 10 Dose Modifications of Peposertib and Radiotherapy During the Study for toxicities other than Diarrhea

	Dose Modifications	
Toxicity	**Peposertib[a]**	**Radiotherapy[b]**
Toxicities in Radiation Field Grade 4		
• Radiation dermatitis.	Temporarily interrupt peposertib. Resume treatment once severity resolves to Grade ≤ 3. Maximum delay of up to and including 7 days; otherwise permanently discontinue study intervention.	Temporarily interrupt treatment. Resume treatment once severity resolves to Grade ≤ 3 and dose distribution may be adjusted to spare skin.
Systemic Toxicities		
Hematologic Toxicities: Any Grade ≥ 3 toxicity, excluding: • Neutropenia lasting for ≤ 5 days and not associated with fever • Isolated Grade 4 lymphocytopenia without clinical correlate • Grade 3 thrombocytopenia without bleeding.	Temporarily interrupt peposertib. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or baseline. Maximum delay of 7 days; otherwise permanently discontinue peposertib. If there is a second recurrence at the same grade, permanently discontinue peposertib.	No action to be taken.
Nonhematologic Toxicities: Any Grade ≥ 3 toxicity, excluding: • Nausea and vomiting (< 3 days duration) with adequate and optimal therapy • Fatigue or headache (< 7 days duration) following initiation of adequate supportive care • Any other single laboratory values out of the normal range that have no clinical significance, and that resolve to Grade ≤ 2 with adequate measures within 7 days. Treatment-related hepatocellular damage for more than 3 days, such as Grade ≥ 3 ALT or AST with or without elevation of serum total bilirubin to > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) or other apparent clinical causality.	Temporarily interrupt peposertib. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or baseline. Maximum delay of 7 days; otherwise permanently discontinue study intervention. If there is a second recurrence, permanently discontinue peposertib. If Grade ≥ 3 liver enzyme values, the participant must be monitored at least every 4 days until recovery to Grade ≤ 2.	No action to be taken.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal.

a As all treatments with peposertib will be given in combination with radiotherapy, an interruption in the administration of radiotherapy would lead to an interruption in treatment with peposertib.

b A maximum radiotherapy delay of up to and including 7 days in total is allowed within the complete treatment period. If radiotherapy and peposertib treatment have to be delayed by more than 7 days, the participant must be discontinued from peposertib.

Severity of adverse events will be graded using the Common Terminology Criteria for Adverse Events (version 5.0) toxicity grades.

6.6.3.4 Radiotherapy Treatment Delay

Within this study, a maximum delay of up to and including 7 days in total is allowed within the complete Treatment period (Table 10). If RT and study intervention must be delayed by more than 7 days, the participant must be permanently discontinued from study intervention.

As all treatments with peposertib will be given in combination with RT, an interruption in the administration of RT would lead to an interruption in treatment with peposertib. Capecitabine can be continued or discontinued according to local guidelines.

If a participant misses RT administration, then the missed RT day will be made up (i.e. the missed RT dose is not skipped); participants should receive a total of 25 or 28 RT fractions.

6.7 Study Intervention After the End of the Study

After a participant has completed the study or has withdrawn prematurely, usual treatment will be administered, if required, in accordance with the study site's SoC and generally accepted medical practice and depending on the participant's individual medical needs.

6.8 Special Precautions

- Participants should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders according to local guidelines.
- Caution should be exercised with the intake of anticoagulants, phenytoin and/or leucovorin, and of drugs mainly metabolized by CYP3A with a narrow therapeutic index.
- Care should be exercised when capecitabine is coadministered with CYP2C9 substrates, e.g. phenytoin. Participants taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Participants taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (prothrombin time or international normalized ratio) and the anticoagulant dose adjusted accordingly.
- Capecitabine dosing should be discontinued in the event of severe mucocutaneous reactions. Capecitabine dosing should be interrupted in the event of hand-and-foot syndrome, hyperbilirubinemia, and low neutrophil or platelet counts.

Further details of special precautions for capecitabine are available in the Product Information/SmPC.

See Section 5.3.1 for dietary restrictions.

6.9 Management of Adverse Events of Interest

For peposertib no AEs of special interest have been defined so far. Specific toxicities identified during the conduct of the study will be closely monitored and specific instructions for monitoring and management of expected toxicities will be incorporated into the protocol and the Investigator's

Brochure. When further safety data for this study intervention combination become available, risk assessment and mitigation activities will be reviewed to assess the continued appropriateness.

The management of toxicity due to capecitabine administration is described in Section 6.6.3.2.

Toxicities related to RT will be managed according to the local institute's guidelines.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

The participant must be withdrawn from the study intervention in the event of any of the following:

- Therapeutic failure requiring urgent additional medication, such as administration of new anticancer therapy that is considered more suitable according to the Principal Investigator
- Discontinuation of RT if participant is unable to tolerate < 80% of the planned RT dose
- Adverse events that cause RT delays of > 7 days
- Occurrence of AEs, if discontinuation of study intervention is desired or considered necessary by the Investigator, or if after temporary treatment interruption the AE does not resolve or worsens in severity
- Pregnancy of participant
- Prohibited concomitant therapy (as defined in Section 6.5.1) where the predefined consequence is withdrawal from the study intervention
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise participant safety or study integrity.

The SoA (Section 1.3) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed. Participants who discontinue study intervention must be followed on study including completion of study assessments, including at minimum tumor assessments until disease progression, until resolution of toxicity or discontinuation from study.

7.1.1 Temporary Discontinuation

Formal criteria for the dose modification, including temporary interruption where applicable, for capecitabine are provided in Section 6.6.3.2, and for peposertib and RT are provided in Section 6.6.3.3.

7.1.2 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator must document this in the site study records.

Participants should be explicitly asked at time of discontinuation of study if they would allow survival information to be collected including verification of medical/public records as permitted by local regulations. These responses should accordingly be captured in the participant's source data and reported in the eCRF accordingly.

The SoA (Section 1.3) specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

Participants who are discontinued/withdrawn from the study will not be replaced.

7.3 Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (Section 1.3).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (e.g. blood count) and obtained before signing of the ICF may be used for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- Regarding the visits from Week 7 to 14 during the short-term safety follow-up (Table 1). The Week 14 visit is mandatory as this is needed for restaging and evaluation. All other visits in this period are optional and needed only in case of acute toxicities until recovery to Grade 1 or baseline.
- A maximum of 255 mL of blood will be collected in any one-month period from each participant in the study, including any extra assessments that may be required.

Screening:

Participants will be screened between Days -28 and -1, prior to first dosing on Day 1. Assessments and procedures to be performed at Screening are detailed in the SoA (Section 1.3). Screening-specific procedures include:

- **Demography:** date of birth, sex (gender), race, and ethnicity.
- **Medical history:** disease history, previous illness and surgeries (e.g. all during the past year and only major ones prior to that), concomitant illness, relevant medication, allergies, therapies stopped or changed at entry into the study, tobacco use including pack years, and alcohol use.
- **Eastern Cooperative Oncology Group Performance Status:** assessed at Screening to assess eligibility (Section 5.1) and then assessed according to the SoA (Section 1.3).
- **Chest-abdominal computerized tomography (CT):** A CT scan of the chest and abdomen will be performed prior to the beginning of study intervention to document the baseline status of the participant. Computerized tomography will be performed with intravenous iodinated contrast unless contraindicated. Evaluation up to 28 days prior to start of study intervention is allowed.

In the case of a rescreen and the screening CT scan is > 28 days from the previous screening scan, the screening CT will need to be repeated.

- **DRE and endoscopy (and EUS if indicated or if performed):** for participants who have received induction chemotherapy prior to start of study

Surgery

Participants will undergo surgery using TME 15 weeks (± 14 days) after start of RT according to a standardized technique, unless there are contraindications for surgery (Ridgway 2003, Parfitt 2007), if the participant refuses, or if the participant has a cCR and is eligible for organ preservation.

The choice of the surgical procedure, abdominoperineal resection or low anterior resection, is at the surgeon's discretion. Further details will be described in a dedicated surgical charter.

8.1 Efficacy Assessments and Procedures

8.1.1 Pathological Complete Response

The pathologic specimens after TME will be evaluated using standard pathological guidelines as described in the Appendix 6. All surgical and pathology reports for the TME resection must be submitted.

The American Joint Committee on Cancer (AJCC) 8th edition (Amin 2017) will be used to categorize the completeness of the TME resection.

Reports must contain information about microscopic involvement and surgical resection margins. If there is residual macroscopic tumor, standard pathological examination will be carried out with 3 to 5 sections to investigate the deepest invasion in the bowel wall. If no macroscopic tumor is present and only a small ulcer is observed, the ulcer with a 2 cm margin will be examined for residual tumor and deepest invasion in the bowel wall. All lymph nodes will be examined according to standard procedures and the circumferential resection margin (CRM) will be measured (Washington 2009). The status of the surgical CRM will be defined as involved if there is tumor within 1 mm of the CRM.

The extent of residual tumor in the resected specimen will be classified according to the Tumor Node Metastases staging system of the 8th edition AJCC, with the prescript "y" to indicate that the tumor had been treated before surgical resection. After preoperative CRT, residual tumor masses will be semi-quantitatively evaluated according to the 4-point regression grading scale Modified Ryan scheme for tumor regression score (see Appendix 6).

A pCR will be defined as the absence of viable tumor cells in the primary tumor and lymph nodes (ypT0N0).

Standard data on pathology, completeness of resection, and the response to neoadjuvant chemotherapy will be collected. The slides will be locally reviewed to record whether there was

macroscopic clearance of the tumor. Assessments of the pathology must be according to international guidelines and will be further described in Appendix 6.

8.1.2 Tumor Evaluation Methods and Response Assessment

Rectal cancer staging, and measurement at baseline and after chemoradiation should be performed as per NCCN Guidelines for Patients Rectal Cancer 2019. For participants who received induction treatment the baseline assessments will be based on MRI, endoscopy and DRE and biopsy, if required. For participants without induction treatment, the baseline assessment will consist of MRI only. For all participants the assessments after chemoradiation (Week 14) will include MRI, endoscopy and DRE and biopsy, if required. This is all based on a modification of tumor evaluation as described by Maas 2015. Tumor assessments done during long-term Safety Follow-up will only include MRI (T_2 weighted and diffusion weighted) or CT scans (Table 1 and Table 2).

Baseline assessments are to be taken not earlier than 4 weeks prior to study intervention start/randomization. After study intervention start/randomization, tumor assessments will be performed at 14 weeks (± 7 days) after study intervention start/randomization (i.e. before surgery) and 27 weeks (± 2 week) after study intervention start/randomization, every 3 months thereafter (± 2 weeks) until 1 year after study intervention start/randomization.

8.1.2.1 Evaluation Methods

MRI: A standard and diffusion-weighted MRI sequences will be obtained in 1.5T or 3T units by using a phased array body coil. All images will be interpreted by expert radiology staff at the participant primary treatment center for participant eligibility, clinical staging, according to standard clinical criteria, including extramural vascular invasion and CRM assessment. For all participants, evaluation up to 28 days prior to start study intervention/randomization is allowed.

If induction chemotherapy was given, an MRI must be done to evaluate tumor changes after chemotherapy. It should be done as described above and within 2 weeks after the last day of chemotherapy but before starting study intervention/randomization.

Endoscopy with photography: Is to be done along with DRE and MRI. The length of the tumor is defined as the difference between the distance of the proximal and distal margins of the lesion in relation to the anal verge.

If participant received induction chemotherapy, endoscopy will be performed 2 weeks (± 14 days) after the last day of chemotherapy but before starting study intervention/randomization to evaluate tumor changes after chemotherapy.

Digital Rectal Exam: If the tumor cannot be reached on digital rectal exam, this should be noted on the checklist and evaluation. The digital rectal exam criteria are applicable to participants with palpable tumor only.

In case induction chemotherapy was given, a DRE must be done to evaluate tumor changes after chemotherapy. It should be done within 2 weeks (± 14 days) after the last day of chemotherapy but before starting study intervention/randomization.

Biopsy: Only to be done during the endoscopy if required and as per institutional guidelines.

8.1.2.2 Tumor Response Evaluation

After induction chemotherapy: Response evaluation after induction chemotherapy and restaging before study intervention with peposertib and CRT are provided in Appendix 5. The evaluation with MRI, endoscopy, and DRE is to be done before starting treatment/randomization (peposertib and CRT). Overall response is evaluated as progressive disease, stable disease, partial response, nearly complete response, or complete response. Participants who present with stable disease, partial response, or nearly complete response may enter the study, participants who present with tumor progression or cCR should be treated according to standard practice per institutional guidelines.

After peposertib and CRT: Response evaluation criteria after treatment and restaging before surgery are provided in Appendix 5. The evaluation with MRI, endoscopy, and DRE is to be done at Week 14 (± 7 days). Overall response is evaluated as progressive disease, incomplete response, nearly complete response, or complete response.

During Long-term Safety Follow-up: Response evaluation is provided in Appendix 5.

If a scan shows progressive disease, it will be indicated whether it is local recurrence, distant recurrence, or both.

Tumor assessments are performed until progressive disease or the participant withdrawal of consent. Tumor assessments will be stopped on subsequent start of new anticancer therapy, with the exception of starting adjuvant treatment described in Section 6.5.

8.1.2.3 Neoadjuvant Rectal Score

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.

The NAR formula 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 formula is as follows:

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

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, and laboratory tests.

The safety observation is divided into the following periods:

- **Baseline:** safety evaluation before the initiation of study intervention
- **Treatment Period:** during study intervention
- **Short-term Safety Follow-up:** evaluations after the Treatment Period, including the perioperative and postoperative observation (until Week 19)
- **Long-term Safety Follow-up:** up to 1 year.

Participants who have already been followed up for more than 1 year (Long-term Safety or Survival Follow-up) will be discontinued from the study after the approval of protocol amendment version 4.0 by the respective Health Authority and Ethics Boards.

Frequency of visits and specific procedures are described in Table 1 and Table 2.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

8.2.1 Physical Examinations

A complete physical examination will be performed at Screening and a brief physical examination will be performed at all other time points indicated in the SoA (Section 1.3).

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height (at Screening) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Investigators will report findings in the irradiated area during the Short- and Long-term Safety Follow-up periods.

For participants with a change in body weight of at least 10% from baseline, individual capecitabine doses should be recalculated. See Section 6.1 for details.

8.2.2 Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 min of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 min). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3 Electrocardiograms

Digital ECGs for all participants will be recorded at the site. Triplicate ECGs will be obtained for participants according to the Schedules of Activities (Table 1).

Electrocardiograms will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the participant. The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided if the abnormality is clinically significant or not clinically significant and the reason for the abnormality will be recorded on the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

- In woman of childbearing potential, pregnancy testing (serum β-human chorionic gonadotropin) will be performed at the visits specified in the SoA (Section 1.3). Participants after menopause (age-related amenorrhea ≥ 12 consecutive months) or participants who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.
- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 8, at the time points listed in the SoA (Section 1.3). All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor or designated organization.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- Analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Nonfasting blood samples are acceptable for this study.

See Appendix 8 for a full list of clinical laboratory assessments that will be performed. Further details will be provided in the Laboratory Manual.

8.2.5 Suicidal Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a serious adverse event (SAE) are in Appendix 7.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the final assessment at 1 year. Any AE assessed as not related to study intervention will be recorded only up to the short-term safety follow-up period. Any AE assessed as related to study intervention will be recorded up to resolution or permanent outcome, irrespective of the time elapsed since the last administration of study intervention.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 7, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention. Any SAE assessed as not related to study intervention must be recorded and reported, as indicated in Appendix 7, only up to Week 27 in the long-term safety follow-up period.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 7.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 7.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the final assessment at 1 year. All SAEs ongoing at the final assessment at 1 year must be monitored and followed-up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is

also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 7 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g. resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the CRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 7, section on Reporting Serious Adverse Events, Adverse Events of Special Interest, and Dose Limiting Toxicities.

Investigators must actively follow-up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose of peposertib greater than 100% of the planned dose will be considered an overdose.

The Sponsor does not recommend specific treatment for an peposertib overdose. The Investigator should use clinical judgment to manage any overdose considering the presenting symptoms and standard evaluation results.

For this study, any dose of capecitabine greater than 100% of the planned dose will be considered an overdose.

Overdose of capecitabine generally results in severe forms of normally occurring adverse reactions. Investigators are asked to check the respective information in the Product Information/SmPC for further advice.

Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 7, section on Reporting Serious Adverse Events, Adverse Events of Special Interest, and Dose Limiting Toxicities.

8.5 Pharmacokinetics

- The following PK parameters will be calculated, when appropriate:

Symbol	Definition
C_{max}	Maximum observed concentration.
T_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the first occurrence if multiple/identical C_{max} values).
AUC_{0-t}	The AUC from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
AUC_{0-24}	The AUC from time zero (= dosing time) to 24 h post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) to infinity post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
$T_{1/2}$	Apparent terminal half-life. $T_{1/2} = \ln(2)/\lambda z$

Symbol	Definition
CL/f	The apparent total body clearance of study intervention following extravascular administration on FD1, taking into account the fraction of dose absorbed. CL/f = Dose p.o./$AUC_{0-\infty}$. The predicted $AUC_{0-\infty}$ should be used.
Vz/f	The apparent volume of distribution during the terminal phase following extravascular administration, based on the fraction of dose absorbed. V_z/f = Dose/($AUC_{0-\infty}$*λ_z) following single dose. V_z/f = Dose/(AUC_{τ}*λ_z) following multiple dose.
$R_{acc}(C_{max})$	The accumulation factor to assess the increase in maximum concentration from FD1 to FD9. $R_{acc}(C_{max})$ = (C_{max} FD9)/(C_{max} FD1).
$R_{acc}(AUC_{0-24})$	The accumulation factor to assess the increase in exposure from FD1 to FD9 during time 0 to 24 h. $R_{acc}(AUC_{0-24})$ = (AUC_{0-24} FD9)/(AUC_{0-24} FD1).
$R_{acc}(AUC_{0-t})$	The accumulation factor to assess the increase in exposure from FD1 to FD9 during time 0 to t h. $R_{acc}(AUC_{0-t})$ = (AUC_{0-t} FD9)/(AUC_{0-t} FD1).
LI	The linearity index after repeated administration calculated as LI= (AUC_{0-24} after multiple dose (at steady state)) / ($AUC_{0-\infty}$ after single dose)

AUC=area under the concentration-time curve, FD=fraction day.

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of peposertib (and/or metabolites), capecitabine, and capecitabine metabolites. Collection times are specified in the SoA (Table 4). PK sampling should be performed within ± 10 min for the first 2 h of sample collection, within ± 20 min for the 3 h and 4 h sample, and within ± 30 min for the 6 h sample. The predose sample(s) should be collected prior to capecitabine and peposertib administration but within 60 min prior to the peposertib administration. A maximum of 3 samples per participant may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24 h clock time) of each sample will be recorded to calculate actual time elapsed since prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The quantification of peposertib, capecitabine and capecitabine metabolites in plasma will be performed using a validated liquid chromatography-tandem mass spectrometry method. Concentrations will be used to evaluate PK of peposertib (and/or metabolites) and capecitabine.
- Remaining samples collected for analyses of peposertib and capecitabine (whole blood) concentration may also be used to evaluate safety and efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

All analyses will be described in detail in the Integrated Analysis Plan.

9.1 Statistical Hypotheses

No formal statistical hypothesis tests will be performed, as the study is designed to be exploratory. Any p-values indicated are to be considered exploratory.

9.2 Sample Size Determination

A Bayesian 2-parameter logistic regression model with overdose control is applied to assist the SMC in dose recommendations. The planned cohort size is 3 participants. The total sample size will depend on the number of cohorts to be evaluated. It is anticipated that 18 to 30 evaluable participants are required.

9.3 Populations for Analyses

The analysis populations are specified below (Table 11).

Table 11 Definition of Populations

Population	Description
Enrolled	All participants who sign informed consent.
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. 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.
FAS/SAF	The FAS/SAF will include all participants who are enrolled in the study and received at least 1 dose of study intervention.
PK	The PK Analysis Set is defined as all participants who receive at least 1 dose of peposertib and have at least 1 quantifiable plasma concentration at a scheduled PK time point postdose.

cCR=Clinical Complete Response, DE=Dose Escalation, DLT=dose limiting toxicity, FAS=Full Analysis Set, PK=Pharmacokinetic, RT=radiotherapy, SAF=Safety.

9.4 Statistical Analyses

The following statistics will be used to summarize the study data (e.g. Baseline characteristics) unless otherwise specified:

- **Continuous variables:** number of nonmissing observations, mean, standard deviation, median, minimum, and maximum, 95% CIs for the mean, as appropriate.
- **Categorical variables:** frequencies and percentages.

9.4.1 Efficacy Analyses

Statistical analysis methods for efficacy endpoints are described in Table 12.

Table 12 Statistical Analysis Methods for Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Secondary	
Composite endpoint of pCR/cCR	Derivation of the pCR/cCR composite endpoint (pCR based on local review) is described in Section 3.1. The proportion of participants with pCR/cCR is indicated together with the 95%-Clopper-Pearson CI. The analysis will be performed on the FAS.
Disease-Free Survival	Disease-free Survival time, defined as the time from first treatment day to the date of the first documentation of objective progressive disease or death due to any cause, whichever occurs first. The analysis will be performed as described below for time-to-event endpoints.
pCR	The definition of pCR is provided in Section 3.1. 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. The analysis will be performed on the FAS

Endpoint	Statistical Analysis Methods
cCR	The definition of cCR is provided in Section 3.1. The proportion of participants with cCR will be reported together with the corresponding 95% CIs. The analysis will be performed on the FAS
Local/distant recurrence	The following analyses will be performed: • Time from surgery to local recurrence • Time from surgery to distant recurrence. The analyses will be performed as described below for time-to-event endpoints.
Neoadjuvant Rectal Score	The neoadjuvant rectal score will be presented in terms of summary statistics (such as mean, median, standard deviation, and quartiles) and graphically. The analysis will be performed on the FAS Population.

cCR=Clinical Complete Response, CI=confidence interval, CR=complete response, FAS=Full Analysis Set, pCR=Pathological Complete Response.

In addition to analyses specified in Table 12, for the primary and main secondary endpoints subgroup analyses on baseline variables such as gender, tumor stage, etc. will be performed.

Analysis of Time-to-event Endpoints

Kaplan-Meier estimates will be presented 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 1982) and CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch 1980). The estimate of the standard error will be computed using Greenwood's formula.

9.4.2 Safety Analyses

Statistical analysis methods for safety endpoints are described in Table 13.

Table 13 Statistical Analysis Methods for Safety Endpoints

Endpoint	Statistical Analysis Methods
Primary	
Occurrence of DLTs	The number and proportion of participants experiencing a DLT confirmed by the SMC during the DLT period will be reported by dose level. Analysis will be based on the DE Analysis Set.
Secondary	
Occurrence of TEAEs and treatment-related AEs according to the CTCAE version 5.0	All AEs will be coded according to the MedDRA, version 21.0 or higher. The severity of AEs will be graded using NCI-CTCAE v5.0 toxicity grades. Adverse events related to study intervention will be defined as any AE considered related to any study intervention. In addition, missing classifications concerning study intervention relationships will be considered related to the study intervention(s). Adverse events observed from the first dose until 30 days after last study intervention administration (i.e. TEAEs) will be summarized according to MedDRA system organ classes and preferred terms. The incidence and type of the following will be analyzed: • TEAEs and SAEs • TEAEs and SAEs related to study intervention • TEAEs with NCI-CTCAE Grades ≥ 3 • TEAEs related to study intervention with NCI-CTCAE Grades ≥ 3 • AEs leading to withdrawal, dose modifications, or permanent study intervention discontinuation • Deaths and reasons for death will be tabulated. In addition, deaths within 30 days from last dose administration and deaths beyond this period up to 90 days follow-up and reasons for death will be tabulated. Analyses will be based on the Safety Analysis Set.
Occurrence of abnormalities (Grade ≥ 3) in laboratory test values and markedly abnormal vital sign measurements, and clinically significantly abnormal ECGs including clinically important increases in QT interval (QTcF)	Laboratory results will be classified by grade according to NCI-CTCAE v5.0. The worst on-study grades after the first study intervention will be summarized. Shifts in toxicity grades from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits. Only participants with postbaseline laboratory values will be included in these analyses. Physical examination, including vital signs (body temperature, respiratory rate, pulse rate, and blood pressure), and 12-lead ECG, recorded at baseline and after administration of study intervention. Analyses will be based on the Safety Analysis Set.

AE=adverse event, DLT=dose limiting toxicity, ECG=electrocardiogram, MedDRA=Medical Dictionary for Regulatory Activities, NCI-CTCAE=National Cancer Institute Common Terminology Criteria of Adverse Events, SAE=serious adverse event, SMC=Safety Monitoring Committee, TEAE=treatment-emergent adverse event.

Analyses for SMC Meetings:

During dose escalation the analysis will focus on safety and available PK data.

The Bayesian escalation approach will be applied to assist the SMC in the choice of the next dose level. The SMC will receive results of a Bayesian 2-parameter dose-toxicity model with overdose control, updated with the observed DLT data. The recommended next dose level will minimize the Bayesian Risk among all considered dose levels, while at the same time limiting the risk of overdose or excessive toxicity (Neuenschwander 2008). The target toxicity is 30%. Details of the model including the prior distribution and toxicity regions are described in Appendix 10.

The following peposertib dose levels will be considered for escalation decisions: 30, 50, 100, 200, 400, 600, and 800 mg; 50 mg is the starting dose. Dose increases will not exceed 100% of the highest dose level considered safe at the time of escalation decision. The SMC may decide to deviate from the suggestion of the Bayesian escalation approach. Also, the SMC may decide to change the dosing regimen. In such a case the model will be extended, or a separate model will be set up.

Analyses for the Bayesian dose escalation will be performed on the DE Analysis Set. Usually decisions on dose escalation are taken once all participants of the most recent cohort have completed the DLT period or dropped out. In exceptional cases, however, the SMC may decide on the next cohort earlier, i.e. before the last participant of a cohort has finished the DLT period (considering the model recommendation and risk of overdose). Per definition of the DLT analysis, participants who have not completed the DLT period are not included for update of the model, unless they experienced a DLT. However, such participants will be included at next SMC (if criteria for the DE Analysis Set are fulfilled).

Details on analyses for SMCs/CSR will be described in the corresponding SAP.

9.4.3 Other Analyses

Baseline Characteristics

Baseline characteristics will be tabulated as described in Section 9.4.

The PK, CCI [redacted] analyses will be specified in the Integrated Analysis Plan finalized before database lock. Integrated analyses across studies, such as the population PK analysis CCI [redacted] will be presented separately from the main CSR.

CCI [redacted]

9.4.4 Sequence of Analyses

The following analyses will be performed:

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.

The cut-off for the primary analysis of the safety and preliminary antitumor activity data from the complete dose escalation will be triggered 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.

Additional analyses might be performed, e.g. for publication purposes.

Follow-up analyses to report further efficacy and safety data will be done at the End of Study.

More details will be described in the Integrated Analysis Plan.

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11 Appendices

Appendix 1 Abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
ATP	Adenosine triphosphate
cCR	Clinical Complete Response
CI	Confidence interval
CRF	Case Report Form
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CSR	Clinical Study Report
CT	Computerized tomography
CTCAE	Common Terminology Criteria of Adverse Events
ctDNA	Circulating tumor DNA
CTV	Clinical target volume
CYP	Cytochrome
DLT	Dose limiting toxicity
DNA-PK	DNA-protein kinase
DRE	Digital rectal examination
DSB	Double-strand break
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EUS	Endoscopic ultrasonography
FD	Fraction day
Gy	Gray
GCP	Good Clinical Practice
HRT	Hormonal replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IR	Ionizing radiation

IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NAR	Neoadjuvant rectal score
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OAR	Organs at risk
pCR	Pathological Complete Response
CCI	CCI
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PTV	Planning target volume
QoL	Quality of life
RP2D	Recommended Phase II dose
RT	Radiotherapy
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TME	Total mesorectal excision
ULN	Upper limit of normal
5FU	5-fluorouracil

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

- The Investigator will complete the participant registration using the IVRS/IWRS (Section 6.3.1). If the participant meets all inclusion criteria and does not meet any of the exclusion criteria, the participant will be registered by IVRS/IWRS. If the participant is ineligible for the study, a participant number will be allocated and documented.

Study Administrative

This clinical study will be sponsored by Merck KGaA, Germany (in all countries except the USA and Canada) and EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), USA, for sites in the USA and Canada.

Site and country selection will be based on historic enrollment data and the results of a feasibility assessment. It is planned to open the dose escalation part in approximately 10 sites in the US and Europe. Sites will include clinical centers and academic centers, mostly in an outpatient setting.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the CSR.

The study will appear in the following clinical studies registries: EudraCT (2018-002275-18) and ClinicalTrials.gov.

An SMC will be formed in this study and will review all available safety data on a regular basis during the study. The SMC consists of Sponsor representatives (including, but not limited to the Medical Responsible, the Patient Safety Strategy Lead, the Biostatistician, and the PK expert) and Investigators. The Medical Monitor from the Contract Research Organization will be a SMC member.

The SMC will be responsible for dose escalation decisions, continuous safety assessment, and will provide input into the selection of a RP2D. The full membership, mandate, and processes of the SMC will be detailed in the SMC charter.

After each cohort has finished the peposertib treatment period (DLT period), the SMC will review the safety, tolerability, and PK data and will provide recommendations for the next cohort, move to the next dose level, stay on the actual dose level, de-escalate to a lower dose level, or explore alternative schedules of peposertib. In addition, the SMC will review safety, tolerability, and PK data when each cohort has finished the 30-day follow-up period after surgery to provide further recommendations on dose escalation.

Details of structures and associated procedures will be defined in separate SMC charters.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
    - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations.
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e. changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
    - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
    - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes provision of a 24-h contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with

the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator, and other relevant committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- Procedures for publication planning and the use of professional writers are not yet known. Questions may be directed to the Sponsor Medical Responsible.

Dissemination of Clinical Study Data

After completion of the study, a CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3, and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the

information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

- All participant study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Clinical Operations Manual and the Data Management Guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the

following demographic and medical information for the participant, and should be as complete as possible:

- Participant's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e. the Sponsor's study number) and participant's study number
- Dates of entry into the study (i.e. signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

- All source data must be filed (e.g. CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator, and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the eCRF guidelines.

Study Start and Site Start and Closure

First Act of Recruitment

- The first act of recruitment **is the signing of the ICF** and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:

  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound.

- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A woman of childbearing potential is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.
3. A postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

Implantable progestogen-only hormone contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion
Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a woman of childbearing potential and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  Oral
  Intravaginal
  Transdermal
  Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  Oral
  Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, male condoms must be used in addition to hormonal contraception.". If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 4 Radiation Therapy

Radiation therapy general techniques

Linear accelerators with a minimum energy of 6MV photons will be used. A multiple-field technique using intensity modulated RT is highly recommended. Radiation will be delivered 5 business days/week, once per day, at 1.8 Gy/day.

Radiation simulation and immobilization

Prior to RT, simulation utilizing CT-based planning with ≤ 3 mm slice thickness will be performed. If possible, participants will be treated in the prone position on a belly board. If prone positioning is not tolerable for the participant, the supine position should be considered but with full bladder technique, if tolerable (participants drink 500 mL of water 1 h prior to scanning and 1 h prior to daily treatment). A suitable immobilization device (such as Aquaplast mold or Alphacradle) should be used with supine positioning.

Oral contrast is recommended to help aid in the identification of the small bowel.

Intravenous contrast can be administered to participants without contrast allergy or compromised kidney function, depending on the clinical scenario.

A radio-opaque marker should be placed at the anal verge.

Contouring and target volume delineation

The following areas should be contoured:

- GTV-P→ primary gross tumor volume
- GTV-N→ nodal gross tumor volume
- Clinical target volume (CTV) (50 or 50.4)→ should include the gross tumor volume (GTV) with up to a 2 to 3 cm superior and inferior margin including the entire rectum, mesorectum, and presacral space.
- CTV45→ should include the entire rectum, mesorectum, perirectal nodes, presacral nodes, internal iliac nodes, and common iliac nodes below the L5-S1 junction.
  - In participants with T4 disease with anterior involvement of an adjacent organ (i.e. prostate, cervix, bladder, and vagina) the external iliac lymph nodes should be added.
  - In participants with disease within 2 cm of the anal verge the inguinal lymph nodes and external iliac lymph nodes should be added.
- The planning target volume (PTV) 50 or 50.4 and PTV45 will consist of a 5 mm expansion around the CTV: 50.4 or CTV50 and CTV45, respectively, to compensate for inter and intrafraction uncertainly.
- Organs at risk (OAR) should include: cauda equina, anus, rectum, large intestinal, small intestine, vagina, external genitalia, bladder, and femoral heads.

- Involved OARs should be delineated for treatment planning and dose volume histograms documentation.
- The International consensus guidelines on Clinical Target Volume for delineation in rectal cancer (Valentini 2016) provides detailed consensus contouring descriptions that can serve as a guide.

Treatment planning techniques

All treatment planning will be performed with computerized dosimetry and the dose should be prescribed to the isodose line that covers the treatment volume at risk.

- A single intensity modulated RT or a volumetric modulated arc therapy plan may involve 1.8 Gy to PTV45 and 2.0 Gy (111% isodose line) to PTV50 for a total of 25 fractions, if applicable.
- No hot spot of dose above 110% should be accepted beyond PTV.
- Alternatively, the PTV45 and PTV50.4 will initially be treated in 25 daily fractions of 1.8 Gy per fraction with a cone down for an additional 3 fractions for the PTV50.4 in a 3D plan.

Dose constraints for target volumes and organs at risk

Table 14 Dose Constraints for Target Volumes and Organs at Risk

		Organs	
PTV	**Small Intestine**	**Large Intestine (Outside of Rectum)**	**Femur Head**
D_{max} < 110%	D_{max} < 50 Gy	D_{max} < 50	D_{max} < 45 Gy
D95 > 95%	V45 < 30 cc	V45 < 30cc	V45 < 5 cc
	Bladder	**External genitalia**	**Cauda**
	V40 < 35%	V20 < 50%	D_{max} < 50 Gy
	V30 < 50%	V30 < 20%	

D_{max}=maximum diameter, PTV=planning target volume.

Listed above OARs must be delineated if involved in the treated area.

Radiation therapy review/quality control

Within 1 week of starting radiotherapy, simulation and treatment planning data must be submitted to a local Quality Assurance body in line with institutional guidelines including:

- Pretreatment CT and MRI reports and images identifying the location of the primary rectal tumor
- Isodose distributions for the composite treatment plan in the axial, sagittal, and coronal planes.
  - The PTV, isocenter, and normalization method must be clearly indicated.

- Dose volume histograms for the composite treatment plan for all target volumes and required OAR.

During RT, daily image guidance with orthogonal kilovoltage imaging is recommended, but is not required, to ensure patient position alignment during treatment and accurate targeting of the tumor and draining lymph node regions.

Appendix 5 Tumor Response Criteria

Table 15 Response Criteria After Induction Chemotherapy and Restaging Before Chemoradiation - Screening Period

Method	Progressive Disease	Stable Disease or Partial Response	Nearly Complete Response	Complete Response
Endoscopy	Increase in tumor size	Partial response or no change in size	• Irregular mucosa • Small mucosal nodules or minor mucosal abnormality • Superficial ulceration • Mild persisting erythema of the scar	• Flat, white scar • Telangiectasia • No ulcer • No nodularity
Digital rectal exam	Palpable tumor	Palpable tumor	Smooth induration or minor mucosal abnormalities	Normal
MRI-T2W	Increase in tumor size	• No change in extent of T2 scar if present or further regression in thickness of T2 scar or intermediate tumor. • No new immediate signal not thought to be mural edema. • Stable or further decrease in nodal size (no new nodes)	• Mostly dark T2 signal • Some remaining intermediate signal AND/OR • Partial regression of lymph nodes	• Normal appearing bowel wall without any fibrosis in the tumor bed • Only dark T2 signal, no intermediate T2 signal • No visible lymph nodes or very few, small (< 5 mm nodes)

MRI=magnetic resonance imaging.

Participants who present with stable disease, partial response, or near-complete response may enter the study. Participants who present with tumor progression or cCR should be treated according to standard practice per institutional guidelines.

Table 16 Response Criteria After Chemoradiation and Restaging Before Surgery

Method	Progressive Disease	Incomplete response	Nearly Complete Response	Complete Response
Endoscopy	Increase in tumor size	Visible tumor	• Irregular mucosa • Small mucosal nodules • Superficial ulceration • Mild persisting erythema of the scar	• Flat whitish scar • Telangiectasia • No ulcer • No nodularity
Digital rectal exam	Palpable tumor	Palpable tumor nodules	Smooth induration or minor mucosal abnormalities	Normal
MRI-T2W	Increase in tumor size	• More intermediate than dark T2 signal, • no T2 scar AND/OR • No regression of lymph nodes	• Mostly dark T2 signal, • Some remaining intermediate signal AND/OR • Partial regression of lymph nodes	• Normal appearing bowel wall without any fibrosis in the tumor bed. • Only dark T2 signal, no intermediate T2 signal. • No visible lymph nodes or very few, small (< 5 mm nodes)

MRI=magnetic resonance imaging.

All participants, including those not undertaking surgery after chemoradiation are expected to continue loco-regional status evaluation (Table 17, MRI and optional Endoscopy/Digital), until progressive disease, at the frequency described in Section 8.1.2 and the SoA (Table 2) for Long-term Follow-up evaluations (Week 27, thereafter every 3 months in Year 1: Weeks 39 and 52).

Table 17 Response Criteria During Long-Term Safety Evaluation

Method	Progression	Complete Response
MRI-T2W or CT	• Local recurrence AND/ OR • distant recurrence	• No evidence of disease

Appendix 6 Pathology Assessments

- **Grading** of quality and completeness of the mesorectum in a TME

	Mesorectum	Defects	Coning	CRM
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to the muscularis propria	Moderate/ marked	Irregular

- **Definition of surgical margin status**
  - Margin Type

Proximal margins	The proximal surgical margin refers to the most cephalad portion of the specimen (i.e. closest to participants's head)
Distal margins	The distal margin refers to the most caudad portion (i.e. closest to participant's anus)
Radial margins	The radial margin, synonymously termed circumferential margin refers to the outer circumference of the rectal specimen

  - Margin positivity

Positive	A surgical margin is positive if the pathologist notes tumor within ≤1 mm of any edge of the primary tumor specimen
Close	A surgical margin is close if the pathologist notes tumor > 1 but ≤ 3 mm of any edge of the primary tumor specimen
Negative	A surgical margin is negative if the pathologist notes there is no tumor within 3 mm of any edge of the primary tumor specimen

- **Overall completeness of TME resection**
  - The AJCC 8th edition will be used to categorize the completeness of the TME resection.

R0 resection	All gross disease has been removed and microscopic examination reveals all surgical margins free of tumor. This must include the proximal, distal, and radial margin. Tumor > 1 mm from the tumor resection margins is considered R0.
R1 resection	There is evidence of tumor cells at 1 or more surgical resection margin based on microscopic pathologic assessment of the tumor specimen but there is no macroscopic evidence of tumor at any resection margin nor is there macroscopic evidence of residual tumor based on the surgeon's operative report
R2 resection	The surgical pathologist identifies any macroscopic evidence of tumor at any of the surgical resection margins or there is macroscopic evidence of residual tumor based on the surgeon's operative report
No resection	Removal of the primary tumor was not performed

- Pathology TNM staging: After TME resection, participants will be staged according to AJCC 8th edition.
  - T describes how far the main (primary) tumor has grown into the wall of the intestine and whether it has grown into nearby organs. Because this information will be ascertained from the surgical pathology report it is denoted with a prefix "p". Because it is ascertained after neoadjuvant treatment, the prefix "y" is also added (i.e. ypTx).

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propia with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor invades the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through area of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organ or structures

  - N describes the extent of spread to nearby (regional) lymph nodes based on rectal resection specimen. The prefix "yp" is added as described above.

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1a	1 regional lymph node is positive
N1b	2 or 3 regional lymph nodes are positive.
N1c	No regional lymph nodes are positive, but there are tumor deposits in the: • Subserosa • Mesentary • Non-peritonealized pericolic, or perirectal/ mesorectal tissues
N2a	4 to 6 regional lymph nodes are positive.
N2b	7 or more regional lymph nodes are positive.

  - M describes the extent of spread to distant sites outside the pelvis

M0	No distant metastasis outside the pelvis
M1a	Metastasis to 1 site or organ is identified without peritoneal metastasis
M1b	Metastasis to 2 or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastasis

- Pathologic AJCC 8th Edition staging summary

When T is…	and N is…	and M is…	Stage group is
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2b	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVa
Any T	Any N	M1b	IVb
Any T	Any N	M1c	IVc

- **Degree of pathological treatment response**
  - Pathologic treatment response will be based on the assessment of the surgical specimen at the primary treatment site.
  - Modified Ryan scheme for tumor regression score.

Description	Tumor regression score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near-complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

- **Pathological complete response (pCR)**
  - A pCR must include no gross or microscopic tumor identified anywhere within the surgical specimen. This must include both:
    - No evidence of malignant cells in the primary tumor specimen

    AND
    - No evidence of malignant cells in the lymph nodes
- **Pathological response other than a pathological complete response**
  - The definition of non-pCR will include any surgical specimen that has any evidence of residual tumor manifest in the primary or regional lymph nodes

Appendix 7 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE, version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death.

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g. sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other nonstudy interventions, radiation therapy) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g. anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs, AEs of special interest and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g. an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e. undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.2 (Method of Detecting Adverse Events and Serious Adverse Events).

Adverse Events of Special Interest

For peposertib no AEs of special interest have been defined so far. Specific toxicities identified during the conduct of the study will be closely monitored and specific instructions for monitoring and management of expected toxicities will be incorporated into the protocol and the Investigator's Brochure. When further safety data for this study intervention combination will become available, risk assessment and mitigation activities will be reviewed to assess the continued appropriateness.

Recording and Follow-up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT this is documented accordingly.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form in the eCRF following specific completion instructions.

Reporting of SAEs via paper Report Form is required as a back-up method only in case of electronic data capture failure. Names, addresses, and telephone and fax numbers will be included on the paper Report Form. All information reported via paper form must be transcribed into the eCRF as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form must be completed immediately thereafter in the eCRF.

Relevant pages from the CRF may be provided in parallel (e.g. medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g. laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via Study Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Dose Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.6.1, must be recorded in the CRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 8 Clinical Laboratory Tests

Clinical Laboratory assessments are summarized in Table 18.

Table 18 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelets Reticulocytes Hemoglobin Hematocrit		Mean Corpuscular Volume: • MCH	WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Biochemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)	Total Protein
		Chloride		
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Creatinine clearance	Creatine phosphokinase	Lactate dehydrogenase	International normalized ratio
	Magnesium	Phosphorous	Activated partial thromboplastin time	
	Uric acid			
Routine Urinalysis	• pH, glucose, protein, blood, and ketones • Microscopic examination (if blood or protein is abnormal).			
Other Screening Tests	• FSH and estradiol (as needed if not a woman of childbearing potential only) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).			

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, FSH=follicle-stimulating hormone, hCG=human chorionic gonadotropin, MCH=mean corpuscular hemoglobin, WBC=white blood cell.

CCI

[redacted]

Appendix 10 Model for Bayesian Dose Escalation

The Bayesian model will focus on the number of participants experiencing a DLT. The SMC will receive results of a Bayesian 2-parameter logistic regression model with overdose control updated with the observed DLT data (Neuenschwander 2008).

The target toxicity is 30%. Toxicity regions are defined in Table 19.

Table 19 Toxicity Region Definitions

	Probability of DLT	Loss Term (Weight in Loss Function)
Under-dosing	(0.0, 0.20]	1
Targeted toxicity	(0.20, 0.33]	0
Excessive toxicity	(0.33, 0.60]	1
Unacceptable toxicity	(0.60, 1.00]	2

DLT=dose limiting toxicity.

Recommendation on the next dose level by the model is determined as follows:

- Among dose levels that limit the risk of overdose (excessive or unacceptable toxicity) to a maximum of 25% (i.e. the 75% quantile of the estimated DLT risk at the dose level is equal to or below the lower threshold for excessive toxicity of 33%),
- Select the dose level that minimizes the loss function. The loss function is defined as the sum of products of the probability to lie within each of the toxicity regions, and the associated loss term:

$$P(under\text{-}dosing) \times 1 + P(targeted\ toxicity) \times 0 + P(excessive\ toxicity) \times 1 + P(unacceptable\ toxicity) \times 2$$

Furthermore, dose increases must not exceed 100% of the highest dose level considered safe at the time of the escalation decision.

The set of potential dose levels is (30 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg); however, it may be changed at any time by the SMC. The starting dose is 50 mg.

The SMC will be notified once the estimate for DLT probability of the MTD reaches sufficient precision, i.e.:

- The probability that the MTD is above highest planned dose level is > 90%,
- the probability (target toxicity) > 90%,
- or the upper bound of the 95% credible interval is lower than 40%.

The 2-parameter logistic regression model will be set up as follows:

For a dose level d_j, the relationship between dose and probability of toxicity P(DLT) is defined by:

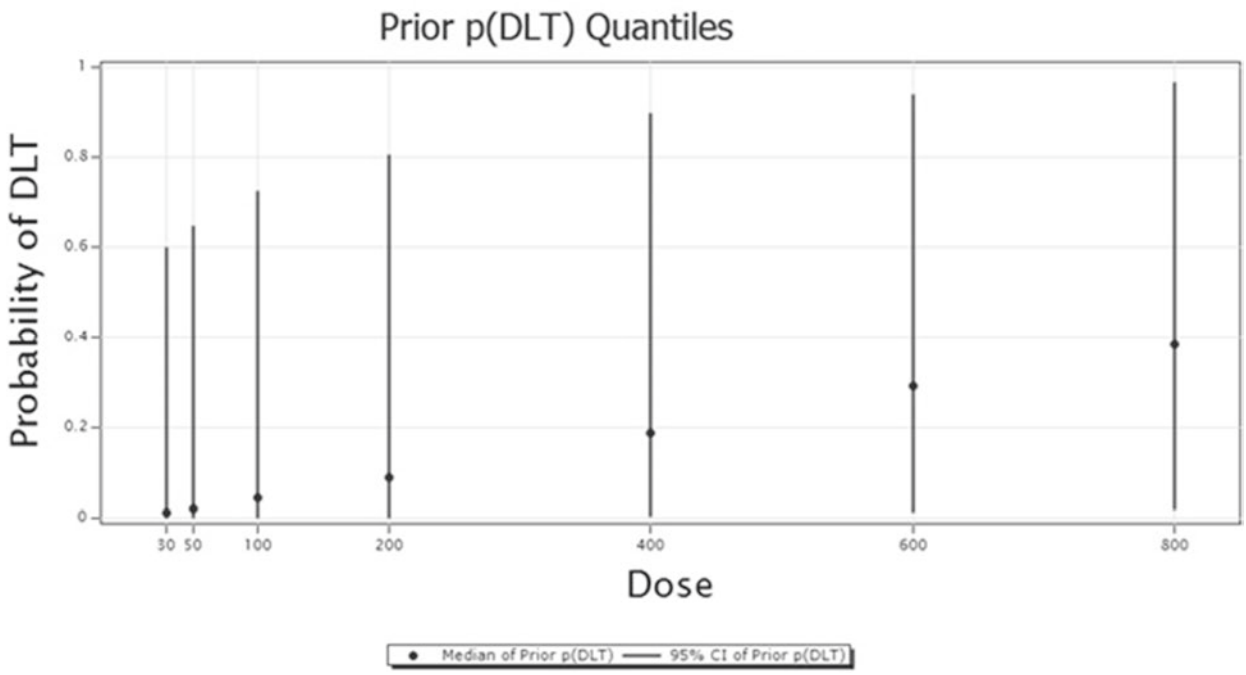
$$P(DLT|d_j, \alpha, \beta) = \frac{\exp\left(\alpha + \exp(\beta) \times \log\left(\frac{d_j}{d_{ref}}\right)\right)}{1 + \exp\left(\alpha + \exp(\beta) \times \log\left(\frac{d_j}{d_{ref}}\right)\right)}$$

with potential dose level d_j, reference dose d_{ref} and bivariate normally distributed parameters (α, β). The parameters are set as follows:

- d_j ε {30 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg}; however, can be changed any time by the SMC
- d_{ref} = 600 mg
- E(α) = -0.847, E(β) = 0.056
- Var(α) = 3.24, Var(β) = 0.64, Cov(α, β) = 0.

The so determined prior distribution is presented in Figure 4.

Figure 4 **Prior Distribution**



CI=credible interval, DLT=dose limiting toxicity.

In case information arises from other studies that changes current knowledge on the dose-toxicity relationship, the prior distribution will be updated prior to the first participant being treated in this study. This change of prior distribution will be documented in the SMC charter.

Posterior distribution and the next dose level recommended by the model will be calculated using EAST version 6.4 or higher (EAST version 6.4, Cytel Inc. Copyright 2016), or R version 3.1.2 or higher with library package Bayesian continual reassessment method (Sweeting 2013).

Appendix 11 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Version 3.0 (11 May 2020): Overall Rationale for the Amendment

The main purpose of this protocol amendment is to provide clearer and more detailed guidance with regards to key therapeutic interventions, such as induction or adjuvant chemotherapy regimens, study treatment specifications (e.g. radiotherapy techniques), and surgical pathology assessment for pathological complete response. By incorporating these changes, the amended protocol aims at bringing more consistency in the above-mentioned procedures and is therefore expected that the variability inherent to a multi-site global study will be minimized, therefore helping with the interpretation of the results. The key changes are as follows:

- Guidance for induction and adjuvant chemotherapy: in line with international guidelines for the treatment of rectal cancer (e.g. NCCN, ESMO), only 5-fluorouracil (5-FU) and oxaliplatin-based combination regimens (i.e. FOLFOX, or CAPEOX) will be allowed to be used for the study participants. Since the chemotherapy regimen utilized may influence outcomes, by having these 2 regimens it is expected that the interpretation of the treatment outcomes within this study (e.g. pathological response, or disease-free survival) will be subject to less variability.
- New radiotherapy techniques such as intensity modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) have been established in the clinical practice in recent years. Therefore, details about these allowed radiotherapy techniques (IMRT, VMAT and 3D) have now been included in the protocol, as well as the dose constraints for target volumes and organs at risk; as these factors play a role in the radiation tolerability, and hence may impact the study treatment safety assessment.
- The modified Ryan criteria for pathological assessment will be utilized to harmonize the pathological evaluation.

In addition to these changes, other relevant changes are:

- A thorax-abdomen CT scan at diagnosis for correct staging will now be mandatory and included at screening. Additional imaging parameters from MRI at Baseline will be described, in order to better characterize the post neoadjuvant (yTNM) tumor staging. The presence (or absence) of extramural venous invasion (EMVI) and the circumferential margin (CRM) parameters will now be collected.
- As a result of the acquired knowledge about the PK properties of peposertib throughout the ongoing clinical studies, the extent of PK sampling has been minimized to reduce patient burden.
- The benefit/risk section has been updated in line with the latest update of the Investigator's Brochure, resulting in the addition of new risks (rash, vomiting, diarrhea) based on nonclinical studies. It should be noted, however, that the benefit/risk assessment for the current study has not changed and remains positive.

- Based on the most recent available clinical evidence regarding the neoadjuvant treatment of rectal cancer, where treatment strategies such as standard 5-FU-based chemoradiation, total neoadjuvant treatment approaches, or the incorporation of additional chemotherapy or new (targeted) agents to the induction chemotherapy regimens (Maas 2010, Dewdney 2012, Sanghera 2008, Pinto 2018, Gérard 2015, Martos 2019, Rödel 2015, Zheng 2017, Petrelli 2020), do not lead to substantial improvements (≥ 7%) of pathological complete response (pCR) rates over the standard of care at final analysis, it has been decided to adjust the interim analysis "go" criteria of this study accordingly, thus reflecting the clinical reality. Hence, the study will now be stopped for futility in the event that the pCR/cCR of the experimental arm is lower than the control arm at the time of the interim analysis, as opposed to the former threshold which mandated a minimum increase of the experimental arm over the control arm of 5%. As detailed above, it was felt that this criterion does not accurately reflect the current treatment trends as shown in updated results of recent clinical studies that have evaluated new drugs in this setting. Notwithstanding, these adjustments do not alter the scientific hypothesis or imply a change of the study sample size and/or any other key statistical assumptions of the study.

Other changes:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints Section 9.4.2 Safety Analyses – Table 15	Triplicate ECGs and QTc evaluation removed from Phase II safety endpoints.	CCI [redacted]
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	PK of peposertib using population PK modeling deleted from Secondary Objectives and included as CCI [redacted]	PK modeling is generally performed once the study is completed and might include integrated data from several studies. Therefore, it will be reported separately, and PK modeling has been removed from the secondary objectives.
Section 1.3 Schedule of Activities (Table 2, Table 3) Section 8.2.4 Clinical Safety Laboratory Assessments	Urinalysis deleted.	Earlier preclinical and clinical studies with peposertib and RT have not revealed any clinically relevant alteration in urinalysis parameters; therefore, this assessment has been removed to reduce burden on participants. However, renal creatinine will continue to be monitored as part of the safety assessments.
Section 1.3 Schedule of Activities (Table 1, Table 2)	Deleted MRI and DRE from the End-of-Treatment visits assessments.	Deleted since not in line with standard of care.
Section 1.3 Schedule of Activities (Table 2) Section 8.2.3 Electrocardiograms	Deleted 12-lead ECG from all study visits except for Screening visit Modified text to delete description of triplicate ECGs.	CCI [redacted]
Section 1.3 Schedule of Activities (Table 3)	Removed need for Week 21 MRI/ CT scan.	In alignment with the current NCCN guidelines.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (Table 5)	Deleted 4-h postdose PK sample on FD1 and FD 9 from Phase II.	As this analysis will be done by population PK, this sample can be skipped to reduce the burden of the participants.
Section 2.3 Benefit/Risk Assessment	Updated to include additional potential risks.	For consistency with the Investigator's Brochure.
Section 3 Objectives and Endpoints	Changed "Genetic polymorphisms of genes involved in the ADME of peposertib" to genes involved in PK.	For greater specificity as to what is being done.
Section 4.1.2 Treatment Period Section 4.3 Justification for Dose Section 6.6.2.3 Radiotherapy	Updated text to clarify RT dose of 50 to 50.4 Gy to the tumor area.	To provide more clarity on the radiotherapy dosage used according to NCCN guidelines.
Section 5.1 Inclusion Criteria	Specified that FOLFOX and CAPEOX are allowed as induction chemotherapies.	To align with the current NCCN guidelines.
Section 6.5 Concomitant Therapy	Specified that FOLFOX and CAPEOX or capecitabine are allowed as adjuvant chemotherapies.	To align with the current NCCN guidelines.
Section 6.6 Dose Selection and Modification	Added statement that the selected RP2D and preliminary safety data from Phase Ib will be communicated to Investigators, Health Authorities and IEC/IRBs prior to initiating the Phase II part of the study, as per Sponsor's internal communication plan.	For consistency with the communication plan.
Section 8	Updated to include a maximum blood volume to be collected in any one-month period from each participant in the study (255 mL).	To comply with new protocol template and EU directives.
Section 9.2 Sample Size Determination – Phase II	Lowered "go-criterion" for interim analysis.	Adjustment of statistical assumptions in line with current results in literature.

ADME=absorption, distribution, metabolism, and excretion, CAPEOX=capecitabine and oxaliplatin, DRE=digital rectal examination, ECG=electrocardiogram, EUS=endoscopic ultrasound, FD=Fraction day, FOLFOX=Folic acid, 5-fluorouracil, and oxaliplatin, IEC=Independent Ethics Committee, IRB=Institutional Review Board, NCCN=National Comprehensive Cancer Network, QTc=corrected Q-T interval, PK=pharmacokinetics, RP2D=recommended Phase II dose, RT=radiotherapy.

Administrative and editorial changes throughout for better clarity:

Section # and Name	Description of Change
Section 1.3 Schedule of Activities (Table 1 and 2)	For the visit of Wk 7 to 14 added a clarification that in case of a pandemic, it is per Investigator's discretion if these visits can be done via a phone call.
Section 1.3 Schedule of Activities (Table 2)	For QoL assessments modified the assessment schedule to assure collection of responses to questionnaires during the treatment and Short-term Safety FU period.

Section # and Name	Description of Change
Section 1.3 Schedule of Activities (Table 3)	Clarified that for Phase Ib samples are collected up to progression and that for Phase Ib no samples are collected during Long-term Safety FU and Survival FU.
Section 1.3 Schedule of Activities (Table 3) Section 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Added statement that SAEs assessed as unrelated to study treatment will be collected up to Week 27 to be in alignment with local practice and to allow late toxicity assessments.
Section 1.3 Schedule of Activities (Table 4)	Clarified that if tissue block is not available, a minimum of 15 slides (and preferably 20 slides) are required.
Section 1.3 Schedule of Activities (Table 4)	Provided separate lists for time plasma samples are collected for Phase Ib and Phase II.
Section 1.3 Schedule of Activities (Table 4)	Clarified that tumor tissue collection during surgery is at the Week 15 surgery.
Section 1.3 Schedule of Activities (Table 6)	CCI [redacted]
Section 4.4 End of Study definition	Added a reference to Appendix 2.
Section 8.1.1 Pathological Complete Response	Added additional text.
Section 8.1.2 Tumor Evaluation Methods and Response Assessment	New text added
Section 8.1.2.1 Evaluation Methods Section 8.1.2.2 Tumor Response Evaluation Section 8.1.2.3 Neoadjuvant Rectal Score	Added new subsections.
Section 8.1.1 Pathological Complete Response	Added additional text.
Section 8.1.2 Tumor Evaluation Methods and Response Assessment	Modified heading name and added additional text describing evaluation methods.
CCI [redacted]	CCI [redacted]
Appendices	Added new appendices for: • Radiation therapy • Tumor response criteria • Pathology assessments Deleted references to various charters and added links to the appropriate appendix.
Appendix 2	Deleted unnecessary paragraph.

FU=Follow-up, IB=Investigator's Brochure, IEC=Independent Ethics Committee; IRB=Institutional Review Board, NCCN=National Comprehensive Cancer Network, QoL=quality of life, SAE=serious adverse event.

Version 2.0/Amendment 1 (17 April 2019): Overall Rationale for the Amendment

The key changes of the protocol are:

- To allow for the inclusion of Stage II rectal cancer patients, who may often benefit from concurrent chemoradiation according to clinical practice.
- To allow for the administration of induction chemotherapy, reflecting evolving clinical practice for locally advanced rectal cancer.
- To adjust the schedule of visits and evaluations to the standard clinical practice.

- To adjust the tumor evaluation procedures for locally advanced rectal cancer reflecting evolving clinical practice.

Other changes are to adjust the protocol language to the current standards and to maintain the protocol consistency and integrity.

Major scientific changes:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 6.3.1 Study Intervention Assignment, and throughout document	The stratification factor in the Phase II part was changed to: "induction chemotherapy" – yes/no.	To introduce the stratification that has an expected substantial impact on pCR/cCR rate
Section 1.1 Synopsis and Section 6.6.2.3 Radiotherapy and throughout document	Updated text to clarify RT dose and duration RT of approximately 50 Gy to the tumor area and 45 Gy to the electively irradiated tissues in 25 or 28 fractions.	To explain the standard dose distribution.
Section 1.3 Schedule of Activities (Table 1, Table 2) and Section 4 Study design	To update the weekly visits from Week 7 to Week 14, applicable for participants with acute toxicities only.	To adjust the schedule of visits to the standard clinical practice.
Section 1.3, Schedule of Activities Table 1, Table 2, Table 3, and Section 8.2.	Removed "evaluation of organs at risk"	The evaluation of organs at risk and reported as adverse events (if applicable) will be part of the general safety evaluations
Section 1.3, Schedule of Activities Table 1 Table 2 Table 3 CCI [redacted]	• Urinalysis method updated to a routine analysis instead of a dipstick urinalysis. • CCI [redacted] • CCI [redacted]	• To update in line with current standard practice. • CCI [redacted] • CCI [redacted]
Table 3 Schedule of Activities – Long term Safety and Survival Follow up Periods – Phase Ib and Phase II and Section 8.3.1	Only treatment related adverse events will be captured in Case Report Form in the long-term FU and survival FU.	Updated in line with local practice and to allow late toxicity assessments

Section # and Name	Description of Change	Brief Rationale
Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information		
Schedule of Activities, Figure 1, Figure 3 footnote and throughout document	To allow a 25 FD radiation schedule.	To align with local standard of care.
Schedule of Activities Table 1 Table 2 and throughout document	Physical examination, vital sign, laboratory assessments during treatment are to be done on a weekly basis, not necessarily on the specified FD.	To align the protocol with local practices.
Section 1.3, Schedule of Activities Table 1, Table 2	Follow-up pregnancy test only on Week 14.	To synchronize this evaluation with planned follow-up visit schedule.
Section 4.1.1 Screening Period and Section 8 Study Assessment and Procedure	A DRE (and EUS if indicated) and endoscopy will be needed at screening for participants with prior chemotherapy.	To determine current stage before starting CRT, in compliance with the inclusion criteria.
Section 5.1 Inclusion Criteria	• To allow for inclusion of participants with Stage II rectal cancer. • Removed leucocyte counts in inclusion criterion 6.	• To include participants who may often benefit from concurrent chemoradiation according to clinical practice. • To focus on neutrophil count as it better represents the WBC ability to tolerate chemoradiotherapy.
	• Participants must have evaluable disease in both phases of the study.	• Since RECIST was removed as tumor evaluation criteria, participants with only evaluable disease can be included.
Section 6.5.1 Prohibited Medicines	• To allow induction chemotherapy. • To allow H_2 blockers under certain circumstances	• To reflect evolving clinical practice for locally advanced rectal cancer. • To improve participant's ability to efficiently control adverse events.
Section 6.6	Added the option that the SMC can decide to decrease the dosing intensity, if needed.	If M3814 dosing interruptions are necessary due to tolerability issues, the dosing schedule can be adapted.
Section 6.6.2.3 Radiotherapy	Removed the sentence: "Generally, a 3 or 4 field technique should be used".	To avoid RT technique suggestion as the focus should be on optimal dose distribution to both tumor and to organs at risk.
Section 8.8	Added optional tumor biopsies and a mandatory post-surgical specimen collection.	Additional tumor tissue samples to support identification of mechanisms of sensitivity and resistance to the study intervention during and after treatment.
Section 8.1.2 Tumor Response Assessment Figure 2	Removed RECIST 1.1. Updated text of tumor evaluation criteria to clarify that assessments will be based on MRI, endoscopic and	To update in line with current standards for rectal cancer evaluation in the neoadjuvant setting.

Section # and Name	Description of Change	Brief Rationale
and throughout document	digital evaluation, per NCCN guideline.	
Section 9.4.1 Efficacy Analysis and Table14 Statistical Analysis Methods for Efficacy Endpoints	Updated statistical analysis method for “best overall response” and added statistical analysis method R0 resection.	To update in line with current standards for rectal cancer evaluation.
Section 9.4.1 Efficacy Analysis	Added subgroup analyses for baseline characteristics, such as tumor stage.	To increase clarity on planned analyses.
Schedule of Activities, and Section 3.1, Section 4.1.1 Section 8	Addition of endoscopic ultrasonography, if indicated or if performed, to the DRE assessment	An endoscopic ultrasonography if indicated or if performed per local practice, is added to the assessment of palpitations

ctDNA= circulating tumor DNA; DRE=digital rectal examination; FD=Fraction day; FFPE= Formalin-fixed paraffin embedded; FU=Follow up; RECIST=Response evaluation criteria in solid tumors; RT=Radiotherapy; SoA=Schedule of activities.

Administrative and editorial changes:

Section # and Name	Description of Change	Brief Rationale
CCI		
Section 1.3 Schedule of Activities Table 5	Predose sampling window updated to 60 min.	To facilitate PK sampling schedule.
Section 2.2 Background	Clinical study information from the ongoing Study EMR100036-002 and completed Study MS100036-0022 were updated.	Text updated to refer to the current IB.
Section 5.1 Inclusion Criteria and Appendix 3	Inclusion criterion #9 (male and female contraception) updated.	To align with the current Merck KGaA/EMD Serono contraception content standards. that are based upon CHMP guidelines, as specified in the Clinical Study Facilitation Group (CTFG) Guidance.
Section 6.6.1	• Removed the separate criterion #2 and 7 from DLT definition	• These criteria were redundant.

Section # and Name	Description of Change	Brief Rationale
	• Added text for drug-induced liver injury with Hy's law.	• To align the text language with FDA's preference.
Section 6.6.3 Management of Toxicities	Added a section for management of toxicities.	To update in line with local practices.
Section 6.6.3, Section 6.6.3.1 Diarrhea and Section 6.6.3.2 Capecitabine Management for Toxicities Other Than Diarrhea and Table 9	• Added a section to mention the charter for diarrhea management. Removed the previous text for capecitabine dose adjustment and CTCAE grading for diarrhea from the protocol. • Replaced thrombocytes with platelets in the capecitabine dose adjustment table.	To update in line with local practices.
Section 6.6.3.3 M3814 and Radiotherapy and Table 11	Table text updated.	To clarify dose modifications of M3814 and radiotherapy during the study for toxicities other than diarrhea.
Section 7.1 Discontinuation of Study Intervention and Section 7.2 Participant Discontinuation/Withdrawal from the Study	Sections updated	To be in line with the current Merck KGaA/EMD Serono content standard intended for clarity and better readability.
Appendix 2 Study Governance	• Text added regarding monitoring plan. • Updated country list, and number of sites for both Phase Ib and Phase II.	• To update the information to align with the current Merck KGaA/EMD Serono content standards. • To update in line with current country plan.
Appendix 5	Updated the laboratory evaluation requirements.	To address standard laboratory evaluation requirement.
Throughout document	Administrative, grammatical, typographical and punctuation changes.	For clarity and better readability.

Appendix 12 Sponsor Signature Page

Study 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
Regulatory Agency Identifying Numbers:	US FDA IND CCI [redacted] EudraCT: 2018-002275-18
Clinical Study Protocol Version:	06 May 2021/Version 4.0

I approve the design of the clinical study:

PPD [redacted]

Signature

PPD [redacted]

Date of Signature

Name, academic degree:	PPD [redacted]
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 13 Coordinating Investigator Signature Page

Study 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
Regulatory Agency Identifying Numbers:	US FDA IND CCI EudraCT: 2018-002275-18
Clinical Study Protocol Version:	06 May 2021/Version 4.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 14 Principal Investigator Signature Page

Study 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
Regulatory Agency Identifying Numbers:	US FDA IND [redacted] EudraCT: 2018-002275-18
Clinical Study Protocol Version:	06 May 2021/Version 4.0
Site Number:	

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:	
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	