Clinical Trial Protocol

Clinical Trial Protocol Number	MS200770-0001
Title	A Phase I, Open-label, Uncontrolled, Multicenter, Dose-escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors
Phase	I
Short Title	M3541 in Combination With Radiotherapy in Solid Tumors
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Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
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List of Abbreviations

AAG	alpha-1-acid glycoprotein
ADME	absorption, distribution, metabolism and elimination, or excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATM	ataxia-telangiectasia mutated
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0-\infty}$/dose	dose-normalized $AUC_{0-\infty}$
AUC_{0-6h}	area under the concentration-time curve from time zero to 6 hour postdose
AUC_{0-last}	area under the concentration-time curve from time zero to the last quantifiable sampling time point
AUC_{0-last}/dose	dose-normalized AUC_{0-last}
BOR	best overall response
BPI-SF	Brief Inventory of Pain – Short Form
C_{avg}	average plasma concentration
CL/F	oral clearance
CLss/F	oral clearance at steady-state
C_{max}	maximum observed plasma concentration
C_{max}/dose	dose-normalized C_{max}
C_{min}	minimum observed plasma concentration

CNS	central nervous system
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
ctDNA	circulating tumor DNA
C_{trough}	predose plasma concentration
CTCAE V4.03	Common Terminology Criteria for Adverse Events, Version 4.03
CYP	cytochrome P450
DLT	dose-limiting toxicity
DSB	double-strand breaks
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
FD	Fraction Day
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
F/W	fractions per week
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	Hormone replacement therapy
iAP	Integrated Analysis Plan

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IPMP	Integrated Project Management Plan
IRB	Institutional Review Board
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NCI	National Cancer Institute
OATPs	organic anion-transporting polypeptides
OCTs	organic cation transporters
PD	progressive disease
PFS	progression-free survival
PGt	pharmacogenetics
PK	pharmacokinetic(s)
PR	partial response
PTD	Post-treatment Day
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected based on Fridericia's formula
$R_{acc}(AUC)$	accumulation ratio for area under the concentration-time curve
$R_{acc}(C_{max})$	accumulation ratio for maximum concentration
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1

RP2D	recommended phase II dose
RT	radiotherapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SMC	Safety Monitoring Committee
SoLD	sum of the longest diameter
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum concentration
TMB	tumor mutational burden
TNM	Tumor Node Metastasis Classification of Malignant Tumors (UICC)
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
V_{ss}/F	apparent volume of distribution at steady-state
V_z/F	apparent volume of distribution during terminal phase
WBC	white blood cell
WOCBP	woman of childbearing potential

1 Synopsis

Clinical Trial Protocol Number	MS200770-0001
Title	A Phase I, Open-label, Uncontrolled, Multicenter, Dose-escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors
Trial Phase	I
IND Number	CCI
FDA covered study	Yes
EudraCT Number	Not applicable
Coordinating Investigator	PPI
Sponsor	EMD Serono Research & Development Institute, Inc, Billerica, MA, USA
Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Trial centers/countries	Up to 15 study centers in the United States are planned to be included in this study.
Planned study period (first subject in-last subject out)	First subject in: Q3, 2017 Last subject out: Q4, 2020
Trial Registry	ClinicalTrials.gov and all other required registries

Objectives:

Primary objective

The primary objective is to determine the maximum-tolerated dose (MTD) and recommended Phase II dose(s) (RP2D) for M3541 in combination with fractionated palliative radiotherapy (RT) in subjects with solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities likely to benefit from palliative RT.

Secondary objectives

The secondary objectives are:

- To evaluate the safety profile and tolerability of M3541 in combination with fractionated palliative RT
- To explore the antitumor activity of M3541 in combination with fractionated palliative RT

- To assess the pharmacokinetics (PK) of M3541 in combination with fractionated palliative RT.

Exploratory objectives

Exploratory objectives are:

- To explore the antitumor activity of M3541 in combination with fractionated palliative RT on the sum of the longest diameter (SoLD) of the irradiated target lesions
- To assess treatment-related changes in pharmacodynamic markers of M3541 in combination with fractionated palliative RT
- CCI [redacted]
- To explore the potential impact on the immune system of M3541 in combination with palliative RT
- CCI [redacted]
- To explore plasma protein binding of M3541
- CCI [redacted]
- CCI [redacted]

Methodology:

This is a Phase I, uncontrolled, open-label, multicenter, dose-escalation study of M3541 given in combination with palliative RT, designed to evaluate the safety, tolerability, PK, pharmacodynamics, and explore antitumor activity of M3541 in combination with fractionated palliative RT in subjects with solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities likely to benefit from palliative RT.

The starting dose, based on nonclinical data using an interspecies scaling approach, is 50 mg M3541 orally once per fraction day (FD) in combination with fractionated palliative RT. Radiotherapy will consist of 10 FDs, to be administered over 2 consecutive calendar weeks (ie, Monday through Friday, with the intervening Saturday and Sunday as a M3541 / RT holiday). The treatment will start on Mondays for all subjects, unless pre-agreed otherwise with the Sponsor. The total RT dose will be 30 Gy given in fractions of 3 Gy/FD, FD 1 to FD 10. After completion of the second cohort of subjects (100 mg M3541 once per FD), cohorts at an assumed dose of 100 mg using 2 intermittent schedules (thrice weekly and twice weekly) can be started (simultaneously) and dose escalation can proceed with these schedules. On the schedule-defined treatment days, M3541 will be administered before RT (1 hour and 45 minutes ± 60 minutes). In the case of an RT interruption, M3541 will not be administered (overall, M3541 will only be administered on RT days). The 2-week dose-limiting toxicity (DLT) follow-up period will start on the day after the last administration of study treatment.

The DLT evaluation period will be 4 weeks in duration, including the scheduled 2-week radiotherapy treatment period (as described above) plus a 2-week DLT follow-up period that

starts on the day after the last administration of M3541 / RT. The DLT evaluation period could exceed the 4-week period only if M3541 / RT has been interrupted and given over a period exceeding 2 weeks.

For the first cohort of 3 subjects, Subject 1 and Subject 2 will be treated at a staggered interval of 3 weeks apart. There will also be a stagger of 3 weeks between Subject 2 and Subject 3.

Dose level selections per treatment schedule will be guided by a Bayesian 2-parameter logistic regression model with overdose control. For each schedule, separate models will be applied. Approximately 8 cohorts are planned with data from 3 subjects (1 cohort) per dose level and schedule. Based on nonclinical assumptions, the pre-planned dose levels for the M3541 once per FD schedule are 50, 100, 200, 300, 500 and 800 mg orally once per administration. Dose escalation for the M3541 once per FD schedule will be continued after the second cohort pending guidance by the Safety Monitoring Committee (SMC).

For the 2 intermittent schedules (thrice weekly and twice weekly) the pre-planned dose levels are as follows: 100, 200, 300 and 400 mg orally; in case the starting dose is not well tolerated, a dose of 50 mg (DL -1) may be chosen for the subsequent cohort. The starting dose will be decided by the SMC. The number of dose levels and the actual dose and schedule to be explored in each subsequent cohort remains to be determined, as well as the number of subjects (aiming for 3 per cohort) and will be decided by the SMC guided by the results of the Bayesian regression model.

After 3 subjects in any cohort have been treated and completed the DLT evaluation period, the SMC will evaluate all available safety data, in particular, the occurrence of DLTs (according to the DLT definition), all serious adverse events (SAEs), all adverse events (AEs), laboratory safety data, vital sign measurements, electrocardiograms (ECG), and available PK and pharmacodynamic data from, at a minimum, up to the previous cohort. The subsequent potential cohort dose level per schedule will be determined by inserting the DLT data into a Bayesian 2-parameter logistic regression model with overdose control. By this approach, prior information including that of all completed cohorts, will be taken into account for the recommendation of the potential next dose level per schedule. The SMC may choose a different dose level (other than the pre-planned protocol described dose level and /or the suggested level by the Bayesian model) per schedule for the next cohort and may deviate from the pre-planned number of 3 subjects per cohort.

Based on available safety and PK / pharmacodynamics data, the SMC will:

- Decide on the relevance of DLTs for the decision on the dose level for the next cohort
- Recommend a subsequent cohort dose level (dose-escalation, dose de-escalation, modification of schedule), or adding a cohort at the same dose level per schedule (ie, new cohorts at a dose level / schedule previously explored). The SMC may choose a different dose level other than the preplanned dose level / schedule or the one's provided by the Bayesian model, in order to adapt and optimize RP2D selection of M3541 (in combination with palliative RT) and MTD per schedule. While changing the schedule, the SMC will ensure to change appropriately (or not) the ECG assessments and PK sampling times

- Decide on suspension of enrollment per treatment schedules or the totality of the study.

For this study, a DLT is defined as any of the following AEs that occur during the DLT evaluation period (except those that are clearly and incontrovertibly due to disease progression or extraneous causes), with severity graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE V4.03):

- Grade ≥ 3 non-hematologic toxicity, except:
  - Nausea, vomiting and / or diarrhea lasting ≤ 3 days in the once per FD and twice weekly schedules or 2 days in the thrice weekly schedule that can be medically managed
  - Worsening of pre-existing tumor pain associated with tumor lesions for which the subject is irradiated in the context of this study
- Evidence of treatment-related hepatocellular injury for > 3 days in the once per FD and twice weekly schedules and 2 days in the thrice weekly schedule, such as ≥ 5 × the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and without any other apparent clinical causality
- Any occurrence of Hy's law (defined as aminotransferases > 3 × ULN, alkaline phosphatase < 2 × ULN, total bilirubin ≥ 2 × ULN, no other reason to account for these abnormalities)
- Febrile neutropenia or Grade 4 neutropenia lasting for > 5 days, Grade 4 thrombocytopenia or any requirement for platelet transfusion (as defined by Grade 4 thrombocytopenia lasting for > 5 days or Grade ≥ 3 thrombocytopenia with bleeding), Grade 4 anemia that is unexplained by the underlying disease
- Any toxicity related to study treatment that causes the subject to interrupt M3541 treatment (defined as having to delay the next scheduled M3541 administration) for:
  - ≥ 4 FDs in the once per FD dosing schedule.
  - > 1 FD in the thrice weekly schedule
  - not to be able to be treated within 24 hours of the scheduled treatment time in the twice weekly schedule
- A related treatment-emergent adverse event (TEAE) that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk.

Information on potential DLTs will be sent by the Sponsor or delegate to the SMC core members within 1 working day of the receipt of documented information.

Subsequent cohorts of M3541 will continue (from the initial 50 mg orally once per FD) until 1 of the following stopping rules apply:

- A maximum number of up to 30 evaluable subjects are included, unless otherwise indicated by the SMC;
- More than 3 cohorts are assigned to the same dose level on the same schedule; or

- The estimate for DLT probability of the MTD reaches sufficient precision.

Planned number of subjects:

It is anticipated that up to 30 evaluable subjects for each of the different schedules may be needed to determine the MTD and RP2D of M3541 unless otherwise indicated by the SMC.

Pending the recommendations of the SMC, it is anticipated that 6 evaluable subjects will be required to validate the dose of each of the schedules.

Primary endpoints:

The primary endpoint is the occurrence of DLTs during the DLT evaluation period, ie, during the M3541 / RT treatment period plus the DLT follow-up period after the last treatment with M3541 / RT.

Secondary endpoints:

The secondary endpoints are:

- Occurrence of TEAEs, Grade $\geq$ 3 AEs, SAEs, and deaths according to NCI-CTCAE V4.03 assessed from the first administration of M3541
- Occurrence of abnormal laboratory tests, findings during physical examinations (reported as AEs), vital signs, and ECGs (including corrected QT [QTc] interval) assessed from the first administration of M3541
- Best overall response as assessed by the Investigator using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) every 6 weeks (starting on Post-treatment Day 42) for the first 6 months, then every 12 weeks thereafter until evidence of disease progression
- Progression-free survival time defined as time from the first dose of M3541 to disease progression (using RECIST 1.1 as assessed by the Investigator), onset of other anticancer therapy, or death from any cause

PK endpoints are:

- FD 1: maximum observed plasma concentration (C_{max}), C_{max}/dose, time to reach maximum observed concentration (t_{max}), apparent terminal half-life ($t_{1/2}$), area under the concentration-time curve from time zero to the last quantifiable sampling time point ($AUC_{(0\text{-last})}$), $AUC_{(0\text{-last})}$/dose, area under the concentration-time curve from time zero to 6 hour postdose ($AUC_{(0\text{-6h})}$), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{(0\text{-}\infty)}$), $AUC_{(0\text{-}\infty)}$/dose, oral clearance (CL/F), and apparent volume of distribution during terminal phase (Vz/F)
- FDs 2 through 9: Predose plasma concentration (C_{min}) and approximate C_{max} of M3541
- FD 9 or FD 10: Minimum observed plasma concentration (C_{min}); average plasma concentration (C_{avg}); C_{max}, C_{max}/dose, t_{max}, $t_{1/2}$, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-last})}$/dose, oral clearance at steady-state (CL_{ss}/F), apparent volume of distribution at steady-state (V_{ss}/F), accumulation ratio for area under the concentration-time curve (R_{acc}[AUC]), accumulation ratio for maximum concentration (R_{acc}[C_{max}]).

Exploratory endpoints:

The exploratory endpoints are:

- SoLD, as assessed by the Investigator using RECIST 1.1 on the irradiated target lesions
- Location of disease progression as assessed by the location where tumor size increase has been observed as well as the location of the newly observed lesions
- Absolute values and changes over time of proteins that may be affected by ataxia-telangiectasia mutated (ATM) inhibition in blood (eg, phospho-ATM) during exposure to M3541
- CCI
- Changes from baseline over time of the total blood cell count and cell subset type of immune cells (eg, T cells, B cells, natural killer cells) during exposure to M3541
- CCI
- CCI
- CCI
- CCI

Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria are as follows:

- Male or female subjects aged ≥ 18 years
- Subjects must have solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities (any histology) likely to benefit from palliative radiotherapy; subjects requiring palliative RT for lesions in the spine or lesions adjacent to the spinal cord are excluded from this study
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2
- Life expectancy ≥ 3 months
- Adequate hematologic, hepatic, and renal function
- Agree to use highly effective contraception (as outlined in the protocol, Section 5.3) if the subject is male or a woman of childbearing potential (female partners of childbearing potential of male subjects must also agree to use highly effective contraception)

Key exclusion criteria include:

- Use of other anticancer therapy (as outlined in the protocol) within 5 x their elimination half-life, but no more than 15 days, before the first dose of M3541 administration. The use of any investigational agent is not allowed within 28 days before the first dose of M3541
- Residual toxicity due to previous anticancer therapy with no return to baseline or ≤ Grade 1 (except alopecia) according to CTCAE V4.03
- Extensive prior RT on more than 30% of bone marrow reserves (by Investigator judgment), or prior bone marrow/stem cell transplantation within 5 years before study start
- Prior RT to the same region that would be irradiated in this study
- Subjects at increased risk for radiation toxicities, such as known collagen vascular disease (eg, scleroderma, Sjogren's disease, etc) or other inherited radiation hypersensitivity syndromes (eg, Gorlin syndrome, Fanconi anemia, ataxia-telangiectasia, etc.)
- Surgical intervention within 28 days prior to the first dose of M3541 administration
- Known central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy. Subjects with CNS metastases incidentally detected during Screening that do not cause clinical symptoms and for which standard of care suggests no therapeutic intervention is indicated, should be discussed with the Sponsor Medical Responsible
- Active difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions (including pancreas deficiency requiring Creon therapy) that may hamper compliance and/or absorption of M3541
- Subjects currently receiving or unable to stop using medications or herbal supplements known to be potent inhibitors of cytochrome P450 (CYP) 3A and / or P-glycoprotein (P-gp) (CYP and / P-gp must stop at least 1 week before treatment with M3541) or potent inducers of CYP3A or P-gp (must stop at least 3 weeks before treatment with M3541) or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior).

Investigational Medicinal Product: Dose/mode of administration:

In this study, the term "Investigational Medicinal Product" (IMP) refers to the investigational drug M3541, which is the only IMP used in this study. The drug is available as tablet dosage form in 10 mg, 50 mg, and 100 mg dose strengths.

Subjects in the first dose-level cohort of the once per FD schedule will be assigned to receive M3541 at a starting dose of 50 mg orally once per FD, which will be given 1 hour and 45 minutes (± 60 minutes) before each RT fraction for up to 10 fractions. The dose of M3541 may be increased in the different treatment schedules according to the dose-escalation rules described. No intrasubject dose-escalation / de-escalation and no change between treatment schedules is permitted.

On the days of M3541 dosing, subjects will be asked to arrive at the clinic ≥ 2 hours prior to scheduled RT having had a light breakfast and will be administered M3541 at the clinic 1 hour and 45 minutes (± 60 minutes) before RT is started. Subjects will take their assigned dose of M3541 with a full glass of water (approximately 240 mL or 8 fluid ounces).

On M3541 dosing days, M3541 should not be taken until the predose PK and ECG collection has been completed. Information on food and grapefruit juice intake prior to M3541 intake that day should be recorded (eg, breakfast yes / no, grapefruit juice yes / no).

Palliative RT will follow institutional guidelines. The total RT dose will be 30 Gy given in 10 fractions over 2 consecutive calendar weeks (ie, 3 Gy/FD, 5 FDs per calendar week, FD 1 to FD 10 over a 2-calendar week period, starting on Mondays). An interruption in the administration of RT will lead to an interruption in treatment with M3541 if RT interruption is on a scheduled M3541 administration day.

If a subject vomits after taking their dose of M3541, they should be given an antiemetic but no further dose will be given that day. Prophylactic antiemetics should then be given before subsequent doses of M3541.

Reference therapy: dose / mode of administration / dosing schedule:

A reference therapy will be applied in combination with the IMP. The reference therapy consists of palliative RT with a total dose of 30 Gy given in 10 fractions (over 10 FDs) over a time period of 2 weeks.

Planned study and treatment duration per subject:

The study period per subject includes an up to 21-day screening period, a scheduled 2-week treatment period, followed by a 2-week DLT follow-up period and follow-up for up to 1 year after RT has been completed (note, after the 1-year follow-up, the Investigator will contact the subject every 3 months [± 1 month, telephone contact is acceptable] until the defined end of the study to enquire and monitor for late appearing RT-related toxicity).

Up to a 3-FD delay during the treatment period will be allowed in the once per FD dosing schedule, which may extend the total treatment period of 2 weeks. The thrice weekly schedule will not allow to delay M3541 dosing (if not treated (due to toxicity or other reasons) on the scheduled timing, no treatment will be given). The twice weekly schedule will allow a 24-hour treatment delay (if not treated on the scheduled day for toxicity or other reasons, as long as treatment-enabling conditions are reached the next radiotherapy day, the subject can be dosed that day).

Statistical methods:

The minimum number of subjects per cohort is 3. The SMC is responsible for dose escalation decisions and may decide to enroll further subjects as guided by the result of the Bayesian 2-parameter logistic regression model with overdose control. This guidance is not binding. A maximum number of up to 30 evaluable subjects is anticipated, unless otherwise indicated by the SMC.

No formal interim analysis is planned. The data cut-off date for each cohort will be triggered by the completion of the DLT evaluation period of the last subject in the respective cohort.

Data cut-off for the primary analyses is defined by the completion of DLT evaluation period of the last subject in the last cohort.

The final analyses will be performed when the study has been completed.

Table 1 Schedule of Assessments: M3541 Once per FD Dosing Schedule

Study Periods	Screening	DLT Evaluation Period (4 weeks)						Short-term Safety FU		Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (2 weeks)					
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 14[c]	PTD 15 to 30		PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 15[c] (+ 2 Days)	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90(± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Signed informed consent	X											
Inclusion / exclusion criteria[d]	X[d]	FD 1										
Demography	X											
Medical history	X											
BPI-SF[e]	X[e]	To be completed on each FD[f]					X[f]		X[f]			
HIV, HBV, and HCV testing[g]	X											
Tumor specimen collection (optional)	X											
β-HCG pregnancy test (if applicable)[h]	X[h]						X[h]					
Vital signs[i]	X	X				X	X	X	X	X	X	X
Physical examination	X	X		X		X	X	X	X	X	X	X
Evaluation of all tissues in RT area[j]	X	FD 6		X		X	X	X	X	X	X	X
ECOG PS	X					X			X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X[c]	X	X	X	X	X[a]

Study Periods	Screening	DLT Evaluation Period (4 weeks)						Short-term Safety FU		Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (2 weeks)					
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 14[c]	PTD 15 to 30		PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 15[c] (+ 2 Days)	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90(± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Concomitant medication	X	X	X	X	X	X	X	X	X	X[k]	X[k]	X[k]
Hematology	X	X		X		X[b]	X	X	X			
Coagulation	X	X		X		X[b]	X	X	X			
Serum chemistry	X	X		X		X[b]	X	X	X			
Urinalysis (dipstick)	X						X		X			
12-lead ECG (including QTcF)[l]	X	See Table 4										
Tumor assessment (RECIST 1.1)	X[m]									X[n]	X[n]	X[n]
PK blood samples[o]		See Table 4										
Blood sampling for plasma protein determination		X[p]				X[q]						
CCI [redacted]												
Pharmacodynamic markers in blood[t]		See Table 4										
Immune cell analysis[u]		See Table 4										

Study Periods	Screening	DLT Evaluation Period (4 weeks)						Short-term Safety FU		Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (2 weeks)					
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 14[c]	PTD 15 to 30		PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 15[c] (+ 2 Days)	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90(± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
M3541[v]		X	X	X	X	X	No Treatment					
RT 3 Gy/FD		X	X	X	X	X						
Follow-up for RT-related toxicity / survival[w]								X	X	X	X	X[w]

AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EoS = End-of-Study; FD = Fraction Day (days when RT and M3541 are given); FU = follow-up; Gy = Gray; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; PTD = Post-treatment Day (starting the day after the last dose of RT and M3541 until 1 year later); QTcF = Fridericia corrected QT interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiotherapy; TEAE = treatment-emergent adverse event.

Note: Where scheduled post-treatment visits coincide with a weekend or holiday, they may be postponed to the next working day (up to + 2 days). The relevance of any safety finding during this additional time in the context of a DLT or any other late toxicity will be reviewed by the Safety Monitoring Committee.

a. All subjects will be followed up for disease progression until 1 year after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (eg, PD, if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EoS occurs prior to PTD 365, all assessments must be done as planned for PTD 365. All subjects will be followed for survival and for delayed AEs for up to 1 year (and beyond for AEs) from PTD1. After the 1 year follow-up, the Investigator will be asked to contact subjects every 3 months (± 1 month, phone call is acceptable) until the defined end of the study (see Section 5.7) to enquire and monitor for late appearing RT-related toxicity.

b. FD 1 is the first dose of M3541 and first fraction of RT. Planning of the RT will follow institutional guidelines and will start on a Monday (with the first Saturday and Sunday as a M3541 / RT holiday). In cohorts where required, subjects will be asked to stay overnight in a supervised environment on FD 1 unless the PK sampling and ECG assessment at 8 and 12 hours postdose can be completed otherwise. FD 10 is the last administration of M3541 / RT and the DLT follow-up period will start on the following day (PTD 1). In case of premature withdrawal from the study during the treatment period, the assessments scheduled for the visit on FD 10 should be performed. In such cases, this visit will be considered the EoS visit. If FD 10 is on a Friday then safety laboratory assessments and urinalysis (as required) must be done on FD 9.

c. The 2-week DLT follow-up period (PTDs 1 through 14) starts on the day after the last administration of M3541 / RT. With the treatment period starting on a Monday, PTD 15 will land on a Saturday. The PTD 15 visit has a + 2 days visit window, thus subjects should present to the clinic on the following Monday for the PTD 15 DLT follow-up visit. PTD 22 will also land on a Saturday. The PTD 22 visit has a ± 2 days visit window, thus subjects should present to the clinic for this safety assessment on either the preceding Thursday/Friday (PTDs 20/21) or the following Monday (PTD 24). Subjects with ongoing AEs should present to the clinic throughout the DLT follow-up period as appropriate and instructed by the Investigator. See Section 6.5 and subsections for allowed and prohibited medications during the DLT period.

d. Subjects must meet all inclusion criteria and not any exclusion criteria prior to enrollment. Hepatitis B and C results obtained within 3 months prior to screening are still valid for the purpose of this study. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered.

e. All subjects will be asked to complete the BPI-SF at Screening and FD 1 prior to other study related assessments. If a subject has no pain in an area to be irradiated as part of the experimental treatment (M3541 + RT), the subject should mark "0" in all pain scales and activity scales. For subjects with cancer pain from lesions to be irradiated as part of the experimental treatment, any pain medication should be documented (name, dose, frequency, including if used on an "as needed" basis) on the appropriate eCRF page.

f. Subjects with cancer pain from lesions to be irradiated as part of the experimental treatment (M3541 + RT) on FD 1 will be asked to complete the BPI-SF on each subsequent FD and on PTD 15 and PTD 30 prior to any other study-related procedures. The subject should only rate pain and interference with daily activity as they relate to areas being irradiated as part of the experimental treatment. The Investigator must also ensure any new pain medication or change in ongoing pain medication (name, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page.

g. Screening for HIV will be performed according to local practice and local regulatory guidance.

h. Serum β-HCG pregnancy test at Screening and urine thereafter.

i. Vital signs include body temperature, respiration rate, pulse, blood pressure, body weight, and height (height only at Screening).

j. Areas to be irradiated should be examined at baseline. Worsening of a condition within an irradiated area (eg, skin reactions, bleeding) during the DLT evaluation period should be reported as a TEAE with grade and relatedness to RT and / or M3541. Improvement of a condition within an irradiated area (eg, improved pain, reduced bleeding) should be reported on the appropriate efficacy-related eCRF page.

k. Only new anticancer therapies and any change in treatment given for treatment-related SAEs will be documented.

l. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. Standard ECGs will be evaluated by the Investigator for safety assessment. See Table 4 for details of ECG acquisition timing during the treatment period.

m. Tumor imaging by CT, MRI, or bone scan at baseline to document extent of lesions according to RECIST 1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts. A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks.

n. Tumor assessments using the same method used at baseline are to be completed every 6 weeks beginning on PTD 42 of the Mid-term Safety Follow-up period through the Long-term Safety Follow-up period (ie, PTD 180) for a total of 4 assessments. During the survival follow-up period (ie, PTD 181 to 365) tumor assessments will occur approximately on PTD 270 and PTD 365. Assessments are not required if the subject has started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in the eCRF.

o. See Table 4 for details of PK blood sampling.

p. FD 1 only; see Table 4 for details.

q. FD 5 and10; see Table 4 for details.

r. CCI [redacted]

s. CCI

t. See Table 4 for details of pharmacodynamic marker sample collection.

u. See Table 4 for details of immune cell analysis sample collection.

v. M3541 will be administered at the clinic 1 hour and 45 minutes (± 60 minutes) before RT is started.

w. Can be followed up via phone call every 3 months if no other assessments are required.

x. CCI

Table 2 **Schedule of Assessments: Thrice Weekly Intermittent M3541 Dosing Schedule: Monday / Wednesday / Friday**

Study Periods	Screening	DLT Evaluation Period (5 weeks) Thrice Weekly Schedule						Short-term Safety FU	Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (3 weeks)				
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 21[c]	PTD 22 to 30	PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Signed informed consent	X										
Inclusion / exclusion criteria[d]	X[d]	FD 1									
Demography	X										
Medical history	X										
BPI-SF[e]	X[e]	To be completed on each FD[f]					X[f]	X[f]			
HIV, HBV, and HCV testing[g]	X										
Tumor specimen collection (optional)	X										
β-HCG pregnancy test (if applicable)[h]	X[h]							X[h]			
Vital signs[i]	X	X				X	X	X	X	X	X
Physical examination	X	X		X		X	X	X	X	X	X
Evaluation of all tissues in RT area[j]	X	FD 6		X		X	X	X	X	X	X
ECOG PS	X					X		X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X[c]	X	X	X	X[a]

Study Periods	Screening	DLT Evaluation Period (5 weeks) Thrice Weekly Schedule						Short-term Safety FU	Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (3 weeks)				
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 21[c]	PTD 22 to 30	PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Concomitant medication	X	X	X	X	X	X	X	X	X[k]	X[k]	X[k]
Hematology	X	X		X		X[b]	X	X			
Coagulation	X	X		X		X[b]	X	X			
Serum chemistry	X	X		X		X[b]	X	X			
Urinalysis (dipstick)	X						X	X			
12-lead ECG (including QTcF)[l]	X	See Table 5									
Tumor assessment (RECIST 1.1)	X[m]								X[n]	X[n]	X[n]
PK blood samples[o]		See Table 5					See Table 5				
Blood sampling for plasma protein determination		X[p]				X[q]					
CCI [redacted]											
Pharmacodynamic markers in blood[t]		See Table 5									
CCI [redacted]											
Immune cell analysis[u]		See Table 5									

Study Periods	Screening	DLT Evaluation Period (5 weeks) Thrice Weekly Schedule						Short-term Safety FU	Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (3 weeks)				
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 21[c]	PTD 22 to 30	PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
M3541[v]		X		X		X	No Treatment				
RT 3 Gy/FD		X	X	X	X	X					
Follow-up for RT-related toxicity / survival[w]								X	X	X	X[w]

AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EoS = End-of-Study; FD = Fraction Day (days when RT and M3541 are given); FU = follow-up; Gy = Gray; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; PTD = Post-treatment Day (starting the third day after the last dose of RT and M3541 until 1 year later); QTcF = Fridericia corrected QT interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiotherapy; TEAE = treatment-emergent adverse event.

a. All subjects will be followed up for disease progression until 1 year after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (eg, PD, if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EoS occurs prior to PTD 365, all assessments must be done as planned for PTD 365. All subjects will be followed for survival and for delayed AEs for up to 1 year (and beyond for AEs) from PTD1. After the 1 year follow-up, the Investigator will be asked to contact subjects every 3 months (± 1 month, phone call is acceptable) until the defined end of the study (see Section 5.7) to enquire and monitor for late appearing RT-related toxicity.

b. FD 1 is the first dose of M3541 and first fraction of RT. Planning of the RT will follow institutional guidelines and will start on a Monday (with Saturday and Sundays as a M3541 / RT holiday). In cohorts where required, subjects will be asked to stay overnight in a supervised environment on FD 1 unless the PK sampling and ECG assessment at 8 and 12 hours postdose can be completed otherwise. FD 10 is the last administration of M3541 / RT and in all cases will be followed by a 2-day M3541 / RT holiday before the start of the DLT follow-up period. In case of premature withdrawal from the study during the treatment period, the assessments scheduled for the visit on FD 10 should be performed. In such cases, this visit will be considered the EoS visit. If FD 10 is on a Friday then safety laboratory assessments and urinalysis (as required) must be done on FD 9.

c. The 3-week DLT follow-up period (PTDs 1 through 21) starts on the third day after the last administration of M3541 / RT. With the treatment period starting on a Monday, PTD 21 will land on a Sunday. Subjects should present to the clinic that following Monday for the DLT follow-up visit. Subjects with ongoing AEs should present to the clinic throughout the DLT follow-up period as appropriate and instructed by the Investigator. See Section 6.5 and subsections for allowed and prohibited medications during the DLT period.

d. Subjects must meet all inclusion criteria and not any exclusion criteria prior to enrollment. Hepatitis B and C results obtained within 3 months prior to screening are still valid for the purpose of this study. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered.

e. All subjects will be asked to complete the BPI-SF at Screening and FD 1 prior to other study related assessments. If a subject has no pain in an area to be irradiated as part of the experimental treatment (M3541 + RT), the subject should mark "0" in all pain scales and activity scales. For subjects with cancer pain from lesions to be irradiated as part of the experimental treatment, any pain medication should be documented (name, dose, frequency, including if used on an "as needed" basis) on the appropriate eCRF page.

f. Subjects with cancer pain from lesions to be irradiated as part of the experimental treatment (M3541 + RT) on FD 1 will be asked to complete the BPI-SF on each subsequent FD and on PTD 21 and PTD 30 prior to any other study-related procedures. The subject should only rate pain and interference with daily activity as they relate to areas being irradiated as part of the experimental treatment. The Investigator must also ensure any new pain medication or change in ongoing pain medication (name, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page.

g. Screening for HIV will be performed according to local practice and local regulatory guidance.

h. Serum β-HCG pregnancy test at Screening and urine thereafter.

i. Vital signs include body temperature, respiration rate, pulse, blood pressure, body weight, and height (height only at Screening).

j. Areas to be irradiated should be examined at baseline. Worsening of a condition within an irradiated area (eg, skin reactions, bleeding) during the DLT evaluation period should be reported as a TEAE with grade and relatedness to RT and / or M3541. Improvement of a condition within an irradiated area (eg, improved pain, reduced bleeding) should be reported on the appropriate efficacy-related eCRF page.

k. Only new anticancer therapies and any change in treatment given for treatment-related SAEs will be documented.

l. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. Standard ECGs will be evaluated by the Investigator for safety assessment. See Table 5 for details of ECG acquisition timing during the treatment period.

m. Tumor imaging by CT, MRI, or bone scan at baseline to document extent of lesions according to RECIST 1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts. A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks.

n. Tumor assessments using the same method used at baseline are to be completed every 6 weeks beginning on PTD 42 of the Mid-term Safety Follow-up period through the Long-term Safety Follow-up period (ie, PTD 180) for a total of 4 assessments. During the survival follow-up period (ie, PTD 181 to 365) tumor assessments will occur approximately on PTD 270 and PTD 365. Assessments are not required if the subject has started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in the eCRF.

o. See Table 5 for details of PK blood sampling.

p. FD 1 only; see Table 5 for details.

q. FD 9 only; see Table 5 for details.

r. CCI [redacted]

s. CCI [redacted]

t. See Table 5 for details of pharmacodynamic marker and gene expression analysis sample collection.

u. See Table 5 for details of immune cell analysis sample collection.

v. M3541 will be administered at the clinic 1 hour and 45 minutes (± 60 minutes) before RT is started.

w. Can be followed up via phone call every 3 months if no other assessments are required.

Table 3 Schedule of Assessments: Twice Weekly Intermittent M3541 Dosing Schedule: Monday / Thursday

Study Periods	Screening	DLT Evaluation Period (5 weeks) Twice Weekly Schedule						Short-term Safety FU	Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (3 weeks)				
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 21[c]	PTD 22 to 30	PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Signed informed consent	X										
Inclusion / exclusion criteria[d]	X[d]	FD 1									
Demography	X										
Medical history	X										
BPI-SF[e]	X[e]	To be completed on each FD[f]					X[f]	X[f]			
HIV, HBV, and HCV testing[g]	X										
Tumor specimen collection (optional)	X										
β-HCG pregnancy test (if applicable)[h]	X[h]							X[h]			
Vital signs[i]	X	X				X	X	X	X	X	X
Physical examination	X	X		X		X	X	X	X	X	X
Evaluation of all tissues in RT area[j]	X	FD 6		X		X	X	X	X	X	X
ECOG PS	X					X		X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X[c]	X	X	X	X[a]

Study Periods	Screening	DLT Evaluation Period (5 weeks) Twice Weekly Schedule						Short-term Safety FU	Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (3 weeks)				
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 21[c]	PTD 22 to 30	PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Concomitant medication	X	X	X	X	X	X	X	X	X[k]	X[k]	X[k]
Hematology	X	X		X		X[b]	X	X			
Coagulation	X	X		X		X[b]	X	X			
Serum chemistry	X	X		X		X[b]	X	X			
Urinalysis (dipstick)	X						X	X			
12-lead ECG (including QTcF)[l]	X	See Table 6									
Tumor assessment (RECIST 1.1)	X[m]								X[n]	X[n]	X[n]
PK blood samples[o]		See Table 6					See Table 6				
Blood sampling for plasma protein determination		X[p]			X[q]						
CCI											
Pharmacodynamic markers in blood[t]		See Table 6									
CCI											
Immune cell analysis[u]		See Table 6									

Study Periods	Screening	DLT Evaluation Period (5 weeks) Twice Weekly Schedule						Short-term Safety FU	Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (3 weeks)				
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 21[c]	PTD 22 to 30	PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
M3541[v]		X			X		No Treatment				
RT 3 Gy/FD		X	X	X	X	X					
Follow-up for RT-related toxicity / survival[w]								X	X	X	X[w]

AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EoS = End-of-Study; FD = Fraction Day (days when RT and M3541 are given); FU = follow-up; Gy = Gray; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; PTD = Post-treatment Day (starting the third day after the last dose of RT and M3541 until 1 year later); QTcF = Fridericia corrected QT interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiotherapy; TEAE = treatment-emergent adverse event.

a. All subjects will be followed up for disease progression until 1 year after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (eg, PD, if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EoS occurs prior to PTD 365, all assessments must be done as planned for PTD 365. All subjects will be followed for survival and for delayed AEs for up to 1 year (and beyond for AEs) from PTD1. After the 1 year follow-up, the Investigator will be asked to contact subjects every 3 months (± 1 month, phone call is acceptable) until the defined end of the study (see Section 5.7) to enquire and monitor for late appearing RT-related toxicity.

b. FD 1 is the first dose of M3541 and first fraction of RT. Planning of the RT will follow institutional guidelines and will start on a Monday (with Saturday and Sundays as a M3541 / RT holiday). In cohorts where required, subjects will be asked to stay overnight in a supervised environment on FD 1 unless the PK sampling and ECG assessment at 8 and 12 hours postdose can be completed otherwise. FD 10 is the last administration of M3541 / RT and in all cases will be followed by a 2-day M3541 / RT holiday before the start of the DLT follow-up period. In case of premature withdrawal from the study during the treatment period, the assessments scheduled for the visit on FD 10 should be performed. In such cases, this visit will be considered the EoS visit. If FD 10 is on a Friday then safety laboratory assessments and urinalysis (as required) must be done on FD 9.

c. The 3-week DLT follow-up period (PTDs 1 through 21) starts on the third day after the last FD. With the treatment period starting on a Monday, PTD 21 will land on a Sunday. Subjects should present to the clinic that following Monday for the DLT follow-up visit. Subjects with ongoing AEs should present to the clinic throughout the DLT follow-up period as appropriate and instructed by the Investigator. See Section 6.5 and subsections for allowed and prohibited medications during the DLT period.

d. Subjects must meet all inclusion criteria and not any exclusion criteria prior to enrollment. Hepatitis B and C results obtained within 3 months prior to screening are still valid for the purpose of this study. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered.

e. All subjects will be asked to complete the BPI-SF at Screening and FD 1 prior to other study related assessments. If a subject has no pain in an area to be irradiated as part of the experimental treatment (M3541 + RT), the subject should mark "0" in all pain scales and activity scales. For subjects with cancer pain from lesions to be irradiated as part of the experimental treatment, any pain medication should be documented (name, dose, frequency, including if used on an "as needed" basis) on the appropriate eCRF page.

f. Subjects with cancer pain from lesions to be irradiated as part of the experimental treatment (M3541 + RT) on FD 1 will be asked to complete the BPI-SF on each subsequent FD and on PTD 21 and PTD 30 prior to any other study-related procedures. The subject should only rate pain and interference with daily activity as they relate to areas being irradiated as part of the experimental treatment. The Investigator must also ensure any new pain medication or change in ongoing pain medication (name, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page.

g. Screening for HIV will be performed according to local practice and local regulatory guidance.

h. Serum β-HCG pregnancy test at Screening and urine thereafter.

i. Vital signs include body temperature, respiration rate, pulse, blood pressure, body weight, and height (height only at Screening).

j. Areas to be irradiated should be examined at baseline. Worsening of a condition within an irradiated area (eg, skin reactions, bleeding) during the DLT evaluation period should be reported as a TEAE with grade and relatedness to RT and / or M3541. Improvement of a condition within an irradiated area (eg, improved pain, reduced bleeding) should be reported on the appropriate efficacy-related eCRF page.

k. Only new anticancer therapies and any change in treatment given for treatment-related SAEs will be documented.

l. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. Standard ECGs will be evaluated by the Investigator for safety assessment. See Table 6 for details of ECG acquisition timing during the treatment period.

m. Tumor imaging by CT, MRI, or bone scan at baseline to document extent of lesions according to RECIST 1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts. A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks.

n. Tumor assessments using the same method used at baseline are to be completed every 6 weeks beginning on PTD 42 of the Mid-term Safety Follow-up period through the Long-term Safety Follow-up period (ie, PTD 180) for a total of 4 assessments. During the survival follow-up period (ie, PTD 181 to 365) tumor assessments will occur approximately on PTD 270 and PTD 365. Assessments are not required if the subject has started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in the eCRF.

o. See Table 6 for details of PK blood sampling.

p. FD 1 only; see Table 6 for details.

q. FD 9 only; see Table 6 for details.

r. CCI [redacted]

s. CCI [redacted]

t. See Table 6 for details of pharmacodynamic marker and gene expression analysis sample collection.

u. See Table 6 for details of immune cell analysis sample collection.

v. M3541 will be administered at the clinic 1 hour and 45 minutes (± 60 minutes) before RT is started. If not taken on the scheduled day, it could eventually be taken 1 day later. Next dose should be as per next field in this table.

w. Can be followed up via phone call every 3 months if no other assessments are required.

Table 4 Electrocardiogram, Pharmacokinetic, and Biomarker Assessments: M3541 Once per FD Dosing Schedule

		Hours Postdose (± minutes)										
	Predose	0.5 (± 5)	1.0 (± 5)	1.5 (± 15)	2.25 (± 15)	3 (± 15)	4 (± 15)	6 (± 30)	8 (± 30)	12 (± 30)	72 (± 24h)	240 (± 24h)
Electrocardiogram[a]												
FD 1[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]			
FDs 2, 5, 6, and 7[a]	X				X							
FD 10[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]			X[d]	X[d]
Pharmacokinetic[e]												
FD 1	X	X	X	X	X	X	X	X	X[c]			
FDs 2, 5, 6, and 7	X				X							
FD 10	X	X	X	X	X	X	X	X			X[d]	X[d]
Plasma protein determination												
FD 1, 5, and 10	X											
Pharmacodynamic marker analysis[e]												
FDs 1 and 6	X		X			X						
FDs 2, 4, 7, and 9	X											
Immune cell sampling[e]												
FDs 1, 6, and 9	X											

ECG = electrocardiogram; FD = Fraction Day (days when RT and M3541 are given); PK = pharmacokinetics; PTD = post-treatment day.

a. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and evaluated by the Investigator for safety assessment. All ECGs should be collected prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. The ECG should be obtained using a Holter recorder. An ECG on PTD 1 is only required if the PTD 1 optional PK sample is drawn.

b. At the indicated times, additional digital ECG recordings equivalent to triplicate ECGs are to be recorded for quantitative analysis by a central ECG laboratory (after the end of the study). The ECG recordings must be acquired immediately prior to the PK sample scheduled for the same time point. The ECG should be obtained using a Holter recorder.

c. The 8 and 12 hour PK samples and ECG assessments are optional.

d. The 72 and 240-hour timepoints correspond to PTD 1 and 8, respectively. The 72-hour PK sample is optional and will only be taken if the patient has a visit on PTD 1.

e. The predose sample should be taken within 1 hour before dosing at each sampling day. PK and pharmacodynamic sampling should occur after any required ECG recording.

Table 5 **Electrocardiogram, Pharmacokinetic, and Biomarker Assessments: Thrice Weekly Intermittent M3541 Dosing Schedule: Monday / Wednesday / Friday**

		Hours Postdose (± minutes)									
		1	3	4	6	8	12	24	26	72	240
	Predose	(± 5)	(± 30)	(± 30)	(± 30)	(± 30)	(± 30)	(± 120)	(± 120)	(± 24h)	(± 24h)
Electrocardiogram[a]											
FD 1 (M3541 dosing)	X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]	X[b,c]	X[b,d]	X[b,d]		
FD 3, 5, 6, and 8 (M3541 dosing)	X		X								
FD 10 (M3541 dosing)	X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]	X[b,c]			X[b,e]	X[b,e]
Pharmacokinetic[f]											
FD 1 (M3541 dosing)	X	X	X	X	X	X[c]	X[c]	X[d]	X[d]		
FD 3, 5, 6, and 8 (M3541 dosing)	X		X								
FD 10 (M3541 dosing)	X	X	X	X	X	X[c]	X[c]			X[e]	X[e]
Plasma protein determination											
FD 1	X										
FD 10	X										
Pharmacodynamic marker CCI CCI											
FDs 1, 6, and 8	X	X	X					FD 1 only			
FD 2	X										
Immune cell sampling[f]											
FDs 1, 6, and 9	X										

ECG = electrocardiogram; FD = Fraction Day (RT days); PK = pharmacokinetics; PTD = post-treatment day.

a. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and evaluated by the Investigator for safety assessment. All ECGs should be collected prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. The ECG should be obtained using a Holter recorder. An ECG on PTD 1 is only required if the PTD 1 optional PK sample is drawn.

b. At the indicated times, additional digital ECG recordings equivalent to triplicate ECGs are to be recorded for quantitative analysis by a central ECG laboratory (after the end of the study). The ECG recordings must be acquired immediately prior to the PK sample scheduled for the same time point. The ECG should be obtained using a Holter recorder.

c. The 8 and 12-hour PK samples and ECG assessments are optional.

d. The 24 and 26-hour timepoints will happen on FD 2 and may be adapted, keeping a minimal interval of 2 hours between the 24 and the 26-hour samples

e. The 72 and 240-hour post dose timepoints correspond to PTDs 1 and 8, respectively No M3541 dosing on this day. The 72-hour PK sample is optional and will only be taken if the patient has a visit on PTD 1.
f. The predose sample should be taken within 1 hour before dosing at each sampling day. PK and pharmacodynamic sampling should occur after any required ECG recording.

Table 6 **Electrocardiogram, Pharmacokinetic, and Biomarker Assessments: Twice Weekly Intermittent M3541 Dosing Schedule: Monday / Thursday**

		Hours Postdose (± minutes)										
		1	3	4	6	8	12	24	26	48	96	264
	Predose	(± 5)	(± 30)	(± 30)	(± 30)	(± 30)	(± 30)	(± 120)	(± 120)	(± 120)	(± 24h)	(± 24h)
Electrocardiogram[a,b]												
FD 1 (M3541 dosing)	X[c]	X[c]	X[c]	X[c]	X[c]	X[c,d]	X[c,d]	X[c]	X[c]	X[c]		
FD 4 (M3541 dosing)	X		X									
FD 6 (M3541 dosing)	X		X									
FD 9 (M3541 dosing)	X[c]	X[c]	X[c]	X[c]	X[c]	X[c,d]	X[c,d]	X[c]	X[c]		X[c,e]	X[c,e]
Pharmacokinetic[f]												
FD 1 (M3541 dosing)	X	X	X	X	X	X[d]	X[d]	X	X	X		
FD 4 (M3541 dosing)	X		X					X	X			
FD 6 (M3541 dosing)	X		X					X	X	X		
FD 9 (M3541 dosing)	X	X	X	X	X	X[d]	X[d]	X	X		X[e,g]	X[e]
Plasma protein determination												
FD 1	X											
FD 9	X											
Pharmacodynamic marker CCI CCI												
FDs 1, 6, and 9	X	X	X									
FD 2	X											
Immune cell sampling[f]												
FDs 1, 6, and 9	X											

ECG = electrocardiogram; FD = Fraction Day (RT days); PK = pharmacokinetics; PTD = post-treatment day.

a. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and evaluated by the Investigator for safety assessment. All ECGs should be collected prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. The ECG should be obtained using a Holter recorder. An ECG on PTD 1 is only required if the PTD 1 optional PK sample is drawn.

b. In case dosing is delayed on FD 4 and FD 6, PK sampling will be done at dosing day. In case dosing is delayed from FD 9 to FD 10, the 24h and 26h ECGs and PK samples may be skipped.

c. At the indicated times, additional digital ECG recordings equivalent to triplicate ECGs are to be recorded for quantitative analysis by a central ECG laboratory (after the end of the study). The ECG recordings must be acquired immediately prior to the PK sample scheduled for the same time point. The ECG should be obtained using a Holter recorder.
d. The 8 and 12-hour PK samples and ECG assessments are optional.
e. The 96 and 264-hour post dose timepoints correspond to PTDs 1 and 8, respectively. The 96-hour PK sample is optional and will only be taken if the patient has a visit on PTD 1.
f. The predose sample should be taken within 1 hour before dosing at each sampling day. PK and pharmacodynamic sampling should occur after any required ECG recording.

2 Sponsor, Investigators and Study Administrative Structure

The Sponsor of this clinical study with M3541 is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA.

A Contract Research Organization (CRO), IQVIA, Durham, NC, USA, will undertake the operational aspects of this study, with oversight from the Sponsor. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP) maintained by IQVIA. The IPMP will be prepared by the IQVIA Clinical Project Manager in cooperation with other IQVIA Operational Team Leads.

2.1 Investigational Sites

Up to 15 study centers in the United States are planned to be included in this study.

2.2 Study Coordination / Monitoring

The Sponsor will supply the study medication, M3541, to the sites. Packaging and distribution of clinical supplies will be performed by the Clinical Trial Supplies department of the Sponsor and the contracted manufacturing organization.

Safety laboratory assessments will be performed locally by investigational sites. Pharmacokinetic (PK), pharmacodynamic, CCI , and biomarker assessments will be performed centrally under the responsibility of the Sponsor.

The Global Drug Safety Department, Merck KGaA, Darmstadt, Germany or their designated representatives will perform safety surveillance and perform safety monitoring on serious adverse events (SAEs, see Section 7.4.1.4).

Quality assurance of the study conduct will be performed by the Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

The Sponsor's department of Global Biostatistics will supervise the statistical analyses (with the exception of the PK data analyses), which will be outsourced to a CRO.

The Coordinating Investigator (Appendix IV) represents all Investigators for decisions and discussions regarding this study, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to study design and execution and is responsible for the review and signoff of the clinical study report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix IV.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

The study will appear in ClinicalTrials.gov and all other required registries.

2.3 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will serve as both a safety monitoring and decision-making body. The SMC is responsible for dose-escalation / de-escalation decisions (such as adding new cohorts at different previously non-explored dose level or modifying dose schedules) and may decide to enroll additional subjects at a previously explored dose level and / or schedule, which will be considered a new cohort at that dose level. While changing the schedule, the SMC will ensure to change appropriately (or not) the ECG assessments and PK sampling times. The SMC may recommend to stop the study based on the observed safety profile. The decisions of the SMC will be guided by the results of the Bayesian regression model with overdose control (see Section 5.1). The recommendation according to the Bayesian regression model is not binding and the final decision is to be made by the SMC.

The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

3 Background Information

Many patients with cancer are administered treatments which generate DNA damage, such as radiotherapy (RT) (ionizing radiation) and certain chemotherapeutic drugs. DNA strand breaks are difficult to repair, especially highly genotoxic double-strand breaks (DSB) and if left unrepaired, may lead to cell cycle arrest, cell death, or senescence. Double-strand breaks in DNA are remedied by 2 major distinct mechanisms; the homologous recombination repair and the nonhomologous end joining pathway.

Ataxia-telangiectasia mutated (ATM) is a ubiquitously expressed serine / threonine protein kinase primarily activated by DSBs. It phosphorylates a network of key proteins (eg, H2AX, CHK2, p53, KAP1). Beside DSB repair, ATM affects the DNA damage checkpoint and thereby controls cell cycle arrest, and irreversible physiological responses such as senescence or cell death. In addition, ATM is part of other signaling networks, including cell metabolism and growth, oxidative stress, and chromatin remodeling, all of which are able to affect cancer progression. The inhibition of ATM kinase results in a synergistic enhancement of DNA DSB-inducing treatment modalities, such as RT, certain chemotherapeutic drugs, and the combination of both, chemoradiotherapy.

3.1 M3541

M3541 is a highly potent, and selective adenosine triphosphate-competitive inhibitor of the ATM kinase. As a result of the mechanism of action, M3541 enhances the therapeutic effect of DNA DSB-inducing treatment modalities. In vivo, M3541 has been shown to improve the antitumor

efficacy of RT. In contrast, M3541 alone shows very limited activity in nonclinical pharmacodynamics studies.

Further information about the nonclinical data to date can be found in the Investigator's Brochure (IB).

3.1.1 M3541 Pharmacology in Animal Models

M3541 showed efficacy in 4 different nude mice xenograft models of human cancer (FaDu, NCI-H460, NCI-H1975, and Capan-1) when combined with medically relevant doses of radiation. In the FaDu model, complete tumor regression was observed in 80% and 90% of the animals treated with 25 mg/kg and 50 mg/kg of M3541, respectively, and tumors did not regrow during the study period (160 days). At doses of 100 mg/kg, tumor xenograft regressed in all 10 animals and none had relapsed at the end of the study. In the NCI-H460 model, tumors treated with RT only rapidly progressed under treatment; however, the tumors treated with RT and M3541 regressed during the treatment and observation periods up to approximately Day 60. The NCI-H1975 and Capan-1 xenograft models showed regression under RT treatment; 10% complete regression in the NCI-H1975 model and 30% complete regression in the Capan-1 model. In combination with M3541, the results showed strong additional treatment effect resulting in 100% regression with no regrowth during the study period (140 days). In all studies, the treatment was generally well-tolerated. During the treatment period, the animals in all treatment groups (including a RT only control group) showed moderate body weight loss that was fully reversible and likely due to the daily treatment procedures (ie, oral gavage, anesthesia, and RT over a period of 6 weeks).

Nonclinical safety pharmacology studies on the function of the cardiovascular, respiratory, and nervous systems and the toxicity profile of M3541 showed no prohibitive findings with respect to clinical development.

3.1.2 M3541 Pharmacokinetics and Metabolism in Animal Models

The plasma concentrations of M3541 in male and female rats and dogs were determined during 4-week oral toxicity studies. Following oral administration of M3541 (SDD formulation) to rat and dog, absorption was rapid with median time to reach maximum concentration (t_{max}) between 1 and 2 hours. M3541 was systemically available in both rat and dog. In rat, systemic exposure increased roughly in proportion to dose from 10 to 75 mg/kg in terms of area under the concentration-time curve (AUC), but less so in terms of maximum observed plasma concentration (C_{max}). No relevant gender-related differences in exposure were observed. In dog, between the 3 and 10 mg/kg/day dose groups, area under the AUC and C_{max} increased with increasing dose in a roughly dose-proportional manner; however, only marginal increases in AUC and C_{max} were observed with a further dose increase to 30 mg/kg/day. No relevant gender-related differences in exposure were observed.

In an in vitro blood distribution study, M3541 distributed mainly into plasma with mean blood to plasma concentration ratios < 1 cross-species (0.67 mouse, 0.80 rat, 0.85 monkey, 0.57 dog, and

0.64 human). In all PK and toxicokinetic studies the determination of unchanged M3541 was performed in plasma.

The binding of M3541 to plasma proteins was high, with mean unbound fractions at therapeutic concentrations of approximately 3.2% (mouse), 4.0% (rat), and 8.0% (monkey). An increase of the free fraction across the tested concentration range (1 to 30 µM) was observed for dog and human, indicating saturation of plasma protein-binding sites involved. The comparison of plasma protein binding to individual protein fractions suggested that human serum albumin and alpha-1-acid glycoprotein (AAG) contributed to the overall binding of M3541 in human plasma. Binding to AAG showed concentration dependency.

Following intravenous dosing, the volume of distribution was low in the dog (0.66 L/kg) and moderate to high (0.8 to 9.0 L/kg) in mouse, rat, and monkey as compared with their total body water, indicating a general wide tissue distribution in mouse, rat, and monkey. Tissue distribution studies with radiolabel have not been performed to date.

Metabolism is the likely predominant elimination pathway before excretion and no human specific metabolites were identified.

An assessment of the human cytochrome P450 (CYPs) enzymes responsible for the in vitro metabolism of M3541 has been made using recombinant CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5. Results demonstrated that M3541 was mainly metabolized by CYP1A2 and CYP3A4/5. The human in vitro clearance of M3541 was very low and the relative contributions of these enzymes to total oxidative metabolic clearance of M3541 was determined by inhibition experiments with selective CYP inhibitors in a human HepatoPac co-culture system. A major contribution by CYP3A4/5 and a minor contribution of CYP1A2 to the total oxidative metabolic clearance of M3541 was confirmed.

Current data suggest that the clinical relevance of P-glycoprotein (P-gp) and hepatic uptake transporter-mediated drug-drug interactions cannot be excluded and the metabolic clearance of M3541 may potentially be affected by co-administered drugs that are known to be CYP3A4/5 inhibitors or inducers.

3.1.3 Scientific Rationale for the Study

Approximately 50% of all patients with malignant diseases receive RT treatment during the course of their treatment history, either as a single modality treatment or as chemoradiotherapy, with curative or palliative intent. The optimal efficacy of RT is often constrained by the requirement to limit the RT dose in order to protect the surrounding normal tissue from radiation-induced toxicity. Inhibition of ATM exerts anticancer activity only in the presence of DNA DSBs, which can be specifically and locally induced with RT. As M3541 inhibits ATM activity, it is therefore believed that M3541 will enhance the localized antitumor effects of RT, allowing for lower doses of RT. Nonclinical data suggests that when M3541 is given in combination with RT there is an increase in response rate, local tumor control, and time to recurrence. The mechanism of action of M3541 means that all patients treated with RT could potentially benefit from M3541 when given in combination. Furthermore, adverse events (AEs) induced by RT are local, which allows for the

simultaneous determination of AEs due to systemic M3541 exposure. This provides a rationale to studying the combination of M3541 and RT in this First-in-Human (FIH) dose-escalation study.

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

The clinical study will be conducted in compliance with the clinical study protocol, ICH, GCP, and any other additional applicable regulatory requirements.

3.1.4 Rationale for Starting Dose

For this FIH study, the recommended starting dose is 50 mg orally once daily when given with RT. This dose was selected using an interspecies scaling approach in accordance with the ICH S9 guideline and the Guidance for Industry on the Estimation of Safe starting dose (refer to Section 4.3.7 of the current IB).

Based on nonclinical scaling, M3541 is predicted to have a low clearance and volume of distribution, resulting in a moderate plasma half-life of approximately 8 hours, compatible with once daily dosing. Accumulation of drug after multiple oral doses is not expected.

The biologically effective dose range for M3541 in humans is anticipated to be 150 to 480 mg orally once daily. This is based on the extrapolation of the unbound biologically effective concentration of approximately 7 µg/L in mouse, at which complete tumor regression was seen in combination with RT. Given the high uncertainty in the human absorption and clearance estimates, some clinical efficacy may already be seen at the starting dose of 50 mg.

M3541 has a low and pH-dependent solubility and its absorption may be improved with concomitant food intake. To standardize the subject population, subjects will be asked to consume a light breakfast prior to arriving at the clinic.

3.1.5 Rationale for Treatment Schedule Changes

At the time of submission of this protocol amendment (Version 5.0 / Amendment 4.0), preliminary data on M3541 safety and plasma concentrations from 8 subjects dosed at 50, 100, or 200 mg once per radiotherapy fraction day (FD; Cohort 1 n=3, 50 mg, cohort 2 n=4, 100 mg and cohort 3 n=1, 200 mg) were available. M3541 was shown to be safe at these dose levels. No DLT or SAEs assessed as related to M3541 were observed. M3541 was detectable in all plasma samples after dosing of the subject, with a rapid early absorption phase. The current PK sampling timepoints, based on a daily M3541 dosing, allowed only for an accurate calculation of C_{max} but not for PK parameters for a drug with a terminal half-life ($t_{1/2}$) going beyond 24 hours. An extrapolation of the terminal elimination phase derived from postdose plasma concentrations on a non-treatment day and predose after the weekend treatment break suggested a $t_{1/2}$ of more than 48 hours (versus the anticipated 8 hours based on predictions). Overall, the observed exposure was higher than expected for the 50 mg once per FD dose level and accumulation was observed for each subject. The safety profile was favorable with at most Grade 1 treatment-related toxicities.

Given these findings, a modification of the dosing schedule is indicated and the proposal takes into account the longer $t_{1/2}$ and the potential of M3541 accumulation: The ECG and PK sampling schedule is modified accordingly.

The starting dose for the intermittent dose schedules will be based on the available safety and PK data gathered in the first 2 cohorts of the once per FD schedule. As for all dose cohorts, the SMC will finally decide on the dose for each of the 2 intermittent schedules. On an intermittent dosing schedule, the biologically effective dose is expected to be in the range of 100 to 200 mg unless a non-linear exposure increase is observed. However, at the time of submission of the current protocol amendment (Version 5.0 / Amendment 4.0), it is not anticipated that subjects will be dosed according to the intermittent dose schedules as these are unlikely to confer any advantage compared with daily dosing.

3.1.6 Summary of the Overall Benefit and Risk

The benefit-risk ratio has been carefully considered in the planning of the study. The mode of action of M3541 is known and has been characterized in vitro and in vivo with animal models of proven relevance.

Based on the nonclinical data available to-date, the conduct of the study is considered justifiable using the dose(s) and dosage regimen(s) of M3541 as specified in this clinical study protocol. The inclusion and exclusion criteria were chosen to minimize potential risk to subjects and maximize possible benefit from M3541 treatment in combination with RT. A SMC is planned for the ongoing assessment of the risks (see Section 2.3). The study will be discontinued in the event of any new findings that indicate a relevant deterioration of the benefit-risk balance and would render continuation of the study unjustifiable.

The protocol includes close monitoring of the main target organs (determined to be lymphatic and hematopoietic systems, pancreas, kidneys, lung, liver, stomach, and intestine). A decrease in B-lymphocytes and infections could also be a potential risk. Further, hematological and clinical chemistry monitoring will include white blood cell (WBC) count and any indication of infection as well as the monitoring of liver, renal, and pancreas enzymes.

Current data suggest that the clinical relevance of P-gp and hepatic uptake transporter-mediated drug-drug interactions cannot be excluded and the metabolic clearance of M3541 may potentially be affected by co-administered drugs that are known to be CYP3A4/5 inhibitors or inducers; therefore, medications or herbal supplements known to be potent inhibitors or inducers of CYP3A or P-gp, organic anion-transporting polypeptides (OATPs) or organic cation transporters (OCTs), or drugs mainly metabolized by CYP3A with a narrow therapeutic index should be used with caution. For subjects currently receiving or unable to stop using medications or herbal supplements known to be potent inhibitors of CYP3A or P-gp, inclusion in this study should only be considered if in the opinion of the Investigator the subject may benefit from treatment with M3541, and approval is provided by the Sponsor (see Section 5.3.2).

The safety data obtained from dose levels 50 and 100 mg show a favorable safety profile with no DLTs and no treatment-related SAEs observed, leading to the SMC decision on escalation to an

M3541 dose of 200 mg once per FD, which is currently under evaluation. Currently, the clinical benefit of M3541 is unknown. Nonclinical pharmacology data show that M3541 can enhance the therapeutic effect of RT, when used in combination with RT, by increasing and maintaining the extent of unrepaired DNA damage. Nonclinical safety pharmacology studies on the function of the cardiovascular, respiratory, and nervous systems and the toxicity profile of M3541 showed no prohibitive findings with respect to clinical development. Subjects are expected to benefit from the palliative radiotherapy. The extent to which this will be improved by M3541 administration is unknown.

In conclusion, the results from a comprehensive series of safety pharmacology, PK, and toxicology studies, together with the primary pharmacology data, support the clinical testing of this new antitumor agent with the maximum recommended starting dose for the FIH study of 50 mg orally once daily while the data obtained in the first cohorts of the M3541 once per FD regimen support exploration of the different dose schedules (M3541 thrice and twice weekly schedules) using a starting dose of 100 mg. Moreover, the safety data obtained from the first cohorts (dose levels 50 and 100 mg) support the shortened DLT period.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M3541 may be found in Section 3.1.3 and the Investigator's Brochure.

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

4 Study Objectives

The following primary, secondary, and exploratory objectives apply to each of the explored M3541 dosing schedules.

4.1 Primary Objective

The primary objective is to determine the maximum-tolerated dose (MTD) and recommended Phase II dose(s) (RP2D) for M3541 in combination with fractionated palliative RT in subjects with solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities likely to benefit from palliative RT.

4.2 Secondary Objectives

The secondary objectives are:

- To evaluate the safety profile and tolerability of M3541 in combination with fractionated palliative RT
- To explore the antitumor activity of M3541 in combination with fractionated palliative RT
- To assess the PK of M3541 in combination with fractionated palliative RT.

4.3 Exploratory Objectives

Exploratory objectives are:

- To explore the antitumor activity of M3541 in combination with fractionated palliative RT on the sum of the longest diameter (SoLD) of the irradiated target lesions
- To assess treatment-related changes in pharmacodynamic markers of M3541 in combination with fractionated palliative RT
- CCI
- To explore the potential impact on the immune system of M3541 in combination with palliative RT
- CCI
- To explore plasma protein binding of M3541
- CCI
- CCI

5 Investigational Plan

5.1 Overall Study Design and Plan

This is a Phase I, uncontrolled, open-label, multicenter, dose-escalation study of M3541 given in combination with palliative RT.

This dose-escalation study will evaluate the safety, tolerability, PK, pharmacodynamic, and explore antitumor activity of M3541 in combination with fractionated palliative RT in subjects with solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities likely to benefit from palliative RT.

For the M3541 once per FD daily dosing schedule, subjects will receive oral administration of M3541 at a starting dose of 50 mg (first dose level) once per FD in combination with fractionated palliative RT. Radiotherapy will be administered over 2 consecutive calendar weeks (ie, Monday through Sunday, with Saturday and Sunday as M3541 / RT holidays). The treatment will start on Mondays for all subjects, unless pre-agreed otherwise with the Sponsor. The total RT dose will be 30 Gy given in 10 fractions 3 Gy/FD on FD 1 to FD 10 (see Figure 1).

Subsequent dose-escalation cohorts will explore intermittent M3541 treatment schedules (thrice weekly, ie, Monday / Wednesday / Friday or twice weekly, ie, Monday / Thursday) in combination with fractionated RT given in 10 fractions 3 Gy/FD on FD 1 to FD 10 (given over 2 consecutive treatment weeks with treatment starting on Mondays).

On M3541 treatments days, M3541 will be administered before RT (1 hour and 45 minutes ± 60 minutes).

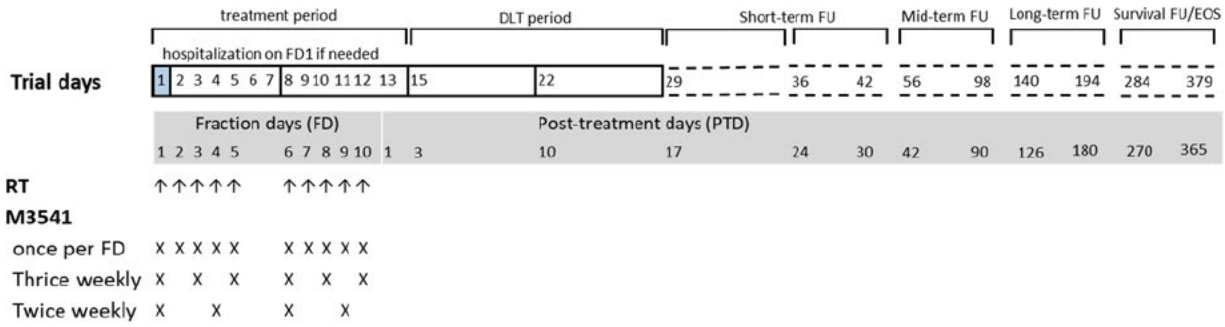
Treatment delays will be handled according to instructions in Section 6.2.1.

In cohorts where required, subjects will be asked to stay overnight in a supervised environment on FD 1 unless the PK sampling and ECG assessment at 8 and 12 hours postdose can be completed otherwise.

The DLT evaluation period will be 4 weeks in duration and comprises the 2-week treatment period (including a 2-day M3541 / RT holiday after FD 5) plus the 2-week DLT follow-up period that starts after the last administration of M3541 / RT (see Figure 1). The DLT evaluation period could only exceed the 4-week period if M3541 / RT has been interrupted and given over a period exceeding 2 weeks. All effort should be made to complete 10 FDs if possible. Post-treatment follow-up measures are described in Section 7.1.4.

For the first cohort of 3 subjects in the M3541 once per FD cohort, Subject 1 and Subject 2 will be treated at an interval of 3 weeks apart. There will also be a stagger of 3 weeks between Subject 2 and Subject 3.

Figure 1 Study Treatment, Evaluation, and Follow-up Periods (Updated)



DLT: Dose Limiting Toxicity; EOS: End of Study; FU: Follow Up; RT: Radiotherapy

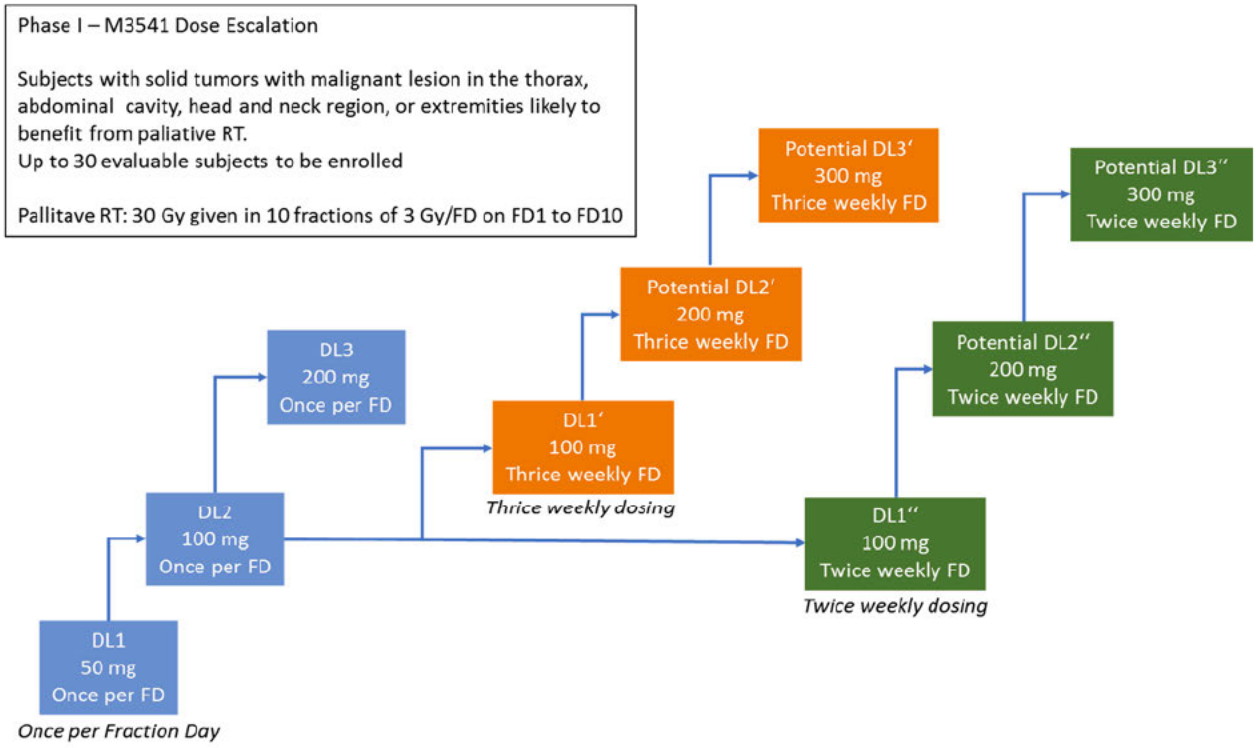
Note: Following implementation of Protocol Amendment 4.0, the DLT follow-up period will start on the day after the last administration of M3541 and will be of 2 weeks' duration.
FD = fraction day; PTD = Post-treatment Day.

After 3 subjects in any explored cohort have been treated and completed the DLT evaluation period, the SMC will evaluate all safety data from that cohort, and, at a minimum, all available PK and PD data from the previous dose step, and decide either to escalate to the next dose level / schedule, stay on the actual dose level by recommending to add an additional cohort of subjects at the same dose level / schedule, or to de-escalate to a lower dose level in a treatment schedule. The SMC may recommend to stop a treatment schedule or the study, or to investigate additional dose levels and / or schedules in order to adapt and optimize the M3541 treatment, in combination with RT, in support of the R2PD selection.

Up to 8 cohorts are planned with data from 3 subjects per dose level (1 cohort). Based on nonclinical assumptions prior to the first subject receiving the first M3541 dose, the pre-planned dose levels are 50, 100, 200, 300, 500, and 800 mg orally once per FD (Figure 2); however, the number of cohorts and schedules and the actual dose to be explored in each subsequent cohort remains to be determined, as well as the number of subjects (aiming for 3 per cohort) and will be finally decided upon by the SMC guided by the results of the Bayesian model.

The criteria for initiating subsequent cohorts of subjects, representing dose-escalation or other treatment decisions, such as schedule changes and / or additional or altered assessments, are made by the SMC and will be based on the observed safety profile and on the occurrence of DLTs (according to the below DLT definition in Section 5.1.1), SAEs, AEs, laboratory data, vital sign measurements generated during the DLT evaluation period, and all available PK data from, at a minimum, up to the previous cohort. The results derived from a Bayesian 2-parameter logistic regression model with overdose control will guide the SMC on the choice for the dose level / schedule for the next cohort of subjects. This guidance of the Bayesian regression model is not binding. The final decision is to be taken by the SMC. By this approach, all prior information, including all data from previous completed cohorts, will be taken into account for the recommendation of the next dose level. The SMC may also choose a different dose level (other than the pre-planned protocol described dose level and /or the suggested by the Bayesian regression model) per schedule for the next cohort and may deviate from the pre-planned number of 3 subjects per cohort.

Figure 2 Study Design Diagram



DL = dose level; F/W = fractions per week; MTD = maximum-tolerated dose; Ph I = Phase I; PK = pharmacokinetics;

QD = once daily; RP2D = recommended Phase II dose; SMC = Safety Monitoring Committee.

The study design for dose-escalation employs a Bayesian 2-parameter logistic regression model with overdose control analysis for sequential dose level cohorts of 3 subjects in order to guide the SMC on the choice for the next dose level from a predicted set of acceptable doses or to provide an alternative dose level, all enable the SMC to determine finally the RP2D / MTD.

5.1.1 Dose-limiting Toxicity

For this study, a DLT is defined as any of the following AEs that occur during the DLT evaluation period (except those that are clearly and incontrovertibly due to disease progression or extraneous causes), with severity graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE V4.03):

- Grade ≥ 3 non-hematologic toxicity, except:
  - Nausea, vomiting and / or diarrhea lasting ≤ 3 days in the once per FD and twice weekly schedules or 2 days in the thrice weekly schedule that can be medically managed
  - Worsening of pre-existing tumor pain associated with tumor lesions for which the subject is irradiated in the context of this study
- Evidence of treatment-related hepatocellular injury for > 3 days in the once per FD and twice weekly schedules and 2 days in the thrice weekly schedule, such as ≥ 5 × the upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) and without any other apparent clinical causality
- Any occurrence of Hy's law (defined as aminotransferases > 3 × ULN, alkaline phosphatase < 2 × ULN, total bilirubin ≥ 2 × ULN, with no other reason to account for these abnormalities)
- Febrile neutropenia or Grade 4 neutropenia lasting for > 5 days, Grade 4 thrombocytopenia or any requirement for platelet transfusion (as defined by Grade 4 thrombocytopenia lasting for > 5 days or Grade ≥ 3 thrombocytopenia with bleeding), Grade 4 anemia that is unexplained by the underlying disease
- Any toxicity related to study treatment that causes the subject to interrupt treatment (defined as having to delay the next scheduled M3541 administration) for:
  - ≥ 4 FDs in the once per FD dosing schedule.
  - > 1 FD in the thrice weekly schedule
  - not to be able to be treated within 24 hours of the scheduled treatment time in the twice weekly schedule
- A related treatment-emergent adverse event (TEAE) that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk.

Information on DLTs will be sent by the Sponsor or delegate to the SMC core members within 1 working day of the receipt of documented information.

Dose escalation of M3541 will start from 50 mg orally once per FD until 1 of the following stopping rules apply:

- A maximum number of up to 30 evaluable subjects over all treatment schedules are included, unless otherwise indicated by the SMC;
- More than 3 cohorts are assigned to the same dose level on the same schedule; or
- The estimate for DLT probability of the MTD reaches sufficient precision.

The study will end as defined in Section 5.7.

5.1.2 Planned Treatment and Study Duration

The planned study duration for an individual subject includes a 21-day screening period, a scheduled 2-week M3541 / RT treatment period plus follow-up, which includes a 2-week DLT follow-up period and safety and survival follow-up for up to 1 year after the end of the M3541 / RT treatment period. Beyond 1 year and for the duration of the study, the Investigator will be asked to contact subjects every 3 months (± 1 month, by phone is acceptable) until the defined end of the study (see Section 5.7) to enquire and monitor for late appearing RT-related toxicity.

The total duration of the study is related to the number of cohorts enrolled. With 8 cohorts a total study duration of up to 32 months is estimated (including enrollment and 1-year post-treatment survival follow-up).

Overall timing for the study:

- Planned first subject in: Q3, 2017
- Planned date last subject out (including follow-up): Q4, 2020.

5.2 Discussion of Study Design

This Phase I, uncontrolled, open-label, multicenter, dose-escalation study of M3541 in combination with palliative RT will explore the safety, tolerability, PK, pharmacodynamics, and signs of clinical efficacy of M3541. Subjects with advanced solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities likely to benefit from palliative RT will receive M3541 plus RT (3 Gy/FD, 5 FDs per calendar week, FD 1 to FD 10 over a 2-calendar week period).

The inclusion and exclusion criteria were chosen to maximize the potential for subject safety and possible benefit from M3541 in combination with palliative RT.

An open-label design is considered appropriate for a dose-escalation study in subjects with cancer.

The first dose-level cohort of 3 subjects will receive M3541 orally at a dose of 50 mg per FD. This dose was selected using an interspecies scaling approach in accordance with the ICH S9 guideline and the Guidance for Industry on the Estimation of Safe starting dose (see Section 3.1.4).

At the starting dose level, no DLTs, no SAEs and no Grade ≥ 3 AEs occurred during the DLT period. In view of a longer $t_{1/2}$ (more than 48 hours) than predicted in this cohort, a decision to amend the study protocol was made to allow exploration of intermittent treatment schedules (ie, thrice weekly and twice weekly administration) during dose escalation and adjusting PK sampling times accordingly.

The study design employs a Bayesian 2-parameter logistic regression model with overdose control analysis and sequential cohorts of 3 subjects in order to enable the SMC to select the next dose level per schedule from a predicted set of acceptable dose levels or schedules or to provide an alternative dose level per schedule, and to determine the MTD. This design aims to maximize the protection of subjects by reducing the number of subjects exposed to possible drug toxicities at each new dose level per schedule and minimize the number of subjects exposed to suboptimal dose levels. The SMC may decide to stop further dose finding at any dose level or schedule based on available safety and PK data. The primary objective of the study is to establish the MTD and a RP2D of M3541 administered continuously or intermittently in combination with palliative RT; therefore, the primary endpoint chosen was occurrence of DLTs, which is standard for FIH studies.

M3541 has a low and pH-dependent solubility and its absorption may be improved with concomitant food intake. To standardize the subject population, subjects will be asked to consume a light breakfast prior to arriving at the clinic.

Nonclinical safety studies with M3541 have shown an acceptable profile to support the clinical development in advanced-stage cancer patients. Refer to Section 4 of the current IB.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Study Population

The criteria in Sections 5.3.1 (Inclusion Criteria) and 5.3.2 (Exclusion Criteria) are designed to enroll only subjects, 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 subject 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.

Individuals meeting all inclusion criteria and no exclusion criteria may be enrolled into the study as subjects. Prior to performing any study assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled.

1. Male or female subjects aged ≥ 18 years
2. Ability to understand the purpose of the study, provide signed and dated informed consent, and comply with all study visits and procedures and assessments
3. Subjects must have solid tumors with malignant lesions in the thorax, abdominal cavity, head and neck region, or extremities (any histology) likely to benefit from palliative radiotherapy; subjects requiring palliative RT for lesions in the spine or lesions adjacent to the spinal cord are excluded from this study
4. Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2
5. Life expectancy ≥ 3 months
6. Adequate hematological function defined by WBC count ≥ 3×10^9/L with absolute neutrophil count ≥ 1.5×10^9/L, lymphocyte count ≥ 0.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/ dL, ie, 5.59 mmol/L (in absence of blood transfusion within prior 2 weeks)
7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 3 × ULN, and an ALT level ≤ 3 × ULN. For subjects with tumor involvement in their liver, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 1.5 × ULN is acceptable
8. Adequate renal function defined by either serum creatinine ≤ 1.5 × ULN or an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula
9. A male subject must agree to the following during the study treatment period and for at least 100 days after the last dose of study treatment:

- Refrain from donating sperm

PLUS, either:

- Abstain from intercourse with a woman of childbearing potential (WOCBP)

OR

- Use a male condom:
    - When having sexual intercourse with a WOCBP, who is not currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of less than 1% per year, as described in Appendix III, since a condom may break or leak

10. A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

    - Not a WOCBP (defined in Appendix III).

    OR

    - If a WOCBP agrees to use a highly effective contraceptive method (ie, with a failure rate of less than 1% per year), preferably with low user dependency, as described in Appendix III for the following time periods:
        - Before the first dose of study treatment, 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 at least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

AND

A barrier method, as described in Appendix III.

- During the treatment period:
- After the treatment period (ie, after the last dose of study treatment is administered) for at least 40 days after the last dose of study treatment

  The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study treatment
- Have a negative serum pregnancy test, as required by local regulations, within 21 days before the first dose of study treatment.

- Additional requirements for pregnancy testing during and after study treatment are in Table 1, Table 2, and Table 3.
- 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.

5.3.2 Exclusion Criteria

Subjects are not eligible for this study if they fulfill any of the following exclusion criteria:

1. Use of other anticancer therapy (see Section 6.5.2) within 5 x their elimination half-life, but no longer than 15 days, before the first dose of M3541 administration. The use of any investigational agent is not allowed within 28 days before the first dose of M3541
2. Residual toxicity due to previous anticancer therapy with no return to baseline or Grade ≤ 1 (except alopecia) according to CTCAE V4.03
3. Extensive prior RT on more than 30% of bone marrow reserves (by Investigator judgment), or prior bone marrow / stem cell transplantation within 5 years before study start
4. Prior RT to the same region that would be irradiated in this study
5. Subjects at increased risk for radiation toxicities, such as known collagen vascular disease (eg, scleroderma, Sjogren's disease, etc) or other inherited radiation hypersensitivity syndromes (eg, Gorlin syndrome, Fanconi anemia, ataxia-telangiectasia, etc.)
6. Major surgical intervention within 28 days prior to the first dose of M3541 administration

7. Significant cardiac conduction abnormalities, including a history of long corrected QT interval (QTc) syndrome and / or pacemaker, or impaired cardiovascular function such as New York Heart Association classification score > 2
8. Hypertension uncontrolled by medication
9. Known central nervous system (CNS) metastases causing clinical symptoms or metastases that require therapeutic intervention. Subjects with a history of treated CNS metastases (by surgery or radiation therapy) are not eligible unless they have fully recovered from treatment, demonstrated no progression for at least 2 months, and do not require continued steroid therapy. Subjects with CNS metastases incidentally detected during Screening that do not cause clinical symptoms and for which standard of care suggests no therapeutic intervention is indicated, should be discussed with the Sponsor Medical Responsible
10. Known human immunodeficiency virus (HIV) positivity, known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (eg, Hepatitis B virus [HBV] or Hepatitis C virus [HCV]; HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive HCV antibody with reflex to positive HCV RNA), current alcohol abuse, or cirrhosis of the liver (Child-Pugh B and C are not eligible)
11. Ongoing active infection (requiring systemic treatment) or treatment with live or live attenuated vaccine within 30 days of dosing
12. Active difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions (including pancreas deficiency requiring Creon therapy) that may hamper compliance and/or absorption of M3541
13. History of any other significant medical disease such as major gastric or small bowel surgery, recent drainage of significant volumes of ascites or pleural effusion or a psychiatric condition that might in the assessment of the Investigator preclude participation in the study
14. Known hypersensitivity or allergic reaction to the study treatments or to 1 or more of the excipients used
15. Subjects currently receiving or unable to stop using medications or herbal supplements known to be potent inhibitors of CYP3A or P-gp (CYP and / P-gp must stop at least 1 week before treatment with M3541) or potent inducers of CYP3A or P-gp (must stop at least 3 weeks before treatment with M3541) or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior). See list at http://medicine.iupui.edu/clinpharm/ddis.
16. Pregnant or breastfeeding
17. Legal incapacity or limited legal capacity.

5.4 Criteria for Initiation of Study Treatment

The inclusion and exclusion criteria will be checked at the Screening visit after the subject has signed the ICF. Eligible subjects will be enrolled before treatment start after verification of fulfilling all inclusion criteria without fulfilling any exclusion criterion.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Study Therapy

The subject must be withdrawn from M3541 in the event of any of the following:

- Withdrawal of consent
- Development of unacceptable toxicity
- Occurrence of progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1 (RECIST 1.1) or initiation of any other anticancer therapy
- Occurrence of any condition that is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and / or Sponsor prior to treatment completion
- TEAEs that cause a treatment delay of > 3 FDs of radiotherapy.
- Occurrence of RT-related Grade ≥ 3 AEs, or any AE if discontinuation of IMP is desired or considered necessary by the Investigator and /or the subject (if applicable)
- Occurrence of pregnancy
- Use of a non-permitted concomitant drug (including any other drug with known anticancer activity unless specified otherwise in Section 6.5.2)
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise subject safety or study integrity.

Planned tumor assessments will continue as scheduled if a subject does not complete the protocol defined study therapy (unless subject withdraws consent).

5.5.2 Withdrawal from the Study

Subjects are free to withdraw from the study at any time without giving their reasons.

A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent
- Participation in any other study during the DLT evaluation period

A subject may also be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons but will be followed for survival and delayed AEs for up to 1 year.

If a subject fails to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the study, the assessments scheduled for the Short-term Safety Follow-up (Post-treatment Day [PTD] 30) and End-of-Study visits should be performed, if possible. In any case, the appropriate electronic case report form (eCRF) section must be completed.

Additional subjects will be enrolled for each subject who withdraws from the study after signing consent and successfully meeting entry criteria (ie, enrolls) but did not receive M3541. In addition, subjects excluded from the DLT analysis set will be replaced.

5.6 Premature Termination of the Study

The clinical study may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk-benefit judgment for any IMP. The Sponsor may discontinue the study if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

In addition, the study may be discontinued at the discretion of the Sponsor upon recommendation by the SMC in the event of the occurrence of AEs previously unknown in respect to their nature, severity, and duration, or an unexpected incidence of known AEs.

Health Authorities and Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

5.7 Definition of End of Study

The study will end after the last subject has completed the 1-year survival follow-up period.

A subject has completed the study if she/he has completed all study parts, including the last visit or the last scheduled procedure as shown in the Schedule of Assessments (Table 1, Table 2, and Table 3).

6 Investigational Medicinal Product and Other Drugs Used in the Study

The term "Investigational Medicinal Product" refers to an active substance or a placebo being tested or used as a reference therapy in a clinical study, including products that have a marketing

authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

In this study, the term "Investigational Medicinal Product" refers to the investigational drug M3541, which is the only IMP used in this study.

A reference therapy will be applied in combination with the IMP. The reference therapy consists of palliative RT with a total dose of 30 Gy given in 10 fractions (over 10 FDs) over a time period of 2 weeks.

6.1 Description of the Investigational Medicinal Product

M3541, CCI , is a white to pale brown powder.

M3541 is a Biopharmaceutics Classification System Class II compound with poor solubility at weakly acid to neutral pH. CCI The drug is available as tablet dosage form in 10 mg, 50 mg, and 100 mg dose strength. The white tablets are film-coated and of round (10 mg and 50 mg) or oblong shape (100 mg).

6.2 Dosage and Administration

Subjects in the first dose-level cohort will be assigned to receive M3541 at a starting dose of 50 mg orally once per FD, which will be given 1 hour and 45 minutes (± 60 minutes) before RT fraction. The dose of M3541 can be changed from 1 cohort to another according to the dose-escalation rules described in Section 5.1 for the different dose levels and dosing regimens. No intrasubject dose escalation / de-escalation is permitted.

Subjects will be asked to arrive at the clinic ≥ 2 hours prior to scheduled RT on M3541 treatment days, having had a light breakfast, and will be administered M3541 at the clinic 1 hour and 45 minutes (± 60 minutes) before RT is started. Subjects will take their assigned dose of M3541 with a full glass of water (approximately 240 mL or 8 fluid ounces).

The subsequent doses should not be taken until the predose PK and pharmacodynamic (as appropriate) blood collection has been completed.

If a subject vomits after taking their dose of M3541, they should be given an antiemetic but no further dose will be given that day. Prophylactic antiemetics should then be given before subsequent doses of M3541. Any change from the dosing schedule, ie, dose interruptions, should be recorded in the eCRF.

6.2.1 General Dose Modification and Discontinuation Guidelines

There is no intrasubject dose reduction or escalation planned for M3541. In general, each subject will stay on M3541 at the dose level and schedule assigned at study entry unless treatment needs

to be interrupted or stopped. If the Investigator believes that a TEAE is due to RT, M3541 will also be stopped.

Maximum delays or M3541 administrations missed within the complete 10-FD treatment period are:

- For the once per FD schedule:
  - If RT and M3541 treatment must be interrupted for ≥ 4 FDs, subjects must be discontinued from M3541
- For the thrice weekly schedule:
  - If M3541 cannot be administered on the scheduled day / time, the M3541 dose will be skipped
  - If RT and M3541 treatment must be interrupted for ≥ 2 FDs, subjects must be discontinued from M3541
- For the twice weekly schedule:
  - If M3541 cannot be administered on the scheduled day / time, then M3541 administration should until 24 hours later, and if not possible, the dose will be skipped
  - If RT and M3541 treatment must be interrupted for ≥ 1 FDs, subjects must be discontinued from M3541

M3541 should not be administered if no radiotherapy is scheduled for that day. If the subject must be discontinued from M3541; RT can be resumed at the discretion of the Investigator.

6.3 Assignment to Treatment Cohorts

The Investigator or delegate will assign a unique subject identifier number to eligible subjects in chronological order at the time of informed consent signature. Subject identifiers will be comprised of digits representing the study number, the site number, and the subject number, which is allocated sequentially. Subject enrollment will be managed manually.

6.4 Noninvestigational Medicinal Products to be Used

6.4.1 Radiotherapy

Radiotherapy will follow institutional guidelines with the first day of RT treatment on a Monday (FD 1). The total dose of RT is 30 Gy given in 10 daily fractions (ie, 3 Gy/FD, 5 FDs per calendar week, FD 1 to FD 10 over a 2-calendar week period). An interruption in the administration of RT will result in an interruption of M3541 for as long as the RT is interrupted (see Section 6.2.1).

All effort should be made to complete 10 FDs if possible. The formal criteria for dose modification in the study are included in Table 7. The study site will provide the Sponsor with irradiation simulation details when required.

Table 7 Dose Interruption for M3541 and Radiotherapy

Toxicity	Dose Modifications	
	M3541[a]	Radiotherapy[b]
Toxicities in Radiation Field • Observations occurring in field of irradiation (which can't be explained by the disease or any other extraneous cause) such as mucositis, radiation dermatitis, cystitis, proctitis, nausea, vomiting, etc	**Grade 3** Permanently discontinue M3541. In case of liver-related transaminase increases, treatment should be permanently discontinued unless the transaminase rise is undeniably due to major tumor response. **Grade 4** Permanently discontinue M3541	Temporarily interrupt RT during M3541 interruption. If interruption is longer than allowed in Section 6.2.1, RT without M3541 can be resumed at the discretion of the Investigator.

Systemic Toxicities Considered to be Unrelated to RT, Hematologic
• 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
  • Any grade of anemia
	Temporarily interrupt treatment. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or baseline. See Section 6.2.1 for dose delay allowances.	Temporarily interrupt RT during M3541 interruption. If interruption is longer than allowed in Section 6.2.1, RT without M3541 can be resumed at the discretion of the Investigator.

Systemic Toxicities Considered to be Unrelated to RT, Hepatocellular • Treatment-related hepatocellular injury for more than 3 days, such as Grade ≥ 3 ALT or AST (≥ 5 × ULN) 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 treatment. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or baseline. See Section 6.2.1 for dose delay allowances.	Temporarily interrupt RT during M3541 interruption. If interruption is longer than allowed in Section 6.2.1, RT without M3541 can be resumed at the discretion of the Investigator.

Toxicity	Dose Modifications	
	M3541[a]	Radiotherapy[b]

Systemic Toxicities, Other
• Nonhematologic Toxicities
  • Any Grade ≥ 3 toxicity, excluding:
  • Diarrhea (≤ 3 days duration) following adequate and optimal therapy
  • 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
	Temporarily interrupt treatment. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or baseline. See Section 6.2.1 for dose delay allowances.	Temporarily interrupt RT during M3541 interruption. If interruption is longer than allowed in Section 6.2.1, RT without M3541 can be resumed at the discretion of the Investigator.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE V4.03 = Common Terminology Criteria for Adverse Events, Version 4.03; FD = fraction day; IMP = investigational medicinal product; RT = radiotherapy; ULN = upper limit of normal

Note: Severity of AEs will be graded using the CTCAE V4.03 toxicity grades.

a As all treatments with M3541 will be given in combination with RT, an interruption in the administration of RT would lead to an interruption in treatment with M3541.

b A maximum RT interruption of ≤ 3 FDs in total is allowed within the complete treatment period. If RT / M3541 treatment have been interrupted by more than > 3 radiotherapy days, the subject must be discontinued from M3541. All effort should be made to complete 10 FDs if possible.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject from the date of signature of informed consent through the Short-term Safety Follow-up (PTD 30), are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration, and indication of each drug. For pain medication taken for pain in lesions treated with per-protocol treatment (radiotherapy + M3541), the Investigator must ensure any change in ongoing pain medication or any new pain medication (name, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page.

Starting at PTD 31 (start of the Mid-term Safety Follow-up), only anticancer drug treatments and any change in treatment given for treatment-related SAEs should be recorded.

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

6.5.1 Permitted Medicines

Any medications (other than those excluded by the appropriate sections of the clinical study protocol) that are considered necessary for the subjects' welfare and will not interfere with the IMP may be given at the Investigator's discretion.

The following medications are permitted:

- Local, topical, or short-term (ie, < 7 days) systemic corticosteroids
- Anti-infectious drugs
- Hematopoietic growth factors, if medically indicated

The Investigator will record all concomitant medications taken by the subject and any concomitant procedures provided to the subject during the study, from the date of signature of informed consent, in the appropriate sections of the eCRF.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

6.5.2 Prohibited Medicines

Subjects must not have received chemotherapy, immunotherapy, biologic therapy, or any other anticancer therapy within 5 x their elimination half-life, but no longer than 15 days, before the first dose of IMP administration (6 weeks for nitrosoureas or mitomycin C). Thus, the washout period for prior anticancer therapy is defined as 5 x the elimination half-life of the relevant anticancer therapy, up to a maximum of 15 days.

These therapies are generally prohibited during the treatment period and the DLT follow-up period.

Subjects with functional neuroendocrine tumor who have progressed clinically or radiographically on octreotide or lanreotide may remain on octreotide or lanreotide for control of hormonal syndromes and still be allowed on study. Similarly, subjects under stable hormone therapy (having received hormone therapy for > 3 months) may remain on hormone therapy and are allowed in the study.

Radiotherapy (involving < 30% of bone marrow) to any other lesion is allowed at any time beyond PTD 7.

Medications or herbal supplements known to be potent inhibitors or inducers of CYP3A or P-gp, OATP or OCT or drugs mainly metabolized by CYP3A, with a narrow therapeutic index are prohibited (unless as otherwise agreed to by the Sponsor). Refer to Drug Development and Drug Interactions for a classification of in vivo inhibitors (see Appendix II).

If the administration of a prohibited concomitant drug becomes necessary during the treatment period, eg, due to AEs, the subject should be discontinued from the study treatment and complete all assessments listed under the Safety Follow-up (PTDs 15, 22, and 30) and End-of-Study visits.

6.5.3 Other Interventions

The following non-drug therapies must not be administered or performed during the study (and within 28 days before the start of study treatment):

- Major surgery
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)
- Subjects should not abuse alcohol or other drugs during the study

6.5.4 Special Precautions

Based on nonclinical safety findings, the main target organs of toxicity are lymphatic and hematopoietic systems, pancreas, kidneys, lung, liver, stomach, and intestine. In association with the decrease in B-lymphocytes, infections may be a potential risk; therefore, subjects receiving M3541 should be monitored for adverse effects of lymphatic and hematopoietic systems, gastrointestinal system (including liver and pancreas), kidneys, and respiratory system should be considered. Further, hematological and clinical chemistry monitoring should include WBC count and monitoring of liver, renal, and pancreas enzymes.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

No specific AEs or ADRs of particular concern have been identified. The Investigator should use clinical judgment and follow the guidelines in Table 7 the management of AEs / ADRs.

6.6 Packaging and Labeling of the Investigational Medicinal Product

The M3541 film-coated tablets will be ready for oral use. The tablets will be packed into high density polyethylene bottles (10 tablets per bottle) “child proof system” bottles with desiccant.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.7 Preparation, Handling, CCI of the Investigational Medicinal Product

CCI Do not freeze. Detailed information can be found in the pharmacy manual.

6.8 Investigational Medicinal Product Accountability

The Investigator is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing and / or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.

- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical study and prepared at the site.
  - The use of each dose by each subject.
  - The disposition (including return, if applicable) of any unused IMP.
  - Dates, quantities, batch numbers, expiry dates, and the individual subject study numbers.

The Investigator site should maintain records that adequately document that subjects were provided the doses specified in this protocol and all IMPs provided were fully reconciled.

The Sponsor's Monitor will periodically collect and review the IMP accountability forms and where applicable, will check all returns (both unused and used containers) before arranging for their return or authorizing their destruction by the study site.

At the conclusion or termination of this study, study site personnel and the Clinical Study Monitor will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Study Monitor will be supplied with a copy for filing of the Investigational Drug Accountability Forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on:

- All administered units
- All unused units
- All destroyed units (during the study)
- All destroyed units at the end of the study
- Date of destruction(s)
- Name and signature of the Investigator / pharmacist.

It must be ensured at each study site that the IMP is not used

- After the expiry date, and
- After the retest date unless the IMP is reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Study Monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

As M3541 is administered at the clinic, no special compliance monitoring is required; however, the exact time of M3541 administration and start of RT should be recorded appropriately in the eCRF.

6.10 Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical study protocol or planned for an individual subject enrolled in the study. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the study medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.1.4.

There is no established treatment for overdose with M3541. The Investigator should use clinical judgment to manage any overdose and should be guided by the nature of the presenting symptoms and standard evaluation results, and use standard treatment for those observations.

6.13 Medical Care of Subjects after End of Study

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

Upon withdrawal from the study, subjects may receive whatever care they and their physicians agree upon. Subjects will be followed for survival as specified in Section 7.1.4.

7 Study Procedures and Assessments

7.1 Schedule of Assessments

Schedules of Assessments are provided in Table 1 through Table 6.

7.1.1 Screening and Baseline Procedures and Assessments

During the Screening period and before any study-related investigations and assessments are started that are not part of routine medical care for the subject, the subject will be asked to sign the relevant Informed Consent Forms (ICFs) as described in Section 9.2.

The washout period for prior anticancer treatment is defined in Section 6.5.2. Major surgery is not permitted within 28 days before the start of study treatment (Section 6.5.3). Hematology and chemistry laboratory samples must be drawn and reviewed within 24 hours prior to first dose administration.

The subjects' information that will be documented during Screening includes the demographic information (birth date, sex, ethnicity, and race) and the complete medical history, including the history of the tumor disease and prior anticancer therapies, previous medications (prior 30 days to signing of ICF), concomitant medications, and baseline medical condition (the information of concomitant medications and AEs will be monitored throughout the study treatment period). Moreover, an Emergency Medical Support card will be handed out at the baseline assessments visit.

All subjects will be asked to complete the Brief Pain Inventory – Short Form (BPI-SF) at Screening prior to other study-related assessments. If a subject has no pain in an area to be irradiated as part of the experimental treatment (M3541 + RT), the subject should mark "0" in all pain scales and activity scales. For subjects with cancer pain from lesions to be irradiated as part of the experimental treatment, any pain medication should be documented (name, dose, frequency, including if used on an "as needed" basis) on the appropriate eCRF page.

During Screening, subjects will undergo a complete physical examination, dermatological assessments (assessments for skin lesions or rash with biopsy of suspicious lesions), vital signs assessments (body temperature, respiration rate, pulse, blood pressure), body weight and height (height only at Screening), 12-lead electrocardiogram (ECG), determination of the ECOG PS (Appendix I) and laboratory assessments, including hematology / coagulation, serum chemistry, and urinalysis as outlined in Table 1, Table 2, or Table 3 as appropriate.

During Screening, a serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed for females of child bearing potential (see detailed information in Appendix III).

Subjects must be tested for HBV and HCV at Screening (as these conditions are study entry exclusion criteria) unless test results obtained within 3 months prior to Screening are available. Screening for HIV will be performed according to local practice and local regulatory guidance.

Although not mandatory, all efforts should be made by the study site to request a historical tissue sample before the first dose of study drug (see Section 7.6).

The tumor evaluation (type / staging, etc) should be performed at Screening (see Section 7.2.5 for details). Bone scans should be performed as clinically indicated. A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks.

7.1.2 Treatment Period

The treatment period consists of 10 FDs (FD 1 to FD 10 over a 2-calendar week period) of palliative RT (5 FDs per week with FD 1 on a Monday and with the Saturday and Sunday between FD 5 and FD 6 as an RT holiday). M3541 is administered either on a once per FD schedule

(Table 1), or on an intermittent schedule of thrice weekly (Table 2) or twice weekly (Table 3) schedules, with M3541 always administered on RT FDs. In case the Investigator inserts RT holidays (interruption due to toxicity, see Section 6.2.1), M3541 treatment should be suspended and should be restarted with RT at the next first RT day for which M3541 is scheduled to be given.

All effort should be made to complete RT with 10 FDs if possible. Subjects will be asked to visit the investigational site according to the Schedule of Assessments (see Table 1, Table 2, or Table 3 as appropriate) in order to receive M3541 and RT and for study assessments to be performed.

The following instructions should be followed:

- All subjects will be asked to complete the BPI-SF on FD 1 prior to other study-related assessments. Subjects with cancer pain from lesions to be irradiated as part of the experimental treatment (M3541 + RT) on FD 1 will be asked to complete the BPI-SF on each subsequent FD prior to any other study-related procedures. The subject should only rate pain and interference with daily activity as they relate to areas being irradiated as part of the experimental treatment. The Investigator must also ensure any new pain medication or change in ongoing pain medication (drug, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page
- Subjects should be instructed to consume a light breakfast prior to arriving at the clinic for M3541dose administration
- CCI [redacted]
- On M3541 treatment days, M3541 should be given at the study site 1 hour and 45 minutes (± 60 minutes) before RT is started
- On M3541 treatment days when samples for PK and pharmacodynamics determination are scheduled, M3541 should not be given until the predose PK and pharmacodynamics (as appropriate) collection has been completed (see Table 4, Table 5, or Table 6 as appropriate)
- ECGs will be acquired according to Table 4, Table 5, or Table 6 as appropriate and should be collected prior to any associated PK and pharmacodynamic blood sampling. The ECG should be obtained using a Holter recorder.

7.1.3 Dose-limiting Toxicity Evaluation Period

The DLT evaluation period will be 4 weeks in duration, including the 2-week treatment period (including a 2-day M3541 / RT holiday after FD 5) plus a 2-week DLT follow-up period that starts on the day after the last administration of M3541 / RT (see Figure 1). After the M3541 / RT treatment period, subjects will return to the clinic on PTD 15 (+ 2 days) for assessments (including the BPI-SF as applicable) as outlined in Table 1. The DLT evaluation period could exceed the 4-week period only if M3541 / RT has been interrupted and given over a period exceeding 2 weeks.

Subjects with ongoing AEs should present to the clinic throughout the DLT follow-up period as appropriate and instructed by the Investigator (see Section 6.5 and subsections for allowed and

prohibited medications). It is expected that the Investigator will follow his / her subjects and will ask subjects to come in to the clinic (and document) when AEs are known to happen. In absence of any new or major toxicity / AE during the DLT follow-up period, the subject need only be seen on PTD 15 (+ 2 days) and PTD 22 (± 2 days).

7.1.4 Post-treatment Follow-up

All subjects will be followed for response until 1 year after the end of the M3541 / RT treatment period or earlier due to any reason whereby tumor assessments are no longer applicable (eg, if a new treatment is started, withdrawal of consent). All subjects will be followed for survival and for AEs (short term) and delayed AEs (late appearing RT-related toxicity) for up to 1 year after the end of the M3541 / RT treatment period, after which only delayed RT-related toxicity events will be collected. The post-treatment follow-up period is divided into:

- Short-term (PTD 22; ± 2 days and PTD 30; ± 2 days)
- Mid-term (PTDs 42 and 90; ± 7 days)
- Long-term (PTDs 126 and 180; ± 14 days)
- Survival follow-up / End-of-Study (PTDs 270 and 365; ± 21 days) visits
- Post 1-year Safety Follow-up to collect RT-related toxicity events every 3 months (± 1 month, telephone contact is acceptable) until the defined end of the study (see Section 5.7).

Subjects will be asked to return to the clinic on the designated days (± the visit window) for assessments as outlined in Table 1.

At any point during the post-treatment follow-up, if the subject withdraws from the study prematurely, the assessments scheduled for the Short-term Safety Follow-up (PTD 30) and End-of-Study visits should be performed.

7.2 Demographic and Other Baseline Characteristics

The assessments and procedures described in this section must be performed during the Screening period.

7.2.1 Demographic Data

The following demographic data will be recorded:

- Date of birth
- Sex
- Ethnicity
- Race.

7.2.2 Diagnosis of Tumor

The tumor disease information that will be documented and verified at the Screening visit for each subject includes:

- Detailed history of the tumor, including histopathological diagnosis, grading and staging in accordance with the Union Internationale Contre le Cancer Tumor Node Metastasis Classification at diagnosis (UICC TNM)
  - The M category (M0 or M1) of the tumor at the time of study entry, based on screening assessments
- All therapy used for prior treatment of the tumor (including surgery, radiotherapy and chemotherapy, immunotherapy, etc)
- Any other conditions that were treated with chemotherapy, radiation therapy, or immunotherapy
- Current cancer signs and symptoms and side effects from current and / or previous anticancer treatments
- Current cancer disease status.

7.2.3 Medical History

To determine the subject's eligibility to the study, a complete medical history of each subject will be collected and documented during Screening, which will include, but may not be limited to, the following:

- Past and concomitant non-malignant diseases and treatments
- All medications taken and procedures carried out within 30 days prior to Screening.

For the study entry, all the subjects must fulfill all inclusion criteria described in Section 5.3.1, and none of the subjects should have any exclusion criterion from the list described in Section 5.3.2.

7.2.4 Vital Signs and Physical Examination

Vital signs including body temperature, respiratory rate, pulse (after 5-minute rest), arterial blood pressure (after 5-minute rest), and body weight will be recorded at study entry prior to any (scheduled) blood draw. Height will be measured at Screening only.

Physical examinations will be performed.

The ECOG PS will be documented during the Screening phase.

7.2.5 CT or MRI Scans and Bone Scans for Tumor Assessment at Baseline

A CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest, abdomen, and pelvis (at a minimum and other established assessments of tumor burden if CT / MRI imaging is not sufficient for the individual subject; other regions as specifically required for specific tumor indications) will be performed within 28 days prior to study treatment start in order to document the baseline status of the tumor disease using RECIST 1.1 target and non-target lesions. If the results of a CT scan or MRI performed within 4 weeks prior to first treatment are available, the Screening CT / MRI does not need to be performed.

A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter, brain CT / MRI scan should be performed if clinically indicated by development of new specific symptoms.

A bone scan should be done at Screening as clinically indicated.

7.2.6 Cardiac Assessments

A 12-lead ECG will be recorded at Screening. The ECG will be recorded after the subject has been in a supine position breathing quietly for 5 minutes and prior to any associated PK blood sampling. The ECG should be obtained using a Holter recorder. The ECG results will be used to evaluate the heart rate, atrial-ventricular conduction, QR, QT, and QTc intervals, and possible arrhythmias. All ECG and ECG extract results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject.

The Investigator will judge the overall ECG interpretation as normal or abnormal. If abnormal, it will be decided if the abnormality is clinically significant or not clinically significant and the abnormality will be recorded on the eCRF. Any clinically significant ECG abnormality (cardiac assessment) will be recorded as an AE or SAE as appropriate (see Section 7.4.1 and subsections).

In presence of a Grade $\geq$ 3 QTc prolongation (QTc $\geq$ 501 ms and / or an increase with at least 60 ms over baseline, on 2 separate consecutive ECGs that cannot be explained by the underlying medical condition or concomitant therapy) the treatment with M3541 should be interrupted and the subject evaluated by a cardiologist. The IMP M3541 will be re-introduced only after recovery of QTc to $\leq$ 480 ms (Grade 1) if recovery is within 3 days and the QTc prolongation was deemed unrelated to M3541. In case of incomplete recovery (QTc between 480 and 500 ms) and in the presence of demonstrated clinical benefit to the subject, described as CR, PR, or a minor response (minor response being a regression of at least 20%), M3541 may be re-introduced if the QTc prolongation was deemed unrelated to M3541 and upon agreement with the cardiologist and in consultation with the Sponsor, and with the agreed expectation that the clinical benefit of resuming M3541 treatment with RT is greater than the potential risk.

7.2.7 Clinical Laboratory Tests

Blood samples will be collected for clinical laboratory parameter evaluations. These clinical laboratory test results will serve not only as the baseline values for subsequent safety clinical laboratory evaluations during the study, but also help to make sure that each enrolled subject fulfills all the study entry criteria for laboratory parameters as listed in Section 5.3.1 and does not meet any of the study exclusion criteria as listed in Section 5.3.2. Detailed description of laboratory assessments is provided in Section 7.4.3.

7.3 Efficacy Assessments

For all subjects, tumor response assessment will be performed by CT scan or MRI (if MRI is used, CT of chest is mandatory) of the chest / abdomen / pelvis (plus other regions as specifically required for specific tumor types) and other established assessments of tumor burden if CT / MRI imaging is insufficient for the individual subject. All the scans performed at Baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

A brain CT / MRI scan (either, with contrast preferred) is required at Screening if not performed within the previous 6 weeks. Thereafter brain CT / MRI scan should be performed, if clinically indicated by development of new specific symptoms. A bone scan should be performed at Screening and beyond as clinically indicated. Skin metastasis can be used as target lesions according to RECIST 1.1 using measurements by caliper, if they fulfill RECIST 1.1 for target lesions as described below. The presence of new cutaneous lesions will be considered diagnostic of progression for RECIST 1.1, even if not imaged. For each subject, the Investigator will ensure appropriate assessment of the irradiated lesion to follow for determining response: CT or MRI images of primary and / or metastatic tumor masses, physical examination findings. All available images collected during the study period will be considered for the follow up of the subject (to determine further additional treatment needs). The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the study have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Assessments (see Table 1).

Bone scans are to be performed according to local and institutional standards.

The following endpoints will be derived based on appropriate tumor assessments according to RECIST 1.1 overall and for lesions within an irradiated field, including those after the end of study treatment until first assessment of PD:

- Progression-free survival: time from start of treatment to first assessment of PD or death, whichever is earlier. Subjects alive without PD will be censored at their last tumor assessment, documenting the overall objective response is either complete response (CR), partial response (PR), or stable disease (SD). This rule will also apply to subjects dying later than 12 or 26 weeks

after their last tumor assessment (ie, censoring subjects who died after 2 missed tumor assessments)

- Objective Response: As assessed by the Investigator using RECIST 1.1
- SoLD: As assessed by the Investigator, using RECIST 1.1 on the irradiated target lesions
- Location of first relapse.

Follow-up: During survival follow-up (up to 1 year), further anticancer treatment as well as all subsequent progressions will also be recorded.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests as specified in the Schedule of Assessments (see Table 1). Special attention will be paid, during the exam as well as the interpretation of the laboratory results, to the organs which are positioned in the irradiation field. Worsening of a condition within an irradiated area (eg, skin reactions, bleeding) during the DLT evaluation period should be reported as a TEAE with grade and relatedness to RT and / or M3541. Improvements of disease-related symptoms should also be reported as improvement of the observed concomitant condition within an irradiated area (eg, improved pain, reduced bleeding) should be reported on the appropriate efficacy-related eCRF page.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not 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.

In case of a fatality, the cause of death is considered as an AE, and the death is considered as its outcome.

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

Investigators will reference the NCI-CTCAE V4.03 (publication date: 14 June 2010) and use the general grading (severity / intensity; hereafter referred to as severity) scale below. If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death

According to Sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE as per Section 7.4.1.4; however, a laboratory abnormality of Grade 4, such as hemoglobin decreased or neutrophil count decreased, is considered serious only if the condition meets 1 of the serious criteria described 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 (for example, 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 IMP / study treatment (including radiation therapy) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP / study treatment include, but may not be limited to, temporal relationship between the AE and the IMP / study treatment, known side effects of IMP / study treatment, medical history, concomitant medication, course of the underlying disease, study procedures.

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as any AE suspected to be related to M3541 or RT.

Serious Adverse Events

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

- Results in death
- Is life-threatening (Note: The term "life-threatening" refers to an event in which the subject 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 (Note: 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 subject 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 an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (eg, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs; however, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Medical actions taken to reduce risks (like surgical interventions to prevent bone fractures of metastatic bone lesions) are not considered SAE despite requiring hospitalization of the subject.

Events Not to Be Considered as AEs / SAEs

Medical conditions present at the initial study visit (such as pain) that do not worsen in severity or frequency during the study (as compared with the subject's history) are defined as Baseline Medical Conditions, reported as medical history, 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 AE / SAE, unless the subject's general condition is more severe than expected for the subject's condition and / or unless the outcome is fatal within the AE reporting period (as defined in Section 7.4.1.3).

Adverse Events of Special Interest

To date, no AEs of special interest have been defined for M3541.

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

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each study visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 eCRF. All SAEs must be additionally documented and reported using the appropriate SAE eCRF page (SAESIDT) as described in Section 7.4.1.4.

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

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the study (date and time of first signature of informed consent) and continues through the study's 30-Day Short-term Follow-up visit, defined as 30 days after last M3541 / RT administration. After the 30-Day Short-term Follow-up visit only AEs that are deemed attributable to M3541 and / or RT by the Investigator should be documented until the End-of-Study visit, which is scheduled 1 year after the end of RT. Thereafter, the Investigator should contact the subject every 3 months (± 1 month) until the defined end of the study (see Section 5.7) to enquire and monitor for late appearing RT-related toxicity.

Any SAE assessed as related to M3541 must be recorded and reported whenever it occurs, irrespective of the time elapsed since the last administration of M3541.

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest 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 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.

In exceptional circumstances, a 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 eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report).

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, or other records where needed) or to any question the Sponsor or 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 the responsible Monitor, although in exceptional circumstances the Global 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 (see Section 5.1) must be recorded in the eCRF within 24 hours after becoming aware of the event. Any DLT meeting criteria for a SAE must also be reported in an expedited manner as SAEs as outlined above. Information on DLTs will be sent by

the Sponsor or delegate to the SMC core members within 1 working day of the receipt of documented information (ie, SAEs and / or DLTs).

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees / Institutional Review Boards and Investigators

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 subjects to the IEC / IRB that approved the study.

In accordance with ICH GCP guidelines, the Sponsor or designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's / IRB's approval / favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor / designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor or 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 or designee and of filing copies of all related correspondence in the Investigator Site File.

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the study (see Section 7.4.1.3) and are assessed for outcome at the PTD 30 Short-term Safety Follow-up Safety visit. All SAEs ongoing at the PTD 30 Short-term Safety Follow-up Safety visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up" or the subject withdraws consent. 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.

A subject 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 subject fails to return to the clinic for a required study visit:

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

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to study treatment (eg, resulting from a drug interaction with a contraceptive medication) are considered to be AEs; however, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page / section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor or designee in an expedited manner of any pregnancy using the paper Pregnancy Report Form, which must be transmitted according to the same timelines as described for SAE reporting in Section 7.4.1.4.

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

The Investigator must notify the Sponsor or designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event, and the Parent-Child / Fetus Adverse Event Report Form will be used if the child / fetus sustains an event.

Any abnormal outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the study, the subject must be discontinued from study medication immediately. The Sponsor or designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

It is essential that the Sponsor be provided with a list of laboratory normal ranges before shipment of IMP. Any change in laboratory normal ranges during the study will additionally be forwarded to the CRO and the Sponsor.

All routine laboratory analyses will be performed at a laboratory facility local to the investigational site and relevant results must be drawn and checked before administration of M3541. The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for the tests listed below will be collected from subjects during the Screening phase as specified in the Schedules of Assessments (Table 1, Table 2, or Table 3 as appropriate).

Laboratory samples:

- Hemoglobin, reticulocytes, red blood cell count, complete white blood cell count (CBC), differential, and platelet count
- Serum chemistry profile, including AST, ALT, gamma-glutamyltransferase, total bilirubin (direct bilirubin when indicated), alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, amylase, lipase, sodium, potassium, calcium, phosphorus, magnesium, chloride, glucose, total protein, albumin, blood urea nitrogen/urea, uric acid, creatinine, and creatinine clearance
- Coagulation parameters international normalized ratio and activated partial thromboplastin time
- Urinalysis: dipstick followed by microscopic examination if abnormal results
- Serum pregnancy test at Screening. If confirmation of a subject's postmenopausal status is necessary, a FSH level will also be performed at Screening, see Section 7.1.1
- Pregnancy testing will be conducted at the end of relevant systemic exposure of the study intervention, ie, at PTD 15 (see Table 1).
- Hepatitis screening: If hepatitis B surface antigen positive and hepatitis B core antibody positive, then reflex to quantitative HBV DNA (PCR); if hepatitis B core antibody positive alone, then reflex to quantitative hepatitis B DNA (PCR); if hepatitis C antibody positive, then reflex to quantitative hepatitis C RNA (PCR).

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs, including body temperature, respiratory rate, pulse (after 5-minute rest), arterial blood pressure (after 5-minute rest), and body weight and height (height only at Screening), physical examination, and ECOG PS will be recorded at Screening and at subsequent visits as indicated in the Schedules of Assessments (Table 1, Table 2, or Table 3 as appropriate) and documented in the eCRF.

The 12-lead resting ECGs will be obtained after the subject has been in a semi-supine position for at least 5 minutes predose and postdose and prior to any associated clinical laboratory (ECG should be obtained using a Holter recorder), PK or pharmacodynamics sample blood draws. All ECGs will be evaluated by the Investigator for safety assessment. At specified time points during the treatment period (Table 4, Table 5, or Table 6 as appropriate), additional digital ECG recordings, equivalent to triplicate ECGs, are to be recorded at the indicated times for quantitative analysis by a central ECG laboratory (at the end of the study).

The time windows for postdose ECGs are ± 5 minutes for ECGs up to 1 hour after administration of M3541, ± 15 minutes for postdose ECGs up to and including 4 hours, and ± 30 minutes for all

others. Electrocardiograms to be sent for evaluation, must be time-linked to the PK samples scheduled for the respective time points, with the PK blood sample withdrawn immediately after the ECG recording.

All newly diagnosed or worsening conditions, signs and symptoms observed after the signing of the ICF, whether related to study treatment or not, are to be reported as AEs and documented in the eCRF Adverse Event section (see Section 7.4.1). Abnormal findings are to be reassessed at subsequent visits.

For female subjects of childbearing potential (see Section 7.1.1) serum β-HCG pregnancy test will be carried out during the Screening and urine β-HCG test will be performed according to the Schedules of Assessments (Table 1, Table 2, or Table 3 as appropriate).

7.4.5 Tumor Pain

All subjects will be asked to complete the BPI-SF at Screening and FD 1 prior to other study-related assessments. If a subject has no pain in an area to be irradiated as part of the experimental treatment (M3541 + RT), the subject should mark "0" in all pain scales and activity scales. For subjects with cancer pain from lesions to be irradiated as part of the experimental treatment, any pain medication should be documented (name, dose, frequency, including if used on an "as needed" basis) on the appropriate eCRF page.

Subjects with cancer pain from lesions to be irradiated as part of the experimental treatment (M3541 + RT) on FD 1 will be asked to continue to complete the BPI-SF as specified in the Schedules of Assessments (Table 1, Table 2, or Table 3 as appropriate). Subjects should complete the BPI-SF prior to any other study-related procedures. The subject should only rate pain and interference with daily activity as they relate to areas being irradiated as part of the experimental treatment. The Investigator must also ensure any new pain medication or change in ongoing pain medication (drug, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page.

The BPI-SF is a 9-item self-administered questionnaire used to evaluate the severity of the subject's pain and the impact of the pain on daily functioning. The subject is asked to rate their worst, least, average, and current pain intensity, and list current treatments and their perceived effectiveness. The subject is also asked to rate on a 1 to 10 scale the degree to which the pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life.

In general, pain related to tumor lesions irradiated in the context of this study, will be considered a concomitant medical condition and not considered an AE / SAE unless the pain is more severe than expected for the subject's condition (see Section 7.4.1.1 – AE / SAEs Observed in Association with Disease Progression).

7.5 Pharmacokinetics

Details for the collection of blood samples, preparation, storage, and shipping will be provided in the Laboratory Manual.

Blood sampling for PK determinations and time windows for postdose sampling are as specified in the Schedules of Assessments (Table 4, Table 5, or Table 6 as appropriate). On M3541 treatment days, the predose sample should be taken within 1 hour before dosing at each sampling day.

The date, exact blood sampling times, and IMP administration time (both M3541 and RT) must be recorded in the eCRF.

The Sponsor may modify the PK sampling schedule based upon PK information collected during the study. The Sponsor is not expected to increase the overall amount of blood to be collected for PK sampling.

In addition to the total plasma concentration of M3541, CCI [redacted]. This will be reported separately.

Additional blood samples will be taken on FD 1, FD 5 and FD 10 for the analysis of plasma proteins that may be involved in plasma protein binding of M3541. This will be reported separately.

Plasma concentrations of M3541 will be determined by a validated method.

7.6 Biomarkers

Optional archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue biopsies (range of 10 to 15 slides) sampled before the start of the treatment will be collected (most recent material). If no archival material is available, then an optional fresh FFPE biopsy should be taken. Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suited. Fine needle aspiration biopsies are not acceptable. Details of archival tissue sample and blood sample collections, processing procedures, storage, and transportation will be summarized in the Laboratory Manual.

To demonstrate target engagement, pharmacodynamic markers such as p-ATM will be evaluated as specified in the Schedule of Assessments (Table 4, Table 5, or Table 6 as appropriate). CCI [redacted] This analysis is exploratory and the aim is mainly to support the identification of additional pharmacodynamic markers.

Depending on the overall knowledge on the ATM pathway and the outcome of the clinical study, the collected optional archival tumor tissue will be analyzed for potential exploratory evaluation of correlations between tumor markers (eg, molecular and morphological) and treatment benefit.

7.7 Other Assessments

7.7.1 Immune System Biomarkers

In addition, the potential impact of M3541 in combination with palliative RT on the immune system (eg, total T cell, total B cell, and total natural killer cell and T cell subset) will be analyzed. Blood samples will be collected as specified in the Schedule of Assessments (Table 4, Table 5, or Table 6 as appropriate)

CCI

8 Statistics

8.1 Sample Size

The planned number of subjects per cohort is 3. The SMC is responsible for dose and schedule change and subject number decisions (see Section 2.3). The decision of the SMC will be guided by the result of the Bayesian 2-parameter logistic regression model with overdose control (see Section 5.1).

The overdose control ensures that the risk of using a too toxic dose is limited. Overdose is defined as a toxicity rate of > 35%. For each dose level, the risk of overdose will be calculated, and only dose levels for which this risk is lower than 25% will be considered for suggestion by the model.

The following model is applied for the M3541 once per FD schedule:

For a dose d_j

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

The relationship between dose and toxicity rate is described by this 2-parametric logistic model with parameters α and β, using the following parametrization:

- Prior for 1st cohort based on best knowledge
  - (α, β) = (-0.847,-0.279)
  - SD(α) = 1.007, SD(β) = 1.636, Cov(α, β) = 0
- Loss function used for the recommendation of the next dose level
  - [0, 0.2) weighted with 1 (too low)
  - (0.2, 0.35) weighted with 0 (in the right range)
  - (0.35, 0.6) weighted with 1.5 (too high)
  - (0.6, 1.0) weighted with 2 (much too high)
- Overdose Control, ie, risk to use a dose d_j with too high toxicity is limited to 25%:
  - Prob(DLT rate > 35% | d= d_j) < 25%.

Based on the model, the recommended next dose level as well as estimates for the risks of an overdose (Prob(DLT rate >35%| d= d_j)) and excessive toxicity (Prob(DLT rate>60%| d= d_j)) for each potential dose level will be provided to the SMC as basis for the decision on the next dose level.

Dose-escalation of M3541 will continue as outlined in Section 5.1.

CCI [redacted]

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoint is the occurrence of DLTs during the DLT evaluation period, ie, during the M3541 / RT treatment period plus the DLT follow-up period after the last treatment with M3541 / RT (see Table 1 and Figure 1).

8.3.2 Secondary Endpoints

The secondary endpoints are the:

- Occurrence of TEAEs, Grade ≥ 3 AEs, SAEs, and deaths according to NCI-CTCAE V4.03 assessed from the first administration of M3541
- Occurrence of abnormal
  - laboratory tests
  - findings during physical examinations (reported as AEs)

- vital signs
- ECGs (including corrected QTc interval)

- Best overall response (BOR) using RECIST 1.1 as assessed by the Investigator every 6 weeks (starting on PTD 42) for the first 6 months, then every 12 weeks thereafter until evidence of disease progression
- Progression-free survival (PFS) time defined as time from the first dose of M3541 to disease progression (using RECIST 1.1 as assessed by the Investigator), onset of other anticancer therapy, or death from any cause
- PK endpoints include:
  - FD 1: maximum observed plasma concentration (C_{max}), C_{max}/dose, time to reach maximum observed concentration (t_{max}), $t_{1/2}$, area under the concentration-time curve from time zero to the last quantifiable sampling time point ($AUC_{(0\text{-}last)}$), $AUC_{(0\text{-}last)}$/dose, area under the concentration-time curve from time zero to 6 hour postdose ($AUC_{(0\text{-}6h)}$), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{(0\text{-}\infty)}$), $AUC_{(0\text{-}\infty)}$/dose, oral clearance (CL/F), and apparent volume of distribution during terminal phase (Vz/F)
  - FDs 2 through 9: Predose plasma concentration (C_{min}) and approximate C_{max} of M3541
  - FD 9 or 10: Minimum observed plasma concentration (C_{min}); average plasma concentration (C_{avg}); C_{max}, C_{max}/dose, t_{max}, $t_{1/2}$, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}last)}$/dose, oral clearance at steady-state (CL_{ss}/F), apparent volume of distribution at steady-state (V_{ss}/F), accumulation ratio for area under the concentration-time curve (R_{acc}[AUC]), accumulation ratio for maximum concentration (R_{acc}[C_{max}]).

8.3.3 Exploratory Endpoints

The exploratory endpoints are the:

- SoLD, as assessed by the Investigator, using RECIST 1.1 on the irradiated target lesions
- Location of disease progression as assessed by the location where tumor size increase has been observed as well as the location of the newly observed lesions
- Absolute values and changes over time of proteins that may be affected by ataxia-telangiectasia mutated (ATM) inhibition in blood (eg, phospho-ATM) during exposure to M3541
- CCI
- Changes from baseline over time of the total blood cell count and cell subset type of immune cells (eg, T cells, B cells, natural killer cells) during exposure to M3541
- CCI

- CCI
- CCI
- CCI

8.4 Analysis Sets

For purposes of analysis, the following populations are defined:

- **Screened Analysis Set:** All subjects who signed an ICF
- **DLT Analysis Set**: All subjects who received at least 1 dose of M3541 and meet at least 1 of the following criteria:
  - Experienced at least 1 DLT during the DLT evaluation period, regardless of the number of doses of M3541 administered
  - For the M3541 once per FD:
    - Received at least 80% of planned dose of each treatment, ie, 8 fractions of RT and 8 of 10 M3541 administrations during the treatment period
  - For the M3541 thrice weekly schedule:
    - Received at least 80% of planned dose of each treatment, ie, 8 fractions of RT and 5 of 6 M3541 administrations during the treatment period
  - For the M3541 twice weekly schedule:
    - Received at least 80% of planned dose of RT and all 4 M3541 administrations during the treatment period

In addition, subjects without DLT must have completed the DLT follow-up period, ie, having a safety assessment on PTD 15 (allowing for a window of + 2 days).

- **Safety Analysis Set:** All subjects who receive at least 1 dose of study treatment (M3541). Subjects will be analyzed according to the actual treatment (ie, dose) they receive
- **PK Analysis Set:** All subjects who receive at least 1 dose of M3541 and have at least 1 measurable plasma concentration at a scheduled PK time point post dose. Data from subjects with a vomiting episode within 2 times of t_{max} for M3541 (about 4 hours postdose in total) may be excluded from the PK analysis set on the case-by-case basis
- **Biomarker Analysis Set:** All subjects who received at least 1 dose of study treatment and have provided at least a blood and / or tumor sample prior to any M3541 treatment, or at least 1 post-treatment blood sample.

8.5 Description of Statistical Analyses

Full details of the planned analyses will be described in the study Statistical Analysis Plan (SAP).

8.5.1 General Considerations

All data recorded during the study will be presented in individual data listings performed on the Safety Analysis Set. All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified in the SAP. All data will be presented in a descriptive manner. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be performed.

Descriptive statistics will be used to summarize the study results, that is, statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. Unless otherwise specified, the calculation of proportions will be based on the sample size of the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

The DLT Analysis Set is the underlying data set for the MTD determination. Safety analyses will be performed on the Safety Analysis Set. Baseline summaries and efficacy analyses will be performed on the Safety Analysis Set. Analyses of PK variables will be performed on the PK Analysis Set. Analyses of biomarkers will be performed on the respective Biomarker Analysis Sets.

Posterior distribution and recommended next dose level will be calculated using EAST Version 6.4 or higher. The estimation of PK parameters will be performed using WinNonlin® Version 6.4 or higher. All other statistical analyses will be performed using SAS® Version 9.2 or higher, or R, Version 3.0.2 or higher.

Data cut-off for the primary analyses is defined by the completion of DLT evaluation period of the last subject in the last cohort.

The final analysis will be performed when the study has been completed (see Section 5.7).

8.5.2 Analysis of Primary Endpoints

The primary endpoint is the occurrence of DLTs during the DLT evaluation period, ie, during the M3541 / RT treatment period plus the DLT follow-up period after the last treatment with M3541 / RT (see Table 1 and Figure 1).

For the final statistical analysis, the following will be analyzed:

- The number and proportion of subjects experiencing a DLT during the DLT period will be reported by dose level and treatment schedule. The analyses will be based on the DLT Analysis set.

The MTD will be determined according to the dose-escalation plan described in Section 5.1.

8.5.3 Analysis of Other Endpoints

8.5.3.1 Efficacy Parameters

Clinical efficacy parameters will be analyzed descriptively.

Summary statistics as described in Section 8.5.1 will be used for the summary of efficacy endpoints by dose level and / or cohort.

The secondary efficacy endpoint of BOR will be according to RECIST 1.1 per Investigator assessment. For a BOR of PR or CR, confirmation of the response according to RECIST 1.1 (Eisenhauer, 2009) will be required. The response at each scheduled tumor assessment and the BOR will be listed for each subject. The objective response rate, defined as the proportion of subjects with BOR of PR or CR, will be tabulated by dose level.

The PFS time (according to RECIST 1.1) will be presented in listings.

The SoLD of irradiated target lesions will also be used as exploratory efficacy endpoint.

Graphical display will be provided for efficacy endpoints as appropriate.

8.5.3.2 Pharmacokinetic Profile

The PK parameters for the M3541 concentration using noncompartmental analysis approaches using the PK Analysis Set as appropriate as described below and detailed in the Integrated Analysis Plan (iAP).

PK endpoints are as described in Section 8.3.2. Formal statistical hypotheses are not set up. All statistical tests will be exploratory. Unresolved missing data may be imputed when the analysis integrity is affected. The conservative principle will be used for data imputation. Details of the statistical analyses will be described in the iAP.

8.5.3.3 Biomarkers

Summary statistics for biomarkers will be provided for all preplanned time points, separately for each dose level or cohort. Changes to baseline levels will also be presented as applicable. Profiles over time will be displayed on a per subject basis. Details of the statistical analysis of biomarkers will be presented in the SAP.

8.5.4 Analysis of Safety Endpoints

The extent of exposure to M3541 will be characterized by number of fraction days, cumulative dose (mg), relative dose intensity (actual dose given / planned dose). A similar analysis will be performed for RT.

Safety analyses will be performed on the Safety Analysis Set. The safety endpoints will be tabulated by dose level or cohort, using descriptive statistics.

Safety assessments will be based on review of the incidence of AEs, treatment-related AEs, and changes in vital signs, ECGs, body weight, laboratory values (hematology and serum chemistry), and ECOG PS.

8.5.4.1 Adverse Events

Adverse events will be coded according to Medical Dictionary for Regulatory Activities. Severity of AEs will be graded using the NCI-CTCAE V4.03 toxicity grading scale.

The incidence of treatment-emergent AEs regardless of attribution and AEs defined as related to M3541 / RT will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to M3541 / RT. Adverse events (serious and non-serious) will be considered TEAEs when emerging in the on-treatment period, defined as the time from the first IMP administration to the last administration date + 30 days (PTD 30) or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated. In addition, the AEs will be described for the period up to 1 year after the last dose of RT.

All premature terminations will be summarized by primary reason for treatment withdrawal.

All reported deaths during therapy and deaths within 60 days after the first dose and deaths within 30 days after the last dose of study treatment as well as reasons for death will be tabulated (for all subjects enrolled). Deaths within 1 year from last dose of RT and reasons for the death will also be tabulated.

8.5.4.2 Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE V4.03. The worst on-study grades after the first IMP administration will be summarized. Shifts in toxicity grading 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 subjects with post-Baseline laboratory values will be included in these analyses.

8.5.4.3 Physical Examination, Including Vital Signs, 12-lead Electrocardiogram, and Performance Status

Vital signs (body temperature, respiratory rate, pulse, and blood pressure), 12-lead ECG, and ECOG PS recorded according to the Schedule of Assessments (Table 1) will be presented. Each parameter will be summarized by descriptive statistics per time point, and changes from baseline will be calculated.

8.6 Interim and Additional Planned Analyses

No formal interim analysis is planned; however, safety and PK data will be presented to the SMC after each cohort. The data cut-off date for each cohort will be triggered by the completion of the DLT evaluation period of the last subject in the respective cohort.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at the site and will ensure that the study is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the study.

According to United States Code of Federal Regulations Part 54.2 (e), for studies conducted in any country that could result in a product submission to the United States Food and Drug Administration for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the Food and Drug Administration [FDA]), the Investigator and all subinvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the study and for 12 months following completion of the study.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the study is written informed consent, which must be given before any study-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the study, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient

time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the study and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each study subject and obtain new written consent for continued participation in the study. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the study as well as in the clinical study database. All subject data collected in the study will be stored under the appropriate subject number. Only the Investigator will be able to link study data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations. All samples collected during the study will be kept confidential. At the clinical study site, a unique code will be placed on each specimen for transfer to the central lab, to any analyzing laboratory (external to the site) and to the storage facility. This code is a random number that does not contain any personally identifying information embedded within it. No personal identifiers will appear on the specimen tubes, nor will be shared with any party outside the clinical study site. Outside the clinical study site where the study will be conducted, no one will be able to link a subject's identity (eg, name) to this code. The link between a subject's identity and the code is only known by a limited number of authorized personnel who are bound by law and contractual obligations to protect subject privacy.

After the end of the study, samples will be stored at a Sponsor's designated biorepository under the supervision of Sponsor.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during study participation in order to provide clinical study subjects with a way of identifying themselves as participating in a clinical study and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical study Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour 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.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, the clinical study protocol will be submitted together with its associated documents (such as the ICF) to the responsible IEC / IRB for its favorable opinion / approval. The written favorable opinion / approval of the IEC / IRB will be filed in the Investigator Site File, and a copy will be filed with the CRO.

The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion / approval from the concerned IEC / IRB. The IEC / IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion / approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion / approval that clearly identifies the study, the clinical study protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical study protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the study in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical study protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Electronic Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The Investigator or designee will be responsible for entering study data in the eCRF provided by the CRO, which will follow the data standards of the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The CRO will be responsible for data review and processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control procedure and quality assurance procedures (if applicable) have been completed. All Portable Document Format files of the eCRFs will be provided to the Investigators at the completion of the study.

10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the study. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Sex
- Race
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Tumor disease information
- Trial identification (MS200770-0001)
- Date of subject's inclusion into the study (that is, date of giving informed consent)

- Subject number in the study
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical study protocol
- All AEs observed in the subject
- Date of subject's end of study
- Date of and reason for early withdrawal of the subject from the study or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI scan images, ECG recordings, laboratory value listings, etc. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

10.3 Investigator Site File and Archiving

Upon initiation of the study, the Investigator will be provided with an Investigator Site File containing all necessary study documents, which will be completed throughout the study and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the study, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be archived include the Subject Identification List and the signed subject ICF. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor / designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and / or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the study site at regular intervals.

The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and

integrity of the study data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all study documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical study protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC / IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC / IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the study requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the study, or completion of a particular cohort or cohorts if applicable, a clinical study report according to ICH Topic E3 will be written by the Sponsor or the designated CRO in consultation with the Investigator.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all study sites that participated in the dose-escalation part of the study.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

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.

11 References Cited in the Text

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Oken M, Creech R, Tormey D, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

12 Appendices

Appendix I Eastern Cooperative Oncology Group Performance Status

ECOG PS[a]	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG PS = Eastern Cooperative Oncology Group Performance Status.

a Oken, 1982.

Appendix II Drug Development and Drug Interactions

In-vitro assays indicate that M3541 is a substrate for human P-glycoprotein (P-gp), organic cation transporters, and organic anion-transporting polypeptides and is mainly metabolized by CYP3A4/5 and CYP1A2. Current data suggest that the clinical relevance of P-gp and hepatic uptake transporter-mediated drug-drug interactions cannot be excluded. Similarly, the importance of oxidative clearance pathways found in preclinical species, the metabolic clearance of M3541 may be potentially affected by co-administered drugs that are known to be CYP3A4/5 inhibitors or inducers.

There is also potential for M3541 to alter the clearance of other drugs metabolized by CYPs, but available data suggest M3541 is not a strong inhibitor or strong inducer of commonly studied CYPs, or likely to cause strong inhibition of uridine glucuronyl transferase (UGT) metabolizing enzymes.

Investigators should use standard precautions when prescribing co-medications, as with any novel therapeutic for which there is limited clinical experience.

Substrates of CYP3A4

Sensitive: alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil

budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Moderate: alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

Inhibitors of CYP3A4

Strong: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole

Moderate: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

Inducers of CYP3A4

Strong: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort (*Hypericum perforatum*)

Moderate: modafinil

For detailed information, see:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Appendix III Contraceptive Guidance and Woman of Childbearing Potential

Definitions

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP 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 (eg, 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 hormone 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 1 of the non-estrogen hormonal highly effective contraception methods if she wishes to continue their HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraceptive Guidance

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner: a highly effective contraception method provided that the partner is the sole sexual partner of a WOCBP 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 and women is consistent with local regulation 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. 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, post-ovulation 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 IV Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Phase I, Open-label, Uncontrolled, Multicenter, Dose-escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors
IND Number:	CCI
Clinical Trial Protocol Date / Version:	04 March 2019 / Version 5.0

Protocol Lead:

I approve t CCI CCI

Signature Date of Signature

Name, academic degree: CCI

Function / Title: CCI

Institution: CCI

Address: Frankfurter Strasse 250
64293 Darmstadt, Germany

Telephone number: CCI

E-mail address: CCI

Signature Page – Coordinating Investigator

Trial Title	A Phase I, Open-label, Uncontrolled, Multicenter, Dose-escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors
IND Number	CCI
Clinical Trial Protocol Date / Version	04 March 2019 / Version 5.0

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct the study according to 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.

CCI _____ CCI _____

Signature Date of Signature

Name, academic degree: CCI

Function / Title: Coordinating Investigator

Institution: CCI

Address: CCI

Telephone number: CCI

Fax number: CCI

E-mail address: CCI

Signature Page – Principal Investigator

Trial Title	A Phase I, Open-label, Uncontrolled, Multicenter, Dose-escalation Study of M3541 in Combination with Palliative Radiotherapy in Subjects with Solid Tumors
IND Number	CCI
Clinical Trial Protocol Date / Version	04 March 2019 / Version 5.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to 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 affirm that I 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 the purpose of complying with the regulatory requirements. I therefore 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:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree	CCI
Function / Title	Senior Expert Biostatistician,
Institution	Merck KGaA
Address	Frankfurter Strasse 250, 64293 Darmstadt, Germany
Telephone number	CCI
Fax number	CCI
E-mail address	CCI

Name, academic degree	CCI
Function / Title	Principal Clinical Trial Lead
Institution	Merck KGaA
Address	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number	CCI
E-mail address	CCI

Appendix V Protocol Amendments and List of Changes

Previous Protocol Amendments

Amendment Number	Submission to Health Authority (Yes/No/ Notification only)	Date	Region or Country	Included in the current document (Y/N)
Amendment 1	Yes	05 July 2017	US	Yes
Amendment 2	Yes	12 October 2017	US	Yes
Amendment 3	Yes	19 March 2018	US	Yes

Amendment Number: Amendment 4.0, 04 March 2019

Rationale: To modify the duration of the DLT follow-up period and the exclusion criterion relating to prior anticancer therapies. These changes are supported by currently available safety data for M3541 and ensure that subjects in the palliative setting may access their next treatment as soon as possible.

Major Scientific Changes:

- The DLT follow-up period will now start on the day after the last dose of study treatment rather than 3 days after the last dose of study treatment
- The duration of the DLT follow-up period has been reduced from 3 weeks to 2 weeks. This modification ensures that study subjects who require additional anticancer treatment can receive it as soon as possible following dosing in the study. The 2-week DLT follow-up period reflects 5 times the half-life of M3541 (approximately 2 days) allowing for intersubject variability and is supported by the observation that there is no evidence that M3541 has an active metabolite with a half-life longer than that of M3541. It is therefore considered appropriate to modify the DLT follow-up period based on the half-life of M3541. In addition, based on the available safety data from subjects dosed in the first 2 cohorts, it is not anticipated that modifying the DLT follow-up period in this way will impact the safety data collected in the study. Moreover, to ensure any potential RT-related late toxicities (as may be enhanced by M3541) that occur sometime after the end of the DLT follow-up period are documented, subjects will continue to be followed-up for up to 1 year after treatment, as defined in the previous version of the protocol
- The washout period for prior anticancer therapies is now based on the elimination half-life of the respective therapy, up to a maximum of 15 days, rather than on a fixed 15-day period (exclusion criterion 1)
- Changes to the overall frequency/number of blood samples for PK and pharmacodynamic assessments. Specifically, some PK samples have been removed to reduce the overall volume of blood collected from subjects enrolled in the study. In addition, PK collection at the end of the treatment period will now be on FD 10 so that the highest M3541 plasma concentration experienced by subjects at the end of treatment can be monitored. Pharmacodynamic sampling times are also amended to provide a more comprehensive monitoring of target inhibition throughout the treatment period. Pharmacodynamic and PK sampling times have been matched

whenever possible, except for FD 4/FD 5 and FD 9/FD 10, where pharmacodynamic samples need to be collected 1 day earlier due to the need to process them within 14 hours.

In addition, where relevant to patient safety or regulatory/legal obligations, the protocol has been updated for consistency with Sponsor mandatory protocol template language.

List of Changes

Main changes to the clinical study protocol text are presented in the table below. Minor typographical, grammatical, formatting, appendix renumbering, or other changes not affecting the study conduct are not included.

Additions and amended text are shown in bold. If the original clinical study protocol text was already bold, changes are shown in bold and underlined, deletions are marked using strike through.

Comparison with Clinical Trial Protocol Version 4.0 / Amendment 3.0, 19 March 2018

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
Mandatory protocol text added	Title Page	1	~~IND Number~~ CCI ~~EudraCT Number~~ ~~Not applicable~~ …… **Regulatory Agency Identifying Number** CCI **ClinicalTrials.gov** **NCT03225105**	Regulatory Agency Identifying Number CCI ClinicalTrials.gov NCT03225105
New Medical Responsible / Protocol Lead	Title Page and Signature Page – Protocol Lead	1 and 99	Medical Responsible: CCI Frankfurter Strasse 250 64293 Darmstadt, Germany (phone: CCI) ~~(fax:~~ CCI) **Email:** CCI	Medical Responsible: CCI Frankfurter Strasse 250 64293 Darmstadt, Germany (phone: CCI) Email: CCI
Mandatory protocol text added	Title page		**Medical Monitor, Name and Contact Information** CCI **Phone:** CCI **Email:** CCI	Medical Monitor, Name and Contact Information CCI Phone: CCI Email: CCI
Update of study duration	Synopsis, Planned study period	11	Last subject out: Q~~2~~4, 2020	Last subject out: Q4, 2020
CCI				
Modification of DLT follow-up period	Synopsis, Methodology	12	…… Radiotherapy will consist of 10 FDs, to be	…… Radiotherapy will consist of 10 FDs, to be

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			administered over 2 consecutive calendar weeks (ie, Monday through **Friday**~~Sunday~~, with the intervening Saturday and Sunday as **a** M3541 / RT holiday~~s~~). ~~A 2-day treatment holiday after the last administration of study treatment will always be included as part of the M3541 / RT treatment period, before t~~**T**he ~~onset of the 3~~**2**-week dose limiting toxicity (DLT) follow-up period **will start on the day after the last dose of study treatment**. The DLT evaluation period will be ~~45~~ weeks in duration, including the scheduled 2-week radiotherapy treatment period (as described above) plus a **2**~~3~~-week DLT follow up period that starts ~~on the third day after the last~~ administration of M3541 / RT ~~(whichever comes latest)~~. The DLT evaluation period could exceed the ~~45~~-week period only if M3541 / RT has been interrupted and given over a period exceeding 2 weeks.	administered over 2 consecutive calendar weeks (ie, Monday through Friday with the intervening Saturday and Sunday as a M3541 / RT holiday). The 2-week dose limiting toxicity (DLT) follow-up period will start on the day after the last dose of study treatment. The DLT evaluation period will be 4 weeks in duration, including the scheduled 2-week radiotherapy treatment period (as described above) plus a 2-week DLT follow up period that starts on the day after the last administration of M3541 / RT. The DLT evaluation period could exceed the 4-week period only if M3541 / RT has been interrupted and given over a period exceeding 2 weeks.
Modification of DLT follow-up period	Synopsis, Methodology	14	For this study, a DLT is defined as any of the following AEs that occur during the ~~scheduled 5 week~~ DLT evaluation period (except those that are clearly and incontrovertibly due to disease progression or extraneous causes), with severity graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE V4.03):	For this study, a DLT is defined as any of the following AEs that occur during the DLT evaluation period (except those that are clearly and incontrovertibly due to disease progression or extraneous causes), with severity graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE V4.03):
Modification of DLT follow-up period	Synopsis, Primary endpoints	15	The primary endpoint is the occurrence of DLTs **during the DLT evaluation period, ie,** during the M3541 / RT treatment period plus the ~~3 week~~ DLT follow-up period after the last treatment with M3541 / RT ~~(ie, through the 5-~~	The primary endpoint is the occurrence of DLTs during the DLT evaluation period, ie, during the M3541 / RT treatment period plus the DLT follow-up period after the last treatment with M3541 / RT.

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			~~week DLT evaluation period)~~.	
Modified PK assessments	Synopsis, Secondary endpoints	15	PK endpoints are: …… • FDs 2 through ~~69~~: Predose plasma concentration (~~C_{trough}~~C_{min}) and approximate C_{max} of M3541	PK endpoints are: …… • FDs 2 through 9: Predose plasma concentration (C_{min}) and approximate C_{max} of M3541
CCI [redacted]				
Mandatory protocol text: contraceptive guidance	Synopsis, Diagnosis and Key inclusion and exclusion criteria: inclusion criteria	16	• Agree to use highly effective contraception (**as outlined in the protocol, Section 5.3**), ~~ie, methods with a failure rate of less than 1% per year)~~ if the subject is male or a **woman of childbearing potential**~~female of childbearing potential~~ (female partners of childbearing potential of male subjects must also agree to use highly effective contraception)	• Agree to use highly effective contraception (as outlined in the protocol, Section 5.3), if the subject is male or a woman of childbearing potential (female partners of childbearing potential of male subjects must also agree to use highly effective contraception)
Revised exclusion criteria for prior anticancer therapies	Synopsis, Diagnosis and Key inclusion and exclusion criteria: exclusion criteria	17	• Use of other anticancer therapy (as outlined in the protocol) within **5 x their elimination half-life** ~~15 days~~**, but no longer than 15 days,** before the first dose of M3541 administration~~ and should not be within the "at risk follow up period" for that specific anticancer therapy~~. The use of any investigational agent is not allowed within 28 days before the first dose of	• Use of other anticancer therapy (as outlined in the protocol) within 5 x their elimination half-life, but no longer than 15 days, before the first dose of M3541 administration. The use of any investigational agent is not allowed within 28 days before the first dose of M3541

Change	Section	Pages	Previous Wording Plus New Wording M3541	New Wording
Modification of DLT follow-up period	Synopsis, Planned study and treatment duration per subject	18	The study period per subject includes an up to 21-day screening period, a scheduled 2-week treatment period, followed by a ~~2~~**3**-week DLT follow-up period and follow-up for up to 1 year after RT has been completed (note, after the 1-year follow-up, the Investigator will contact the subject every 3 months [± 1 month, telephone contact is acceptable] until the defined end of the study to enquire and monitor for late appearing RT-related toxicity).	The study period per subject includes an up to 21-day screening period, a scheduled 2-week treatment period, followed by a 2-week DLT follow-up period and follow-up for up to 1 year after RT has been completed (note, after the 1-year follow-up, the Investigator will contact the subject every 3 months [± 1 month, telephone contact is acceptable] until the defined end of the study to enquire and monitor for late appearing RT-related toxicity).
Updated Schedule of Assessments	Table 1	19-23	See below	See below
Updated Electrocardiogram, Pharmacokinetic, and Biomarker Assessments	Table 4	32-33	See below	See below
Updated safety data	3.1.5 Rationale for Treatment Schedule Changes	42	At the time of submission of this protocol amendment (Version **5**~~4~~.0 / Amendment **4**~~3~~.0), preliminary data on M3541 safety and plasma concentrations from ~~3~~**8** subjects dosed at 50, **100, or 200** mg once per radiotherapy fraction day **(FD; Cohort 1 n=3, 50 mg, cohort 2 n=4, 100 mg and cohort 3 n=1, 200 mg)** were available. M3541 was shown to be safe at the~~se~~**is** dose **level**~~s of 50 mg/FD~~. **No DLT or SAEs assessed as related to M3541 were observed.** …… **However, at the time of submission of the current protocol amendment (Version 5.0 / Amendment 4.0), it is not anticipated that**	At the time of submission of this protocol amendment (Version 5.0 / Amendment 4.0), preliminary data on M3541 safety and plasma concentrations from 8 subjects dosed at 50, 100, or 200 mg once per radiotherapy fraction day (FD; Cohort 1 n=3, 50 mg, cohort 2 n=4, 100 mg and cohort 3 n=1, 200 mg) were available. M3541 was shown to be safe at these dose levels. No DLT or SAEs assessed as related to M3541 were observed. …… However, at the time of submission of the current protocol amendment (Version 5.0 / Amendment 4.0), it is not anticipated that subjects will be dosed according to the

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			subjects will be dosed according to the intermittent dose schedules as these are unlikely to confer any advantage compared with daily dosing.	intermittent dose schedules as these are unlikely to confer any advantage compared with daily dosing.
Updated safety data	3.1.6 Summary of the Overall Benefit and Risk	43	The safety data obtained from ~~the first cohorts (~~dose levels 50 and 100 mg~~) has~~ show~~n no clinically relevant treatment related observations,~~ a **favorable safety profile** with **no DLTs and no treatment-related SAEs** ~~only Grade 1 treatment related AEs~~ observed, leading to the SMC decision on escalation to an M3541 dose of ~~1~~200 mg once per FD, **which is currently under evaluation**. ……. **Moreover, the safety data obtained from the first cohorts (dose levels 50 and 100 mg) support the shortened DLT period.** **More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M3541 may be found in Section 3.1.3 and the Investigator's Brochure.** **Based on the available data to date, the conduct of the study, as specified in this protocol, is considered justifiable.**	The safety data obtained from dose levels 50 and 100 mg show a favorable safety profile with no DLTs and no treatment-related SAEs observed, leading to the SMC decision on escalation to an M3541 dose of 200 mg once per FD, which is currently under evaluation. ……. Moreover, the safety data obtained from the first cohorts (dose levels 50 and 100 mg) support the shortened DLT period. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M3541 may be found in Section 3.1.3 and the Investigator's Brochure. Based on the available data to date, the conduct of the study, as specified in this protocol, is considered justifiable.
Modification of DLT follow-up period	5.1 Overall Study Design and Plan	46	….. The DLT evaluation period will be ~~4~~5 weeks in duration and comprises the 2-week treatment period (including a 2-day M3541 / RT holiday after ~~the last~~ FD 5) plus the ~~2~~3-week DLT follow up period that starts ~~on the third day~~ after the last administration of M3541 / RT (see Figure 1). The DLT evaluation period could only exceed the ~~4~~5-week period if M3541 / RT	….. The DLT evaluation period will be 4 weeks in duration and comprises the 2 week treatment period (including a 2-day M3541 / RT holiday after FD 5) plus the 2-week DLT follow up period that starts after the last administration of M3541 / RT (see Figure 1). The DLT evaluation period could only exceed the 4-week period if M3541 / RT has been

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			has been interrupted **and given over a period exceeding 2 weeks.** All effort should be made to complete 10 FDs if possible. **Post-treatment follow-up measures are described in Section 7.1.4**	interrupted and given over a period exceeding 2 weeks. All effort should be made to complete 10 FDs if possible. Post-treatment follow-up measures are described in Section 7.1.4
Updated Figure 1	Figure 1	46	See below	See below
Modification of DLT follow-up period	5.1.1 Dose-limiting Toxicity	47	For this study, a DLT is defined as any of the following AEs that occur during the ~~5 week~~ DLT evaluation period (except those that are clearly and incontrovertibly due to disease progression or extraneous causes), with severity graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE V4.03):	For this study, a DLT is defined as any of the following AEs that occur during the DLT evaluation period (except those that are clearly and incontrovertibly due to disease progression or extraneous causes), with severity graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE V4.03):
Clarification of planned study duration / Modification of DLT follow-up period	5.1.2 Planned Treatment and Study Duration	49	The **planned** study duration for an individual subject includes a 21-day screening period, a scheduled 2-week M3541 / RT treatment period plus follow-up, which includes a **2~~3~~**-week DLT follow-up period and safety and survival follow-up for up to 1 year after the end of the M3541 / RT treatment period. …… • Planned date last subject out (including follow-up): Q~~2~~4, 2020**.**	The planned study duration for an individual subject includes a 21-day screening period, a scheduled 2-week M3541 / RT treatment period plus follow-up, which includes a 2-week DLT follow-up period and safety and survival follow-up for up to 1 year after the end of the M3541 / RT treatment period. …… • Planned date last subject out (including follow-up): Q4, 2020.
Mandatory protocol text added	5.3 Selection of Study Population	50	**The criteria in Sections 5.3.1 (Inclusion Criteria) and 5.3.2 (Exclusion Criteria) are designed to enroll only subjects, 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 subject is suitable for this study.** **Prospective approval of protocol deviations**	The criteria in Sections 5.3.1 (Inclusion Criteria) and 5.3.2 (Exclusion Criteria) are designed to enroll only subjects, 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 subject is suitable for this study. Prospective approval of protocol deviations to

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.	inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.
Correction	5.3.1 Inclusion Criteria, 7	51	7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ ~~2.5~~**3** × ULN, and an ALT level ≤ ~~2.5~~**3** × ULN. For subjects with tumor involvement in their liver, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 1.5 × ULN is acceptable	7. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × ULN, an AST level ≤ 3 × ULN, and an ALT level ≤ 3 × ULN. For subjects with tumor involvement in their liver, AST ≤ 5.0 × ULN, ALT ≤ 5.0 × ULN, and bilirubin ≤ 1.5 × ULN is acceptable
Mandatory protocol text added / updated contraception guidance	5.3.1 Inclusion Criteria, 9	51	9. A male subject must agree to **the following during the study treatment period and for at least 100 days after the last dose of study treatment:** • **Refrain from donating sperm** **PLUS, either:** • **Abstain from intercourse with a woman of childbearing potential (WOCBP)** OR • **U~~u~~se a male condom**: ~~o~~ **When having sexual intercourse with a WOCBP, who is not currently pregnant, and advise her ~~and to have their female partners agree~~** to use a highly effective contraceptiv~~eon (ie,~~ method~~s~~ with a failure rate of less than 1% per year,~~)~~ as **described ~~detailed~~** in **~~Appendix II~~Appendix III**, **since a condom may break or leak ~~of this protocol during the treatment period, and for at least 90 days after the last dose of study treatment. Male subjects must also~~**	9. A male subject must agree to the following during the study treatment period and for at least 100 days after the last dose of study treatment: • Refrain from donating sperm PLUS, either: • Abstain from intercourse with a woman of childbearing potential (WOCBP) OR • Use a male condom: o When having sexual intercourse with a WOCBP, who is not currently pregnant, and advise her to use a highly effective method with a failure rate of less than 1% per year, as described in Appendix III, since a condom may break or leak

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			~~agree~~ • ~~To refrain from donating sperm during this same period~~	
Mandatory protocol text added / updated contraception guidance	5.3.1 Inclusion Criteria, 10	51	~~9.~~**10**. A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies: • Not a **WOCBP (defined in Appendix III)**~~female of childbearing potential. A female is considered of childbearing potential (that is fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion, or oophorectomy. A postmenopausal state is defined as no menses for ≥ 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (> 40 mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy~~ **OR** • **If a WOCBP** ~~A female of childbearing potential who~~ agrees to use a highly effective contraceptive~~on (ie,~~ method~~s~~ **(ie,** with a failure rate of less than 1% per year), **preferably with low user dependency, as described** ~~detailed~~ in ~~Appendix II~~**Appendix III for the following time periods:** ○ **Before the first dose of study**	10. A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies: • Not a WOCBP (defined in Appendix III) OR • If a WOCBP agrees to use a highly effective contraceptive method (ie, with a failure rate of less than 1% per year), preferably with low user dependency, as described in Appendix III for the following time periods: ○ Before the first dose of study treatment, 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 at least 28 days and has a documented negative pregnancy test using a highly sensitive assay. AND ○ A barrier method, as described in Appendix III. • During the treatment period:

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			treatment, if using hormonal contraception: **o Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses** **OR** **o Has used a depot contraceptive or extended cycle oral contraceptive for at least 28 days and has a documented negative pregnancy test using a highly sensitive assay ~~of this protocol 14 days before start of first dose of study treatment (as appropriate), during the treatment period, and for at least 90 days after the last dose of study treatment~~.** **AND** **o A barrier method, as described in Appendix III.** • **During the treatment period:** **o After the treatment period (ie, after the last dose of study treatment is administered) for at least 40 days after the last dose of study treatment** **o The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study treatment** **o Have a negative serum**	o After the treatment period (ie, after the last dose of study treatment is administered) for at least 40 days after the last dose of study treatment o The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study treatment o Have a negative serum pregnancy test, as required by local regulations, within 21 days before the first dose of study treatment. • Additional requirements for pregnancy testing during and after study treatment are in Table 1, Table 2, and Table 3. • 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.

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			pregnancy test, as required by local regulations, within 21 days before the first dose of study treatment. • **Additional requirements for pregnancy testing during and after study treatment are in Table 1, Table 2, and Table 3.** • **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.**	
Revised washout period for prior anticancer therapies	5.3.2 Exclusion Criteria, 1	51	1. Use of other anticancer therapy (see Section 6.5.2) within ~~15 days~~ **5 x their elimination half-lif~~es~~, but no longer than 15 days,** before the first dose of M3541 administration~~ and should not be within the "at risk follow-up period" for that specific anticancer therapy~~. The use of any investigational agent is not allowed within 28 days before the first dose of M3541	1. Use of other anticancer therapy (see Section 6.5.2) within 5 x their elimination half-life, but no longer than 15 days, before the first dose of M3541 administration. The use of any investigational agent is not allowed within 28 days before the first dose of M3541
Clarification	5.3.2 Exclusion Criteria, 6	52	6. **Major s**~~S~~urgical intervention within 28 days prior to the first dose of M3541 administration	6. Major surgical intervention within 28 days prior to the first dose of M3541 administration
Correction	5.5.1 Withdrawal from Study Therapy	53	The subject must be withdrawn from M3541 in the event of any of the following: ……. • Occurrence of any **condition** ~~exclusion criterion~~ that is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and / or Sponsor prior to treatment completion …….	The subject must be withdrawn from M3541 in the event of any of the following: ……. • Occurrence of any condition that is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and / or Sponsor prior to treatment completion ……. • Use of a non-permitted concomitant drug

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			• Use of a non-permitted concomitant drug (including any other drug with known anticancer activity unless specified otherwise in Section 6.5.2) ~~where the predefined consequence is withdrawal from M3541~~	(including any other drug with known anticancer activity unless specified otherwise in Section 6.5.2)
Mandatory protocol text	5.5.2 Withdrawal from the Study	53	…… **A subject may also be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons but will be followed for survival and delayed AEs for up to 1 year**	…… A subject may also be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons but will be followed for survival and delayed AEs for up to 1 year.
Mandatory protocol text: definition of end of study per subject	5.7 Definition of End of Study	54	The study will end after the last subject has completed the 1-year survival follow-up period. **A subject has completed the study if she/he has completed all study parts, including the last visit or the last scheduled procedure as shown in the Schedule of Assessments (Table 1, Table 2, and Table 3).**	The study will end after the last subject has completed the 1-year survival follow-up period. A subject has completed the study if she/he has completed all study parts, including the last visit or the last scheduled procedure as shown in the Schedule of Assessments (Table `1, Table 2, and Table 3).
Mandatory protocol text	6.5 Concomitant Medications and Therapies	58	**……** **Contact the Medical Monitor for any questions on concomitant or prior medications.**	…… Contact the Medical Monitor for any questions on concomitant or prior medications.
Added definition of washout period for prior anticancer therapies / Modification of DLT follow-up period	6.5.2 Prohibited Medicines	59	Subjects must not have received chemotherapy, immunotherapy, biologic therapy, or any other anticancer therapy within ~~15 days~~ **5 x their elimination half-life, but no longer than 15 days,** before the first dose of IMP administration (6 weeks for nitrosoureas or mitomycin C)~~, and should not be within the "at risk follow-up period"~~**. Thus, the washout period for prior anticancer therapy is defined as 5 x the elimination half-life of the**	Subjects must not have received chemotherapy, immunotherapy, biologic therapy, or any other anticancer therapy within 5 x their elimination half-life, but no longer than 15 days, before the first dose of IMP administration (6 weeks for nitrosoureas or mitomycin C). Thus, the washout period for prior anticancer therapy is defined as 5 x the elimination half-life of the relevant anticancer therapy, up to a maximum of 15

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			relevant anticancer therapy, up to a maximum of 15 days. These therapies are **generally** ~~also~~ prohibited during the treatment period and **the DLT follow-up period**~~up to 21 days after the end of M3541 / RT~~. ~~During the treatment period and up to PTD 21 (after M3541 / RT), any other investigational agent, chemotherapy, extensive RT (involving ≥ 30% of bone marrow), or any other anticancer therapy (biologics or other targeted therapy) and antineoplastic steroid therapy are also prohibited.~~ ; ~~h~~**H**owever, subjects with functional neuroendocrine tumor who have progressed clinically or radiographically on octreotide or lanreotide may remain on octreotide or lanreotide for control of hormonal syndromes and still be allowed on study. Similarly, subjects under stable hormone therapy (having received hormone therapy for > 3 months) may remain on hormone therapy and are allowed in the study. …… ~~In addition, the use of any investigational agent is not allowed within 28 days before the first dose of M3541.~~ Medications or herbal supplements known to be potent inhibitors or inducers of CYP3A or P-gp, OATP or OCT or drugs mainly metabolized by CYP3A, with a narrow therapeutic index are prohibited (unless as otherwise agreed to by the Sponsor). Refer to Drug Development and Drug Interactions for a classification of in vivo inhibitors **(see Appendix II)**. ~~http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/~~	days. These therapies are generally prohibited during the treatment period and the DLT follow-up period. However, subjects with functional neuroendocrine tumor who have progressed clinically or radiographically on octreotide or lanreotide may remain on octreotide or lanreotide for control of hormonal syndromes and still be allowed on study. Similarly, subjects under stable hormone therapy (having received hormone therapy for > 3 months) may remain on hormone therapy and are allowed in the study. …… Medications or herbal supplements known to be potent inhibitors or inducers of CYP3A or P-gp, OATP or OCT or drugs mainly metabolized by CYP3A, with a narrow therapeutic index are prohibited (unless as otherwise agreed to by the Sponsor). Refer to Drug Development and Drug Interactions for a classification of in vivo inhibitors (see Appendix II). If the administration of a prohibited concomitant drug becomes necessary during the treatment period, eg, due to AEs, the subject should be discontinued from the study treatment and complete all assessments listed under the Safety Follow-up (PTDs 15, 22, and 30) and End-of-Study visits

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			~~DrugInteractionsLabeling/ucm093664.htm.~~ If the administration of a **prohibited**~~non-permitted~~ concomitant drug becomes necessary during the treatment period, eg, due to AEs, the subject should be discontinued from the study treatment and complete all assessments listed under the Safety Follow-up (PTDs **15,** 22, and 30) and End-of-Study visits	
Simplification	6.5.3 Other Interventions	60	The following non-drug therapies must not be administered or performed during the study (and within 28 days before the start of study treatment): • Major surgery ~~(excluding prior diagnostic biopsy)~~	The following non-drug therapies must not be administered or performed during the study (and within 28 days before the start of study treatment): • Major surgery
Simplification / correction	7.1.1 Screening and Baseline Procedures and Assessments	63	…… The~~re is a 15-day~~ washout **period** ~~or, as appropriate, an "at risk follow-up" period~~ for prior anticancer treatment **is defined** ~~as detailed~~ in Section 6.5.2**.** ~~and~~ **Major surgery is not permitted within** 28 days ~~for major surgery~~ before the start of study treatment **(Section 6.5.3)**. ~~The use of any investigational agent is not allowed within 28 days before the first dose of M3541~~.	…… The washout period for prior anticancer treatment is defined in Section 6.5.2. Major surgery is not permitted within 28 days before the start of study treatment (Section 6.5.3).
Modification of DLT follow-up period	7.1.2 Treatment Period	64	The treatment period consists of 10 FDs (FD 1 to FD 10 over a 2-calendar week period) of palliative RT (5 FDs per week with FD 1 on a Monday and with **the** Saturday and Sunday **between FD 5 and FD 6** ~~of each week~~ as **an** RT holiday~~s~~). M3541 is administered either on a once per FD schedule (Table 1), or on an intermittent schedule of thrice weekly (Table 2) or twice weekly (Table 3) schedules, with M3541 always administered on RT FDs. In case	The treatment period consists of 10 FDs (FD 1 to FD 10 over a 2-calendar week period) of palliative RT (5 FDs per week with FD 1 on a Monday and with the Saturday and Sunday between FD 5 and FD 6 as an RT holiday). M3541 is administered either on a once per FD schedule (Table 1), or on an intermittent schedule of thrice weekly (Table 2) or twice weekly (Table 3) schedules, with M3541 always administered on RT FDs. In case the

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			the Investigator inserts RT holidays (interruption due to toxicity, see Section 6.2.1), M3541 treatment should be suspended and should be restarted with RT at the next first RT day for which M3541 is scheduled to be given. ~~In all cases, RT FD 10 will be followed by a 2-day M3541 / RT holiday, which is included in the overall M3541 / RT treatment period.~~ All effort should be made to complete RT with 10 FDs if possible.	Investigator inserts RT holidays (interruption due to toxicity, see Section 6.2.1), M3541 treatment should be suspended and should be restarted with RT at the next first RT day for which M3541 is scheduled to be given. All effort should be made to complete RT with 10 FDs if possible.
Modification of DLT follow-up period	7.1.3 Dose-limiting Toxicity Evaluation Period	65	The DLT evaluation period will be ~~45~~ weeks in duration, including the 2-week treatment period (including a 2-day M3541 / RT holiday after ~~the last~~ FD **5**) plus a **2~~3~~**-week DLT follow-up period that starts on the ~~third~~ day after the last administration of **M3541** / RT (see Figure 1). After the M3541 / RT treatment period, subjects will return to the clinic on PTD **15~~22~~** (~~±~~+2 days) for assessments (including the BPI-SF as applicable) as outlined in Table 1. **The DLT evaluation period could exceed the 4-week period only if M3541 / RT has been interrupted and given over a period exceeding 2 weeks.** …… In absence of any new or major toxicity / AE during the ~~21-day~~ DLT follow-up period, the subject need only be seen on **PTD 15 (+ 2 days) and** PTD 22 (± 2 days).	The DLT evaluation period will be 4 weeks in duration, including the 2-week treatment period (including a 2-day M3541 / RT holiday after FD 5) plus a 2-week DLT follow-up period that starts on the day after the last administration of M3541 / RT (see Figure 1). After the M3541 / RT treatment period, subjects will return to the clinic on PTD 15 (+ 2 days) for assessments (including the BPI-SF as applicable) as outlined in Table 1. The DLT evaluation period could exceed the 4-week period only if M3541 / RT has been interrupted and given over a period exceeding 2 weeks. …… In absence of any new or major toxicity / AE during the DLT follow-up period, the subject need only be seen on PTD 15 (+ 2 days) and PTD 22 (± 2 days).
Modification of DLT follow-up period	7.1.4 Post-treatment Follow-up	65	…… • Short-term (**PTD 22; ± 2 days and** PTD 30; ± 2 days)	…… • Short-term (PTD 22; ± 2 days and PTD 30; ± 2 days)
Mandatory protocol	7.4.1.3 Definition	73	Any SAE assessed as related to M3541 must be	Any SAE assessed as related to M3541 must

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
text	of the Adverse Event Reporting Period		**recorded and** reported whenever it occurs, irrespective of the time elapsed since the last administration of M3541.	be recorded and reported whenever it occurs, irrespective of the time elapsed since the last administration of M3541.
Mandatory protocol text; definition of "lost to follow-up"	7.4.1.6 Monitoring of Subjects with Adverse Events	74	**A subject 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 subject fails to return to the clinic for a required study visit:** • **The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wants to or should continue in the study** • **Before a subject is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the subject: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the subject's last known mailing address, and 3) if a subject has given the appropriate consent, contact the subject's general practitioner for information. These contact attempts should be documented in the subject's medical record.** • **Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.**	A subject 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 subject fails to return to the clinic for a required study visit: • The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wants to or should continue in the study • Before a subject is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the subject: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the subject's last known mailing address, and 3) if a subject has given the appropriate consent, contact the subject's general practitioner for information. These contact attempts should be documented in the subject's medical record. • Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.
Mandatory protocol text: examples of abnormal pregnancy	7.4.2 Pregnancy and In Utero	75	Any abnormal outcome **(eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)** must be	Any abnormal outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
outcomes	Exposure		reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.	reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.
Mandatory protocol text	7.4.3 Clinical Laboratory Assessments	75	• **Pregnancy testing will be conducted at the end of relevant systemic exposure of the study intervention, ie, at PTD 15 (see Table 1)**	• Pregnancy testing will be conducted at the end of relevant systemic exposure of the study intervention, ie, at PTD 15 (see Table 1)
Clarification	7.4.4 Vital Signs, Physical Examination, and Other Assessments	76	For female subjects of childbearing potential (see Section 7.1.1) serum β-HCG pregnancy test will be carried out during the Screening and urine ~~or serum~~ β-HCG test will be performed according to the Schedules of Assessments (Table 1, Table 2, or Table 3 as appropriate).	For female subjects of childbearing potential (see Section 7.1.1) serum β-HCG pregnancy test will be carried out during the Screening and urine β-HCG test will be performed according to the Schedules of Assessments (Table 1, Table 2, or Table 3 as appropriate).
Modification of PK sampling schedule	7.5 Pharmacokinetics	77	Additional blood samples will be taken on FD 1**, FD 5** and ~~FD 9 or~~ FD 10 for the analysis of plasma proteins that may be involved in plasma protein binding of M3541. This will be reported separately.	Additional blood samples will be taken on FD 1, FD 5 and FD 10 for the analysis of plasma proteins that may be involved in plasma protein binding of M3541. This will be reported separately.
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Modification of DLT follow-up period	8.3.1 Primary Endpoint	81	The primary endpoint is the occurrence of DLTs **during the DLT evaluation period, ie,** during M3541 / RT treatment period plus the ~~3-week~~ DLT follow-up period after the last treatment with M3541 / RT (~~ie, through 5-week DLT evaluation period,~~ see Table 1 and Figure 1).	The primary endpoint is the occurrence of DLTs during the DLT evaluation period, ie, during the M3541 / RT treatment period plus the DLT follow-up period after the last treatment with M3541 / RT (see Table 1 and Figure 1).
Modification of PK sampling schedule	8.3.2 Secondary Endpoints	81	PK endpoints include: …….	PK endpoints include: …….

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and assessments			○ FDs 2 through ~~69~~: Predose plasma concentration (~~C_{trough}~~C_{min}) and approximate C_{max} of M3541	○ FDs 2 through 9: Predose plasma concentration (C_{min}) and approximate C_{max} of M3541
CCI [redacted]				
Modification of DLT follow-up period / revised for consistency	8.4 Analysis Sets	83	…… In addition, subjects without DLT must have completed the ~~21 days~~ DLT ~~observation~~**follow-up** period, ie, having a safety assessment on PTD **15**~~22~~ (allowing for a window of ~~±~~+ 2 days).	…… In addition, subjects without DLT must have completed the DLT follow-up period, ie, having a safety assessment on PTD 15 (allowing for a window of + 2 days).
Modification of DLT follow-up period	8.5.2 Analysis of Primary Endpoints	84	The primary endpoint is the occurrence of DLTs **during the DLT evaluation period, ie,** during the M3541 / RT treatment period plus the ~~3 week~~ DLT follow-up period after the last treatment with M3541 / RT (~~ie, through 5 week the DLT evaluation period,~~ see Table 1 and Figure 1).	The primary endpoint is the occurrence of DLTs during the M3541 / RT treatment period plus the DLT follow-up period after the last treatment with M3541 / RT (see Table 1 and Figure 1).
Mandatory protocol text: publication policy	10.6.2 Publication	92	….. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission	….. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will

Change	Section	Pages	Previous Wording Plus New Wording	New Wording
			review by the Sponsor. **This allows the Sponsor to protect proprietary information and to provide comments.** The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights. **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.**	require presubmission review by the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights. 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.
Supporting information added to a new appendix	Appendix II Drug Development and Drug Interactions	-	Information previously in the protocol has been expanded and provided as a new appendix for ease of reading. See Appendix II below	
Mandatory protocol text: Contraceptive guidance	Appendix III Contraceptive Guidance and Women of Childbearing Potential	96	Contraceptive Guidance has been updated in line with current Sponsor-approved Contraceptive Guidance (01 February 2019). See Appendix III below	
New Principal Clinical Trial Lead	Sponsor Responsible Persons not Named on the Cover Page	102	Name, academic degree CCI CCI Function / Title Principal Clinical Trial Lead Institution Merck KGaA Address Frankfurter Str. 250, 64293 Darmstadt, Germany Telephone number CCI	Name, academic degree CCI Function / Title Principal Clinical Trial Lead Institution Merck KGaA Address Frankfurter Str. 250, 64293 Darmstadt, Germany Telephone number CCI

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Table 1 Schedule of Assessments: M3541 Once per FD Dosing Schedule

Study Periods	Screening	DLT Evaluation Period (45 weeks)						Short-term Safety FU		Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (23 weeks)					
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 1421[c]	PTD 1522 to 30		PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 1522[c] (±+ 2 Days)	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Signed informed consent	X											
Inclusion / exclusion criteria[d]	X[d]	FD 1										
Demography	X											
Medical history	X											
BPI-SF[e]	X[e]	To be completed on each FD[f]					X[f]		X[f]			
HIV, HBV, and HCV testing[g]	X											
Tumor specimen collection (optional)	X											
β-HCG pregnancy test (if applicable)[h]	X[h]						X[h]		~~X[h]~~			
Vital signs[i]	X	X				X	X	X	X	X	X	X
Physical examination	X	X		X		X	X	X	X	X	X	X
Evaluation of all tissues in RT area[j]	X	FD 6		X		X	X	X	X	X	X	X
ECOG PS	X					X			X	X	X	X

Study Periods	Screening	DLT Evaluation Period (~~45~~ weeks)						Short-term Safety FU		Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (~~23~~ weeks)					
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to ~~14~~24[c]	PTD 1~~5~~22 to 30		PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD ~~15~~22[c] (~~±~~+ 2 Days)	PTD ~~2~~2[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
Adverse event assessment	X	X	X	X	X	X	X[c]	X	X	X	X	X[a]
Concomitant medication	X	X	X	X	X	X	X	X	X	X[k]	X[k]	X[k]
Hematology	X	X		X		X[b]	X	X	X			
Coagulation	X	X		X		X[b]	X	X	X			
Serum chemistry	X	X		X		X[b]	X	X	X			
Urinalysis (dipstick)	X						X		X			
12-lead ECG (including QTcF)[l]	X	See Table 4										
Tumor assessment (RECIST 1.1)	X[m]									X[n]	X[n]	X[n]
PK blood samples[o]		See Table 4										
Blood sampling for plasma protein determination		X[p]			~~X~~[q]	X[q]						
CCI												

Study Periods	Screening	DLT Evaluation Period (45 weeks)						Short-term Safety FU		Mid-term Safety FU	Long-term Safety FU	Survival FU / EoS[a] / Post 1-Year FU
		Treatment Period (2 consecutive calendar weeks) (M3541 + Palliative RT)					DLT FU Period (23 weeks)					
	Day -21 to Day -1	FD 1[b] to FD 10[b]					PTD 1 to 14[c]	PTD 15 to 30		PTD 31 to 90	PTD 91 to 180	PTD 181 to 365
FD / PTD (± visit window)	-21 to -1	FD 1, 6	FD 2, 7	FD 3, 8	FD 4, 9	FD 5, 10[b]	PTD 15[c] (± 2 Days)	PTD 22[c] (± 2 Days)	PTD 30 (± 2 Days)	PTD 42, 90 (± 7 Days)	PTD 126, 180 (± 14 Days)	PTD 270, 365 (± 21 Days)
CCI												
Pharmacodynamic markers in blood[t]		See Table 4										
CCI												
Immune cell analysis[u]		See Table 4										
M3541[v]		X	X	X	X	X	No Treatment					
RT 3 Gy/FD		X	X	X	X	X						
Follow-up for RT-related toxicity / survival[w]								**X**	X	X	X	X[w]

AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ctDNA = circulating tumor DNA; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EoS = End-of-Study; FD = Fraction Day (days when RT and M3541 are given); FU = follow-up; Gy = Gray; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PK = pharmacokinetics; PTD = Post-treatment Day (starting the third day after the last dose of RT and M3541 until 1 year later); QTcF = Fridericia corrected QT interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiotherapy; TEAE = treatment-emergent adverse event.

Note: Where scheduled post-treatment visits coincide with a weekend or holiday, they may be postponed to the next working day (up to + 2 days). The relevance of any safety finding during this additional time in the context of a DLT or any other late toxicity will be reviewed by the Safety Monitoring Committee.

a. All subjects will be followed up for disease progression until 1 year after RT is completed, or earlier due to any reason whereby tumor assessments are no longer applicable (eg, PD, if a new treatment is started, withdrawal of consent). The reason for early discontinuation should be captured in the source document. If EoS occurs prior to PTD 365, all assessments must be done as planned for PTD 365. All subjects will be followed for survival and for delayed AEs for up to 1 year (and beyond for AEs) from PTD1. After the 1 year follow-up, the Investigator will be asked to contact subjects every 3 months (± 1 month, phone call is acceptable) until the defined end of the study (see Section 5.7) to enquire and monitor for late appearing RT-related toxicity.

b. FD 1 is the first dose of M3541 and first fraction of RT. Planning of the RT will follow institutional guidelines and will start on a Monday (with **the first** Saturday and Sunday~~s~~ as a M3541 / RT holiday). In cohorts where required, subjects will be asked to stay overnight in a supervised environment on FD 1 unless the PK sampling and ECG assessment at 8 and 12 hours postdose can be completed otherwise. FD 10 is the last administration of M3541 / RT and ~~in all cases will be followed by a 2 day M3541 / RT holiday before~~ the start of the DLT follow-up period **will start on the following day (PTD 1)**. In case of premature withdrawal from the study during the treatment period, the assessments scheduled for the visit on FD 10 should be performed. In such cases, this visit will be considered the EoS visit. If FD 10 is on a Friday then safety laboratory assessments and urinalysis (as required) must be done on FD 9.

c. The **2**~~3~~-week DLT follow-up period (PTDs 1 through **14**~~21~~) starts on the ~~third~~ day after the last administration of M3541 / RT. With the treatment period starting on a Monday, PTD **15**~~21~~ will land on a **Saturday**~~Sunday~~. **The PTD 15 visit has a + 2 days visit window, thus s**~~S~~ubjects should present to the clinic **on the** ~~that~~ following Monday for the **PTD 15** DLT follow-up visit. **PTD 22 will also land on a Saturday. The PTD 22 visit has a ± 2 days visit window, thus subjects should present to the clinic for this safety assessment on either the preceding Thursday/Friday (PTDs 20/21) of the following Monday (PTD 24).** Subjects with ongoing AEs should present to the clinic throughout the DLT follow-up period as appropriate and instructed by the Investigator. See Section 6.5 and subsections for allowed and prohibited medications during the DLT period.

d. Subjects must meet all inclusion criteria and not any exclusion criteria prior to enrollment. Hepatitis B and C results obtained within 3 months prior to screening are still valid for the purpose of this study. In the case of new clinical laboratory abnormalities detected prior to the first dose, the eligibility of the subject should be reconsidered.

e. All subjects will be asked to complete the BPI-SF at Screening and FD 1 prior to other study related assessments. If a subject has no pain in an area to be irradiated as part of the experimental treatment (M3541 + RT), the subject should mark "0" in all pain scales and activity scales. For subjects with cancer pain from lesions to be irradiated as part of the experimental treatment, any pain medication should be documented (name, dose, frequency, including if used on an "as needed" basis) on the appropriate eCRF page.

f. Subjects with cancer pain from lesions to be irradiated as part of the experimental treatment (M3541 + RT) on FD 1 will be asked to complete the BPI-SF on each subsequent FD and on PTD **15**~~21~~ and PTD 30 prior to any other study-related procedures. The subject should only rate pain and interference with daily activity as they relate to areas being irradiated as part of the experimental treatment. The Investigator must also ensure any new pain medication or change in ongoing pain medication (name, dose, frequency, including any change in "as needed" dosing) is reported on the appropriate concomitant medications eCRF page.

g. Screening for HIV will be performed according to local practice and local regulatory guidance.

h. Serum β-HCG pregnancy test at Screening and urine thereafter.

i. Vital signs include body temperature, respiration rate, pulse, blood pressure, body weight, and height (height only at Screening).

j. Areas to be irradiated should be examined at baseline. Worsening of a condition within an irradiated area (eg, skin reactions, bleeding) during the DLT evaluation period should be reported as a TEAE with grade and relatedness to RT and / or M3541. Improvement of a condition within an irradiated area (eg, improved pain, reduced bleeding) should be reported on the appropriate efficacy-related eCRF page.

k. Only new anticancer therapies and any change in treatment given for treatment-related SAEs will be documented.

l. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. Standard ECGs will be evaluated by the Investigator for safety assessment. See Table 4 for details of ECG acquisition timing during the treatment period.

m. Tumor imaging by CT, MRI, or bone scan at baseline to document extent of lesions according to RECIST 1.1. Baseline tumor evaluation can be up to 28 days old when treatment starts. A brain CT / MRI scan (either, contrast preferred) is required at Screening if not performed within the previous 6 weeks.

n. Tumor assessments using the same method used at baseline are to be completed every 6 weeks beginning on PTD 42 of the Mid-term Safety Follow-up period through the Long-term Safety Follow-up period (ie, PTD 180) for a total of 4 assessments. During the survival follow-up period (ie, PTD 181 to 365) tumor assessments will occur approximately on PTD 270 and PTD 365. Assessments are not required if the subject has started a new antitumor treatment. If a new treatment is started, the date (and regimen) must be reported in the eCRF.

o. See Table 4 for details of PK blood sampling.

p. FD 1 only; see Table 4 for details.

q. FD ~~9~~ **5 and10**~~only~~; see Table 4 for details.

r. CCI

s. CCI

t. See Table 4 for details of pharmacodynamic marker ~~and gene expression analysis~~ sample collection.

u. See Table 4 for details of immune cell analysis sample collection.

v. M3541 will be administered at the clinic 1 hour and 45 minutes (± 60 minutes) before RT is started.

w. Can be followed up via phone call every 3 months if no other assessments are required.

x. CCI

Table 4 Electrocardiogram, Pharmacokinetic, and Biomarker Assessments: M3541 Once per FD Dosing Schedule

		Hours Postdose (± minutes)										
	Predose	0.5 -(± 5)	1.0 (± 5)	1.5 (± 15)	2.25 (± 15)	3 (± 15)	4 (± 15)	6 (± 30)	8 (± 30)	12 (± 30)	72 (± 24h)	240 (± 24h)
Electrocardiogram[a]												
FD 1[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]			
FDs 2, 5, 6, and ~~through~~ 7[a]	X				X							
~~FD 9 and~~FD 10[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]			X[d]	X[d]
Pharmacokinetic[e]												
FD 1	X	X	X	X	X	X	X	X	X[c]			
FDs ~~2 through 6~~2, 5, 6, and ~~8~~7	X				X							
FD 10~~9~~	X	X	X	X	X	X	X	X			X[d]	X[d]
Plasma protein determination												
FD 1, 5, and 10	X											
~~FD9~~	~~X~~											
Pharmacodynamic marker CCI												
FDs 1~~,~~ and 6~~, and 9~~	X		X			X						
FDs 2, 4, 7, and 9	X											
Immune cell sampling[e]												
FDs 1, 6, and 9	X											

ECG = electrocardiogram; FD = Fraction Day (days when RT and M3541 are given); PK = pharmacokinetics; PTD = post-treatment day.

a. 12-lead resting ECGs will be obtained after the subject has been in semi-supine position for at least 5 minutes and evaluated by the Investigator for safety assessment. All ECGs should be collected prior to any blood draws for routine clinical laboratory samples or any associated PK blood sample draws. The ECG should be obtained using a Holter recorder. An ECG on PTD 1 is only required if the PTD 1 optional PK sample is drawn.

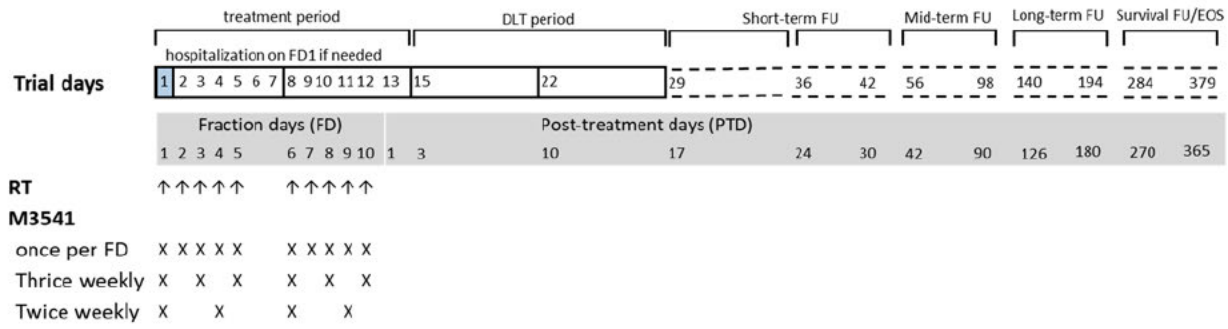
b. At the indicated times, additional digital ECG recordings equivalent to triplicate ECGs are to be recorded for quantitative analysis by a central ECG laboratory (after the end of the study). The ECG recordings must be acquired immediately prior to the PK sample scheduled for the same time point. The ECG should be obtained using a Holter recorder.

c. The 8 and 12 hour PK samples and ECG assessments are optional.

d. The 72 and 240-hour timepoints correspond to PTD 1 and 8, respectively. The 72-hour PK sample is optional and will only be taken if the patient has a visit on PTD 1.

e. The predose sample should be taken within 1 hour before dosing at each sampling day. PK and pharmacodynamic sampling should occur after any required ECG recording.

Figure 1 **Study Treatment, Evaluation, and Follow-up Periods (Updated)**



DLT: Dose Limiting Toxicity; EOS: End of Study; FU: Follow Up; RT: Radiotherapy

Note: Following implementation of Protocol Amendment 4.0, the DLT follow-up period will start on the day after the last administration of M3541 and will be of 2 weeks' duration.
~~DLT = dose limiting toxicity; EoS = End of Study;~~ FD = fraction day; ~~FU = follow up;~~ PTD = Post-treatment Day~~; RT = radiotherapy~~.

Appendix II Drug Development and Drug Interactions

In-vitro assays indicate that M3541 is a substrate for human P-glycoprotein (P-gp), organic cation transporters, and organic anion-transporting polypeptides and is mainly metabolized by CYP3A4/5 and CYP1A2. Current data suggest that the clinical relevance of P-gp and hepatic uptake transporter-mediated drug-drug interactions cannot be excluded. Similarly, the importance of oxidative clearance pathways found in preclinical species, the metabolic clearance of M3541 may be potentially affected by co-administered drugs that are known to be CYP3A4/5 inhibitors or inducers.

There is also potential for M3541 to alter the clearance of other drugs metabolized by CYPs, but available data suggest M3541 is not a strong inhibitor or strong inducer of commonly studied CYPs, or likely to cause strong inhibition of uridine glucuronyl transferase (UGT) metabolizing enzymes.

Investigators should use standard precautions when prescribing co-medications, as with any novel therapeutic for which there is limited clinical experience.

Substrates of CYP3A4

Sensitive: alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil

budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Moderate: alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

Inhibitors of CYP3A4

Strong: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole

Moderate: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

Inducers of CYP3A4

Strong: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort (*Hypericum perforatum*)

Moderate: modafinil

For detailed information, see:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

~~Appendix II Contraceptive Guidance and Woman of Childbearing Potential~~

~~Definitions~~

~~Woman of Childbearing Potential (WOCBP)~~

~~A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.~~

~~Women in the following categories are not considered WOCBP~~

~~1. Premenopausal female with 1 of the following:~~

- ~~Documented hysterectomy~~
- ~~Documented bilateral salpingectomy~~
- ~~Documented bilateral oophorectomy~~

  ~~Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.~~

~~2. Premenarchal~~

~~3. Postmenopausal female~~

- ~~Females who are postmenopausal (age related amenorrhea ≥ 12 consecutive months and increased follicle stimulating hormone [FSH] > 40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.~~
- ~~Females on Hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.~~

~~Contraceptive Guidance~~

~~Highly Effective Contraceptive Methods That Are User Dependent~~
~~Failure rate of <1% per year when used consistently and correctly[a]~~
~~• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]~~ ~~• oral~~ ~~• intravaginal~~ ~~• transdermal~~
~~• Progestogen-only hormonal contraception associated with inhibition of ovulation[b]~~ ~~• oral~~ ~~• injectable~~
~~Highly Effective Methods That Are User Independent~~
~~• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]~~ ~~• Intrauterine device (IUD)~~ ~~• Intrauterine hormone-releasing system (IUS)~~ ~~• bilateral tubal occlusion~~
~~• Vasectomized partner~~ ~~A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.~~
~~• Sexual abstinence~~ ~~(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject).~~
~~NOTES:~~ ~~a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.~~ ~~b. Hormonal contraception may be likely to interact with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study treatment~~

Appendix III Contraceptive Guidance and Woman of Childbearing Potential

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

A WOCBP is not:

1. **Premenarchal**

2. **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 (eg, 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 1 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.**

Contraception Guidance

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 WOCBP 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.

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, post-ovulation 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).