Integrated Analysis Plan
Phase Ia

Clinical Trial Protocol Identification No.	EMR100036-002
Title	An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors
Trial Phase	Ia/Ib (with an ancillary clinical Proof-of-Principle part)
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An Open Label, Phase Ia/Ib Trial of the DNA-PK Inhibitor MSC2490484A in Combination with Radiotherapy in Patients with Advanced Solid Tumors

Approval of the IAP by all Merck Data Analysis Responsible is documented within ELDORADO. With the approval within Eldorado, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

Merck responsible

PPD, Biostatistics	Via ELDORADO approval process
PPD	Via ELDORADO approval process

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ALL	All subjects (Analysis set)
ATC	Anatomical Therapeutic Chemical
AUC0-∞	Area under the concentration-time curve from time zero extrapolated to infinity
AUC0-t	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC	Area under the concentration-time curve
BMK	Biomarker
BOR	Best Overall Response
BSA	Body Surface Area
cPoP	clinical Proof-of-Principle
CL/f	Oral clearance
CLss/f	Oral clearance at steady state
CR	Complete Response
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CRT	Chemoradiotherapy
CTC	Common Terminology Criteria
CTMS	Clinical Trial Management System
CTR	Clinical Trial Report
DE	Dose Escalation (Analysis set)
DLT	Dose Limiting Toxicity
CCI [redacted]	
PBMC	Peripheral Blood Mononuclear Cell
ECG	Electrocardiogram

ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FD	Fraction Day
FU	Follow-up
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HPV	Human Papilloma Virus
IAP	Integrated Analysis Plan
ICF	Informed Consent Form
ICH	International Conference on Harmonization
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
PD	Progressive Disease
CCI [redacted]	
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QD	Once daily
QTcF	Fridericia-corrected QT interval
$R_{accAUC0-4}$	Accumulation ratio for AUC_{0-4}
$R_{acc[Cmax]}$	Accumulation ratio for maximum concentration
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose

RT	Radiotherapy
SAE	Serious Adverse Event
SAF	Safety (Analysis set)
SAP	Statistical Analysis Plan
SD	Stable Disease
Sd	Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time to reach maximum observed concentration
ULN	Upper Limit of Normal
Vz/f	Apparent volume of distribution during terminal phase
Vss/f	Apparent volume of distribution at steady state
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	02 March 2017	PPD	NA
2.0	20 March 2019	PPD	- New template. Replace Statistical Analysis Plan (SAP) with Integrated Analysis Plan (IAP) - Update PPD as coordinated author (replacing PPD) - Add PPD (PPD and PPD as data analysts - Updated PPD as PPD Biostatistics Author (replacing P P) - Updated PPD senior reviewer from PPD - Update protocol version with V9.0 (addition of Arm B: cisplatin exposure added, addition of some baseline characteristics: BSA, HPV, audiogram, adverse events outputs updated with Cisplatin) CCI - Update PK section - Update DLT period and treatment period definitions for Arm B - Add clarification for confirmed BOR derivation - Update concomitant procedures to flag procedures after treatment period - Add details for some listings - Update laboratory parameters section (put Phosphorus as gradable parameter, add clarifications about Uric acid grading - Add clarifications for visits to display for ECG analysis - Update TEAE definition - Added categories for age so in line with BOA - Removal of time-windowing for on-treatment period - Added listing for late toxicities - Added clarification for use of unscheduled visits for Clinical laboratory data and vital signs - Alignement with Protocol v9.0 wording
3.0	18 August 2020	PPD	Update PK section to add analysis of CCI (CCI Add table for disease history. Add analysis to assess COVID-19 impact on the study.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for all analyses of data collected for protocol EMR100036-002 for the Phase Ia (dose escalation part). Results of the analyses described in this IAP will be included in the Clinical Trial Report (CTR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CTR but not identified in this prospective IAP will be clearly identified in the CTR.

The IAP is based upon section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with ICH E9.

A separate IAP will document technical and detailed specifications for the analysis to provide to the SMC members prior to each SMC meeting for the dose escalation phase of Phase Ia.

Additionally, separated IAPs will be issued for the Phase Ib (expansion part) and the ancillary cPOP part of the trial.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) of M3814 in combination with RT (Arm A) and CRT (Arm B)	Primary Endpoint • DLT	15.1
Secondary Objective	To evaluate the safety profile and tolerability of M3814 in combination with RT (Arm A) and CRT (Arm B)	Secondary Endpoint • AE • Laboratory values • Vital signs • Macroscopic signs of bleeding • ECOG • ECG	 15.2 15.4 15.5 15.6.1 15.6.2 15.6.3
	To explore the antitumor activity of M3814 in combination with RT (Arm A) and CRT (Arm B)	Secondary Endpoint • BOR • Tumor size measurements	 14.1 14.1
	To assess the pharmacokinetics (PK) of M3814	• Pharmacokinetic parameters of M3814	16.1
CCI [redacted]			

6 Overview of Planned Analyses

Statistical analyses will be performed using eCRF data obtained until clinical cut-off dates as described below.

In the Phase Ia, the Safety Monitoring Committee (SMC) will decide on DLTs relevant for the treatment and will decide by consensus on dose escalation, dose de-escalation, extension at same dose level, or suspension of enrollment based on safety and PK data.

The cut-off date for dose escalation assessments will be triggered by the completion of the DLT period of the last subject in the respective cohort. For each SMC meeting, a data snapshot will be taken from the clinical database. A dedicated IAP provides more details for the analysis to be sent to SMC members prior to each SMC meeting.

This IAP covers the analyses for efficacy and safety of two milestones:

- Secondary safety analysis
- Final analysis

6.1 Secondary safety analysis

Cut-off date:

This IAP covers the analyses for efficacy and safety based on the data cut-off (see also chapter 9 Data handling after cut-off date). Statistical analyses will be performed using cleaned eCRF data gained up to a clinical cut-off date which is determined when last subject has reached the second post-treatment tumor assessment.

The cut-off date is determined once a data extract (before data base lock) is available which indicates that the last subject has reached the second post-treatment tumor assessment. The clinical cut-off date will be the date on which according to this data extract the last subject has reached the second post-treatment tumor assessment.

6.2 Final Analysis

Cut-off date:

All final, planned analyses identified in the Clinical Trial Protocol and in this IAP will be performed only after the last subject has completed one year of follow-up, all data queries resolved, and the database locked.

A data review meeting will be held prior to database lock. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The protocol specifies the following PK parameters to be reported for Fraction Day 10: CLss/f, Vss/f, AUC_{0-t}, and AUC_{τ}. These will not be calculated or reported due to the limited number of PK samples to be collected in the terminal phase leading to unreliable parameter estimates, please refer to Section 16.1 for a complete list of PK parameters which will be reported. In addition, standard error of the mean will not be a descriptive statistic used to describe PK variables.

In section 8.5.4.3 of the protocol the following analysis is described regarding data coming from the physical examination: "Data will be further analyzed using concentration effect modeling for baseline-corrected QTcF values obtained at Day 1." This analysis will not be performed so will not be included in this analysis plan.

In the protocol a number of biomarker analysis sets are defined. These will not be used and instead the SAF analysis set will be used for biomarker analyses.

7.1 COVID-19 Impact

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

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

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

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

Important protocol deviations will be categorized in to one of the following:

- Subject enrolled and dosed on the study who did not satisfy enrolment criteria
- Subject fulfills withdrawal criteria whilst on the study but is not withdrawn
- Subject is administered the wrong treatment or an incorrect dose
- Subject is administered or takes concomitant medication excluded by the CTP
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data

- Deviations from good clinical practice (e.g. deviations related to informed consent of study participants)
- Other important protocol deviations

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review or programming.

8.2 Definition of Analysis Sets and Subgroups

All Subjects Analysis Set (ALL):

The All subjects (ALL) analysis set will include all the subjects who have signed the ICFs (i.e., screening failures plus subjects enrolled).

Safety Analysis Set (SAF):

The Safety analysis set will include all subjects who receive at least one administration of the trial treatment (either M3814, RT or Cisplatin).

Full Analysis Set (FAS):

The Full Analysis Set will include all subjects who receive at least one administration of the trial treatment.

Dose Escalation Analysis Set (DE) :

The Dose Escalation (DE) analysis set will include all subjects treated in dose escalation cohorts who receive at least 80% of M3814 and RT planned dose and complete the DLT period (through 5 weeks [Phase Ia, Arm A] or 12 weeks [Phase Ia, Arm B] after start of M3814 treatment). The DE set will also include subjects treated in dose escalation cohorts who experience a DLT during the DLT period regardless of the received amount of each drug.

Pharmacokinetics Analysis Set (PK):

The PK evaluation (PK) analysis set in Phase Ia and Phase Ib parts will include subjects who have received at least the first dose of the drug and provided PK samples as per protocol for at least 6 hours following first dosing on Fraction Day 1.

Table 1: Summary of analyses and associated analysis set

Analyses	ALL	SAF	FAS	DE	PK
Disposition and deaths	✓				
Baseline Assessments		✓			
Past and Concomitant Therapies		✓			
Compliance and Exposure		✓			

Analyses	ALL	SAF	FAS	DE	PK
Primary endpoint: DLTs				✓	
Secondary efficacy endpoints			✓		
Safety and tolerability		✓			
Biomarker		✓			
Pharmacokinetics					✓

9 General Specifications for Data Analyses

Statistical analyses will be performed with SAS 9.4 or higher.

Pooling of centers:

Because of the anticipated small number of subjects enrolled in each center, data will be pooled across centers, and the factor center will not be considered in statistical models or for subgroup analyses.

Presentation of continuous and qualitative variables:

All outputs will be provided for each arm separately. No data between arms will be pooled, unless otherwise stated. For each arm, data will be presented by formulation, dose level and overall unless specified otherwise. The dose level will be defined by the planned dose of the corresponding cohort. If several cohorts have same dose level, there will be pooled together for all summary outputs.

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

- Number and percentage of subjects (n (%)), number and percentage of subjects with missing values (Missing (%))
- Mean, 95% confidence intervals, as appropriate
- Standard deviation
- Median
- Q1, and Q3
- Minimum, and maximum

If there are no missing values, this should be indicated by a 0 (0.0).

Missing statistics, e.g, when they cannot be calculated, should be presented as “nd”. For example, if n=1, the standard deviation cannot be computed and should be presented as “nd”.

Qualitative variables will be summarized by frequencies and percentages.

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

Presentation of PK Concentration Data

M3814 and CCI concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max). In $n \leq 2$, only n, Min, and Max will be reported.

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

Mean, Min, Median, Max: 3 significant digits

SD: 4 significant digits

CV%: 1 decimal place

Presentation of PK Parameter Data

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

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

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

Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits

SD: 4 significant digits

CV%, GeoCV%: 1 decimal place

Definition of baseline:

The last measurement prior to first administration of trial treatment (either M3814, RT or Cisplatin) will be used as the baseline measurement.

Definition of treatment day:

Treatment Day 1 is defined as the date of first administration of trial treatment (M3814 and/or RT and/or Cisplatin), the day before is defined as Treatment Day –1 (no Treatment Day 0 is defined).

Definition of on-treatment evaluations for safety analyses:

On-treatment evaluations for safety analyses will be evaluations performed on or after Treatment Day 1 until 30 days after the last dose of trial treatment or the clinical cut-off date (if the treatment is still ongoing).

Definition of duration:

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

Conversion factors:

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

Data handling after cut-off date:

Data after cut-off do not undergo the cleaning process. The only exceptions are the date of death and the date last known to be alive. Data obtained after the cut-off will not be displayed in any listings or used for summary statistics (e.g. laboratory values of samples taken after data cut-off, AE with onset date after data cut-off, etc.) will not be included in any analysis or listing.

For any adverse event or concomitant medication starting before the cut-off date, the end date will not be imputed (even if the end date is after the cut-off date) and will be presented as filled in the eCRF at the time of the data export.

Handling of missing data:

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

- In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of trial treatment then the onset date will be replaced by the minimum of start trial treatment and AE resolution date.

- In all other cases, the missing onset day or onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

In data listings, the documented date as given in the eCRF will be reported (e.g. __May2013 in case of day missing, but month and year available).

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

Table 2: Stopping rules for medication/procedure end dates

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

UNK = Unknown

Table 3: Rules to define previous and/or concomitant medications

Start date of medication/procedure			Stopping rule (see Table 2)	Medication/ procedure
Day	**Month**	**Year**		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	<= Treatment start (year)	Before treatment start	Previous
UNK	UNK	<= Treatment start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Treatment start (year) and <= Treatment end + 30 days (year)	After treatment start	Concomitant

Start date of medication/procedure			Stopping rule (see Table 2)	Medication/ procedure
Day	Month	Year		
UNK	<= Treatment start (month and year)		Before treatment start	Previous
UNK	<= Treatment start (month and year)		After treatment start	Previous and concomitant
UNK	> Treatment start (month and year) and <= Treatment end + 30 days (month and year)		After treatment start	Concomitant
<= Treatment start (date)			Before treatment start	Previous
<= Treatment start (date)			After treatment start	Previous and concomitant
> Treatment start (date) and <= Treatment end + 30 days (date)			After treatment start	Concomitant

UNK = Unknown

Categorization of participants for COVID-19 impact assessment

For the assessment of COVID-19 impact on this study, participants will be categorized as being potentially affected by COVID-19 based on the COVID-19 pandemic start date, defined as the minimum of the first COVID-19 death date per country and 11 March 2020 (WHO-start of world-wide pandemic). First death from COVID-19 per country is determined according to the published data by European Centre for Disease Prevention and Control (Status of 26th June 2020). If the pandemic start is before the end of DLT period, both DLT and FUP periods for the subject will be considered as potentially affected. If it starts during the FUP period, only this period will be considered as potentially affected.

10 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

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

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

- Number of screened subjects*
- Number of subjects discontinued prior treatment start (overall and by reason)*
- Number of subjects who continued beyond screening
- Number of subjects who completed treatment with M3814 ("MSC2490484A Termination" eCRF page)
- Number of subjects who completed treatment with RT ("Radiotherapy Termination" eCRF page)
- Number of subjects who completed treatment with Cisplatin ("Cisplatin Termination" eCRF page)
- Number of subjects discontinued from M3814 overall and by reason ("MSC2490484A Termination" eCRF page)
- Number of subjects discontinued from RT overall and by reason ("Radiotherapy Termination" eCRF page)
- Number of subjects discontinued from Cisplatin overall and by reason ("Cisplatin Termination" eCRF page)
- Number of subjects who completed the trial ("Study Termination" eCRF page).
- Number of subjects discontinued from trial overall and by reason ("Study Termination" eCRF page).
- Number of subjects in follow-up. And for those, the number of subjects last known alive within 3 months before cut-off date and number of subjects last know alive more than 3 month prior to cut-off date

*These will be reported in the overall column only.

A second summary table on analysis sets will be generated:

- Number of subjects in Screened Population
- Number of subjects in SAF Analysis Set (Overall and per dose level)
- Number of subjects in FAS Analysis Set (Overall and per dose level)
- Number of subjects in DE Analysis Set (Overall and per dose level)
- Number of subjects in BMK Analysis Set (Overall and per dose level)
- Number of subjects in PK Analysis Set (Overall and per dose level)

A third summary table will display the number of subjects overall, in each country and in each site (per Analysis Set).

A listing of subject disposition will include the following information (as applicable): Formulation, dose level, subject identification number, date of Informed Consent Form (ICF), Enrolled population, reason for screen failure, date of first and last dose, FAS/SAF analysis set, DE analysis set, BMK analysis set and PK analysis set.

A second listing will include the following trial discontinuation information: Formulation, dose level, subject identification number, end of trial status (completed, ongoing, discontinued), the reason for trial discontinuation, the date of trial termination, time on trial (time from ICF signature to end of trial), and the date of first and last dose of M3814 and RT.

A third listing will include the following M3814 discontinuation information: Formulation, dose level, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for M3814 discontinuation, and the date of first and last dose.

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

For arm B a listing will include the following Cisplatin discontinuation information: Formulation, dose level, subject identification number, end of treatment status (completed, ongoing, discontinued), the reason for Cisplatin discontinuation, and the date of first and last dose.

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

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

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

- Important protocol deviations identified by medical review, including prohibited medications. Important protocol deviations will be reviewed and agreed upon in the Data Review Meeting. This listing will include: formulation, dose level, subject identifier, deviation category,deviation description as displayed in CTMS and if the PD occurred after pandemic start.
- Deviations from inclusion or exclusion criteria, using information provided in "Study Entry" eCRF page. This listing will include: formulation, dose level, subject identifier, inclusion/exclusion criteria not met.

In addition, deviation from treatment compliance, ie. patients who received less than 80% of planned dose will be listed. This listing will include: formulation, dose level, subject identifier, M3814 compliance (%),RT compliance (%), M3814 first and last dose date, RT first and last dose date.

A subject listing of any COVID-19 related PD will also be provided.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

For subjects excluded from the dose escalation analysis set, the reasons for exclusion will be listed. The listing will include: formulation, dose level, subject identifier and the reason for exlusion.

11 Demographics and Other Baseline Characteristics

Population: SAF Analysis Set

All demographics and baseline characteristics will be listed and summarized by dose level and overall using SAF Analysis set.

11.1 Demographics

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

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

Specifications for computation:

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

Note: Technically in case the day or month is not known from at least one of the dates, the day (day and month in case the month is missing) of both dates, the date of birth and the date of informed consent, will be set to 1 and the formula given above will be applied.

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

11.2 Medical History

Population: SAF analysis set

The medical history will be summarized from the "Medical History" eCRF page, using the most recent available version of MedDRA (version 19.1 or later) preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

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

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

11.3 Other Baseline Characteristics

Population: SAF analysis set

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

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

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

Information on disease characteristics collected on the "Disease History" eCRF page will be summarized as follows:

- Site of primary tumor: only non missing categories will be displayed
- Tumor histopathologic / cytologic type: all categories from eCRF will be described
- Tumor histopathologic / cytologic type grade: from GX to G4
- Time since initial cancer diagnosis (months)
- Time since documented, locally advanced, inoperable or metastatic disease diagnosis (months)
- Time since last progression of disease prior to study entry (months)
- TNM classification at initial diagnosis: each T, N, M category will be described (TX, T0, N1, etc.)
- TNM classification at study entry: each T, N, M category will be described (TX, T0, N1, etc.)

In addition, a listing of disease history will be provided including all relevant data.

For Arm B, a listing including HPV status in tumor and a listing including audiogram results will be provided based on date from the "HPV status" eCRF page and "Audiogram" eCRF page respectively.

12 Previous or Concomitant Medications/Procedures

Population: SAF Analysis Set

12.1 Prior Anti-Cancer Treatments and procedures

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

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

- Listing of prior anti-cancer drug therapies,
- Listing of prior surgeries,
- Listing of prior radiotherapy.

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

12.2 Previous Medications

Previous medications are medications, other than trial medications and pre-medications for trial drug, which are taken and stopped before first administration of trial treatment.

Previous medications will be summarized from the "Relevant previous medications" and "Concomitant medications" eCRF pages. The Anatomical Therapeutic Chemical (ATC)-2nd level and PT will be tabulated as given from the World Health Organization Drug Dictionary (most recent available version of WHO-DD, Sept. 2016 or later). If multiple ATC can be assigned to a drug, all ATCs will be reported.

In case the date values will not allow to unequivocally allocate a medication to previous medication, the medication will be considered as previous medication (see section 9 for incomplete or missing dates).

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

12.3 Concomitant Medications

Concomitant treatments are medications, other than trial medications, which are taken by subjects any time on- trial (on or after the first day of study treatment for each subject) or within 30 days for Arm A and 35 days for Arm B after last dose of trial treatment. Medications started after 30 (resp. 35) days will be presented and flagged in listings but will not be taken into account in summary tables.

Concomitant medications will be summarized from the "Concomitant medications" eCRF page. The ATC-2nd level and PT will be tabulated as given from the most recent available version of WHO-DD, Sept. 2016 or later. If multiple ATC can be assigned to a drug, all ATCs will be reported.

In case the date values will not allow to unequivocally allocate a medication to concomitant medication, the medication will be considered as concomitant medication (see section 9 for incomplete or missing dates).

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

12.4 Concomitant Procedures

Concomitant procedures are procedures which are undertaken any time on- trial or within 30 days for Arm A and 35 days for Arm B after last dose of trial treatment. These will be listed according to the CRF page "Concomitant Procedures". Procedures started after 30 (resp. 35) days will be presented and flagged in listing.

In case the date values will not allow to unequivocally allocate a procedure to concomitant procedure, the procedure will be considered as concomitant procedure (see section 9 for incomplete or missing dates).

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

12.5 Anti-cancer post-treatment

Anti-cancer post-treatments will be listed according to eCRF page "Anti-cancer treatment after discontinuation". The listing will include: subject identification number, formulation, dose level and all corresponding collected data-fields on the corresponding eCRF page.

Anti-cancer post-surgeries and post-radiotherapies will also be listed according to eCRF pages "Anti-cancer surgeries after discontinuation" and "Anti-cancer radiotherapy after discontinuation".

13 Treatment Compliance and Exposure

Population: SAF Analysis Set

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

All dosing calculations and summaries will be based on "MSC2490484A Administration", "Radiotherapy Administration" and "Cisplatin Administration" eCRF pages.

In Phase Ia, subjects will receive treatment with M3814 at a starting dose of 100 mg QD for Arm A and 50 mg QD for Arm B, which will be given 1.5 hours before each RT fraction (3 Gy) for up to 10 fractions (Arm A) or 2 Gy for 33 to 35 fractions (Arm B). In addition, in Arm B, on Fraction Days 1 and 31 for the 100 mg/m^2 dose, or weekly for the 40 mg/m^2 dose, cisplatin will be given after oral intake of M3814 and before RT is started. Dose escalation will continue up to a maximum dose of M3814 800 mg/day.

Number of treatment administrations

The number of fraction days of treatment will be summarized for Radiotherapy by dose level and overall.

The number of days of treatment will be summarized for M3814 by dose level and overall.

The number of infusions of Cisplatin will be summarized for both treatment schedules: 100 mg/m^2 twice (FD1, FD31) or 40 mg/m^2 weekly.

Cumulative dose

The cumulative dose (mg) of M3814 will be calculated as the sum of the total daily doses that the subject received.

The cumulative dose (Gy) of RT will be calculated as the sum of the total daily doses that the subject received.

The cumulative dose (mg/m^2) of cisplatin per subject is the sum of the total dose that the subject received at each visit. At a given visit, the total dose (mg/m^2) received is derived as:

Total dose = Total dose administered (mg) / recalculated BSA (m^2)

The recalculated BSA is derived based on formula described in section 11.3, using weight measured at the corresponding visit. In case the weight measurement is missing, the weight measurement closest to the administration date will be used. If there are two measurements which are equal distance away from the missing measurement, the earliest measurement will be used.

Compliance with treatment

The relative dose intensity with the treatment is defined as:

- For M3814:

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

- For RT:

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

Where :

- For Arm A: x = 10
- For Arm B:
  - x = 35 if subject received less than 33 FD, to generate the maximum possible denominator for patients with incomplete dosing

- x = actual number of FD if subject received from 33 to 35 FD

- For Cisplatin:

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

Where cumulative planned dose (mg) is the sum of planned dose at each visit. At a given visit, the planned dose (mg) is derived as:

$$\text{Planned dose} = \text{Planned dose (mg/m}^2\text{)} * \text{recalculated BSA (m}^2\text{)}$$

The recalculated BSA is derived based on formula described in section 11.3, using weight measured at the corresponding visit. In case the weight measurement is missing, the weight measurement closest to the administration date will be used. If there are two measurements which are equal distance away from the missing measurement, the earliest measurement will be used.

The relative dose intensity with the treatments will display using the following categories:

- > 100%
- [80% - 100%]
- [65% - 80%[
- [50% - 65%[
- < 50%

The following summary tables will be provided for M3814 and RT administrations by dose level:

- Number of days of M3814
- Number of FD of RT

Number of infusions of Cisplatin (separately for weekly/twice schedule)

- Cumulative dose of M3814 (mg)
- Cumulative dose of RT (Gy)
- Cumulative dose of Cisplatin (mg/m²)
- Relative Dose Intensity

The listing of exposure assessments (including e.g. date and time of administration, dose, frequency, change in dose) will be provided by subject as recorded from the related eCRF pages and for each M3814, RT and Cisplatin administration.

In addition, a summary listing will be provided with the cumulative dose, the relative dose intensity and the number of fraction days with treatments for each subject and treatment.

In addition, a listing of accountability for M3814 according to page "M3814/Placebo accountability" of eCRF will be produced. This listing will include the subject identification number, and all collected fields of the corresponding eCRF Page.

14 Efficacy Analyses

Secondary efficacy endpoints include Best Overall Response (BOR) and tumor measurements. Tumor assessments are based on local evaluations by the investigator according to RECIST 1.1 criteria. Local evaluations of target, non-target and new lesions are used to derive the BOR.

14.1 Best Overall Response

Population: FAS Analysis Set

The Best Overall Response (BOR) will be defined as the best response per RECIST 1.1 across all time points until determination of Progressive Disease (PD) or cut-off date, using the Investigator reported overall response per time point and excluding assessments after tumor surgery.

BOR will be defined as the best response across all time points (for example, a subject who has stable disease (SD) at the first assessment, partial response (PR) at the second assessment, and PD at the last assessment has a BOR of PR). The order to obtain the BOR is the following: complete response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE).

When SD is believed to be the best response, it must also meet the protocol-specified minimum 6 weeks (42 days) from first day of treatment. If the minimum time is not met, the subject's best overall response depends on the subsequent assessments. For example, a subject who has SD at the first assessment, PD at the second assessment and does not meet the minimum duration for SD, will have a best overall response of PD. The same subject lost to follow-up after the first SD assessment would be considered NE for BOR.

If a subject has missing baseline tumor assessment and/or no tumor assessment on-treatment, BOR will be NE.

The confirmed BOR will be also analyzed. In this case, CR and PR need to be confirmed at a subsequent assessment, at least 4 weeks after initial overall response assessment of CR/PR. Confirmed BOR will be derived as described in RECIST 1.1 guidance.

Overall response first time point	Overall response subsequent time point*	Confirmed BOR
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	PD	SD, if minimum criteria for SD duration met at first time point. Otherwise PD
CR	NE	SD, if minimum criteria for SD duration met at first time point. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, if minimum criteria for SD duration met. Otherwise PD
PR	NE	SD, if minimum criteria for SD duration met. Otherwise NE
NE	NE	NE

* Subsequent time point is not necessarily the direct subsequent scan (eg. PR-SD-PR will have PR as confirmed BOR)
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

To analyze tumor response, it may be necessary to determine the date of tumor assessment, e.g. to check whether SD was asserted after a suitable time limit after baseline. In case of different dates of scans within the same tumor assessment, the earliest scan date is used as the date of tumor assessment.

Both Confirmed and Unconfirmed BOR will be summarized by tabulating the number and percentage of subjects with CR, PR, SD, PD or NE as BOR. In addition, confirmed objective response (confirmed BOR of CR or PR), unconfirmed objective response (unconfirmed BOR of CR or PR and disease control will be summarized. Objective response rate (ORR) and disease control rate (DCR) are indicated together with exact Clopper-Pearson 95%-confidence intervals (Clopper & Pearson, 1934).

The listing of tumor assessments (including e.g. lesion number, description and site, type of lesion, imaging date, assessment method, diameter (mm), sum of diameter of target lesions, BOR (confirmed and unconfirmed) will be provided by subject as recorded from the "Target Lesions", "Sum of Diameters", "Non-Target Lesions", "New Lesions" and "Assessment of disease based on imaging" eCRF pages.

A spider plot will display the percentage change from baseline in sum of longest diameter of target lesion against the date for each subject.

A swimmer plot displaying some key radiological milestones will be produced for each dose level separately. For each subject, the time from treatment start until end of follow-up will be represented (from treatment start to last date known to be alive or date of death). In addition, following information will be displayed: time to best overall unconfirmed response (CR, PR or SD), time to progression and status at the end of the follow-up (alive or dead).

For subjects alive, the following dates will be used to determine the last date known to be alive prior or at data cut-off.

- All patient assessment dates:
  - Laboratory assessments using information from "Serology", "Hematology", "Biochemistry", "Coagulation", "Urinalysis", "Microscopic analysis", "Pregnancy test" and "Platelet aggregation evaluation" eCRF pages (LBDTC variable from LB SDTM domain to be used)
  - Vital signs using information from "Vital signs" eCRF page (VSDTC variable from VS SDTM domain to be used)
  - Performance status using "ECOG Performance status" eCRF page (QSDTC variable from QS SDTM domain to be used)
  - ECG, using information from "Triplicate 12-lead electrocardiogram" (EGDTC variable from EG SDTM domain to be used)
  - Tumor assessments using "Tumor assessments" eCRF pages (TRDTC/TUDTC variable from TR/TU SDTM domain to be used)
  - Study maintenance assessments (XXDTC variable from XX SDTM domain to be used)
- Start and end dates of concomitant medications or anti-cancer therapies administered after study treatment discontinuation using "Concomitant medications", "Anti-cancer treatment after discontinuation details" eCRF pages (CMSTDTC and CMENDTC variable from CM SDTM domain to be used)
- AE start and end dates using "Adverse events details" eCRF page (AESTDTC and AEENDTC variables from AE SDTM domain to be used)
- Study treatment administration dates using "MSCA2490484A Administration", "Radiotherapy Administration" and "Cisplatin Administration" eCRF pages (EXSTDTC variable from EX SDTM domain to be used)
- Macroscopic signs of bleeding using "Macroscopics signs of bleeding" eCRF page (CEDTC or FADTC from CE/FA SDTM domains)
- Survival follow-up dates using "Survival Follow-up page" (YFSTDTC variable from YF SDTM domain where YFTESTCD="SURVSTAT").

In addition, waterfall plot representing the best percentage change in tumor size from baseline per subject will be provided. The unconfirmed BOR will also be presented as an annotation on each vertical bar.

15 Safety Analyses

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

The primary endpoint of the Phase Ia is the occurrence of a DLT for a subject during the DLT observation period (5 weeks after the start of RT for Arm A and 12 weeks after the start of RT for Arm B). Based on the data observed, a recommendation of the next dose level is based on a Bayesian dose escalation design using a two-parametric logistic regression model. More details about the analysis to be provided to SMC members are presented in a dedicated IAP.

15.1 DLT (Primary endpoint)

Population: DE Analysis Set

A table with a summary DLTs during the DLT period, as confirmed by the SMC, will be provided for each dose level and overall with:

- Number of subjects with no DLT
- Number of subjects with DLT: one DLT, at least two DLTs

The listing of all DLTs (identified either by Investigator or by SMC) will also be provided.

15.2 Adverse Events

All TEAEs will be summarized, i.e. those events that are emergent during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state and with onset dates occurring within the first dosing day of trial treatment until 30 days after the last dose of trial treatment. If an adverse event started before treatment start and improved during treatment (i.e. with the same PT directly following, but lower grade) it should not be counted as a TEAE. However, if an adverse event started either before or during the treatment period and worsened during the treatment period this should be reported as a TEAE.

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

- The treatment period is defined from the first dosing day of trial treatment until 30 days after the last dose of trial treatment or the clinical cut-off date.
- If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated.
- Adverse events related to trial treatment are those events with relationship missing, unknown or related to at least one treatment (M3814, RT or Cisplatin).
- Adverse events related to M3814 are those events related to M3814, regardless to relationship with RT and/or Cisplatin

- Adverse events related to RT are those events related to RT, regardless to relationship with M3814 and/or Cisplatin
- Adverse events related to Cisplatin are those events related to M3814, regardless to relationship with M3814 and/or RT
- In case a subject has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

For identification of AE treatment emergence, incomplete dates will be handled using the rules presented in section 9.
AEs will be coded according to the current MedDRA. The severity of AEs will be graded using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 toxicity grades.

15.2.1 All Adverse Events

Population: SAF analysis set

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per subject, using the most recent available MedDRA version (19.1 or later) PT as event category and primary SOC body term as Body System category.

Frequency tables for AEs captured on the "Adverse Events" eCRF pages will be based on TEAEs, i.e. those events with onset dates occurring within the treatment periods (as defined above).

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

- TEAE
- TEAEs related to trial treatment, (i.e. M3814, RT, or Cisplatin)
- TEAEs related to M3814
- TEAEs related to RT
- TEAEs related to Cisplatin
- Serious TEAE
- Serious TEAE related to trial treatment, M3814, RT or Cisplatin
- TEAEs with grade ≥ 3
- TEAEs with grade ≥ 4
- TEAEs with grade ≥ 3 related to trial treatment, M3814, RT or Cisplatin
- TEAEs with grade ≥ 4 related to trial treatment, M3814, RT or Cisplatin

- TEAE leading to study discontinuation
- TEAE leading to death
- TEAE leading to death related to trial treatment, M3814, RT or Cisplatin

In addition, frequency tables summarizing events in the following categories will be prepared by dose level and overall, SOC and PT in alphabetical order:

- TEAEs
- TEAEs related to trial treatment (i.e., M3814, RT, or Cisplatin)
- TEAEs related to M3814
- TEAEs related to RT
- TEAEs related to Cisplatin
- Serious TEAEs
- Serious TEAEs related to trial treatment
- Serious TEAEs related to M3814
- Serious TEAEs related to RT
- Serious TEAEs related to Cisplatin
- TEAEs by worst CTCAE grade: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs related to trial treatment by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs related to M3814 by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs related to RT by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAE related to Cisplatin by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- TEAEs leading to death
- TEAEs related to trial treatment leading to death
- TEAEs related to M3814 leading to death
- TEAEs related to RT leading to death
- TEAEs related to Cisplatin leading to death

All tables will be sorted by alphabetical order of SOC and PT.

The listing for all AEs (whether treatment-emergent or not) will include all the data fields as collected on the "Adverse Events" eCRF pages with the following items:

- Formulation
- Dose level
- Subject identification number,
- First and last dose date
- Reported Term with SOC and PT
- Start and end date with their corresponding treatment day
- Treatment Emergent Adverse Events flag (N/Y)
- Timing related to treatment (if same day of treatment administration)
- TEAE related to M3814 flag (N/Y)
- TEAE related to RT flag (N/Y)
- TEAE related to Cisplatin flag (N/Y)
- Serious Adverse Events flag (N/Y)
- DLT flag (Y/N)
- CTCAE Grade
- Action taken M3814, with RT and with Cisplatin
- Outcome of AE
- AE occurred after COVID-19 pandemic start (Y/N).

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Summary tables for non-serious adverse events excluding SAEs applying frequency threshold of 5% will be provided. The threshold will be applied on preferred term using overall column.

Evaluation of COVID-19 effects on AEs

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

15.2.2 Adverse Events Leading to Treatment Discontinuation

Population: SAF analysis set

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

- TEAE leading to temporary discontinuation of at least one trial treatment, all trial treatments, M3814 (regardless of other trial treatments status), RT (regardless of other trial treatments status), Cisplatin (regardless of other trial treatments status) (corresponding to AEs with action taken = "Drug interrupted" for MSC2490484A or Cisplatin respectively and "Dose skipped" for Radiotherapy)

- TEAE leading to permanent discontinuation of at least one trial treatment, all trial treatments, M3814 (regardless of other trial treatments status), RT (regardless of other trial treatments status), Cisplatin (regardless of other trial treatments status) (corresponding to AEs with action taken = "Drug withdrawn" for M3814, Radiotherapy or Cisplatin respectively)

- TEAE leading to dose time delayed of RT (corresponding to AEs with action taken = "Dose time delayed")

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

- TEAEs leading to temporary discontinuation of at least one trial treatment
- TEAEs leading to temporary discontinuation of all trial treatments
- TEAEs leading to temporary discontinuation of M3814 (regardless of other trial treatments status)
- TEAEs leading to temporary discontinuation of RT (regardless of other trial treatments status)
- TEAEs leading to temporary discontinuation of Cisplatin (regardless of other trial treatments status)
- TEAEs leading to permanent discontinuation of at least one trial treatment
- TEAEs leading to permanent discontinuation of all trial treatments
- TEAEs leading to permanent discontinuation of M3814 (regardless of other trial treatments status)
- TEAEs leading to permanent discontinuation of RT (regardless of other trial treatments status)

- TEAEs leading to permanent discontinuation of Cisplatin (regardless of other trial treatments status)
- TEAEs leading to dose time delayed of RT

15.2.3 Late toxicities

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

- It is the first occurrence of adverse event for this participant on MedDRA preferred term level
- It is a recurring adverse event but there is gap between the end date of the previous occurance and the start date of the re-occurence (start date of reoccurence – end date of previous occurance > 0)
- It is a reccuring adverse event without gap between the end date of the previous occurance and the start date of the re-occurence and the grade has worsened:

The following will be produced for late toxcicites:

- Table of all late toxcities by worst CTCAE grades: any grade (including AEs with missing grade), grades ≥ 3, ≥ 4 and 5
- Listing of all late toxicities related to M3814
- Listing of all late toxicities related to radiotherapy
- Listing of all late toxicities grade ≥ 3

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

15.3.1 Deaths

Population: ALL analysis set

All deaths, deaths within 60 days after first dose, and deaths within 30 days after last dose of trial treatment, as well as reasons for deaths, will be tabulated based on information from all relevant information available in the eCRF:

- Number of deaths
- Number of deaths within 60 days after first dose of trial treatment

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

In addition, date and cause of death will be provided in individual subject data listings together with selected dosing information (date of first / last administration, dose and number of doses).

Subject listing of deaths includes columns for:

- AEs with fatal outcome (list PTs of AEs with outcome=fatal),
- flag for death within 60 days of first dose of M3814
- flag for death within 60 days of first dose of RT
- flag for death within 60 days of first dose of Cisplatin
- flag for death within 30 days of last dose of M3814
- flag for death within 30 days of last dose of RT
- flag for death within 30 days of last dose of Cisplatin

15.3.2 Serious Adverse Events

Population: SAF analysis set

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

In addition, subject listings of SAEs will be provided.

15.3.3 Other Significant Adverse Event

Not applicable.

15.4 Clinical Laboratory Evaluation

Population: SAF analysis set

Local laboratory values converted in standard units (including corresponding normal ranges) will be used for the summaries. Values below the detection limit will be imputed by half of the detection limit.

Laboratory results will be classified according to the NCI-CTCAE version 4.03. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories:

below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges).

Common Terminology Criteria (CTC) gradable parameters

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

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Name in NCI-CTC	Direction of abnormality
	Biochemistry			
Electrolytes	Calcium	CA	Hypocalcemia/Hypercalcemia	Low/High
Electrolytes	Magnesium	MG	Hypomagnesemia/Hypermagnesemia	Low/High
Electrolytes	Phosphorus (Phosphate)	PHOS	Hypophosphatemia	Low
Electrolytes	Potassium	K	Hypokalemia/Hyperkalemia	Low/High
Electrolytes	Sodium	SODIUM	Hyponatremia/Hypernatremia	Low/High
Enzymes/cardial	Creatinine Phosphokinase	CK	CPK increased	High
Enzymes/liver	Alanine Aminotransferase	ALT	Alanine Aminotransferase increased	High
Enzymes/liver	Alkaline Phosphatase	ALP	Alkaline Phosphatase increased	High
Enzymes/liver	Aspartate Aminotransferase	AST	Aspartate Aminotransferase increased	High
Enzymes/liver	Gamma-glutamyltransferase	GGT	GGT increased	High
Enzymes/liver	Total bilirubin	BILI	Blood bilirubin increased	High
Metabolism	Glucose	GLUC	Hypoglycemia/Hyperglycemia	Low/High
Metabolism	Uric acid(1)	URATE	Hyperuricemia	High
Plasma proteins	Albumin	ALB	Hypoalbuminemia	Low
Renal/kidney	Creatinine	CREAT	Creatinine increased	High
Renal/kidney	Creatinine Clearance	CREATCLR	part of Chronic kidney disease	Low
	Hematology			
Platelets	Platelets Count	PLAT	Platelet count decreased	Low
Red blood cells	Hemoglobin	HGB	Anemia/Hemoglobin increased	Low/High
White blood cells/differential	White Blood Cell Count	WBC	White blood cell decreased/Leukocytosis	Low/High
White blood cells/differential	Absolute Lymphocytes Count	LYM	Lymphocyte count decreased/increased	Low/High
White blood cells/differential	Absolute Neutrophils Count	NEUT	Neutrophil count decreased	Low

(1) According to CTCAE grade, if uric acid value is between ULN and 590 µmol/L it should be graded as following:

- Grade 1 if there are no physiologic consequences
- Grade 3 if there are physiologic consequences

For a programming perspective, values between ULN and 590 µmol/L will all be graded as Grade 1 (if any physiologic consequences are observed, it should be completed as an adverse event).

For all CTC gradable parameters, shift tables from baseline to worst grade on-treatment (including scheduled and unscheduled assessments) will be produced. The worst grade per subject will be defined as the highest CTC grade among the on-treatment evaluations. If there is

no on-treatment evaluation, then the worst grade will be set to 'Missing'. Parameters will be grouped by category.

Non-CTC gradable parameters

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

Category	Parameter (LBTEST)	Parameter code (LBTESTCD)	Direction of abnormality
	Biochemistry		
Electrolytes	Phosphorus	PHOS	High/Low
Enzymes/cardial	Lactate dehydrogenase	LDH	High
Plasma proteins	Total protein	PROT	Low
Renal/kidney	Blood Urea Nitrogen	BUN	High
	Hematology		
Red blood cells	Hematocrit	HCT	High/Low
Red blood cells	Mean Corpuscular Hemoglobin	MCH	High/Low
Red blood cells	Mean Corpuscular Hemoglobin Concentration	MCHC	High/Low
Red blood cells	Mean Corpuscular Volume	MCV	High/Low
Red blood cells	Red blood cells (Erythrocytes)	RBC	High/Low
Red blood cells	Reticulocytes	RETI	High/Low
White blood cells/differential	Basophils	BASOLE	High
White blood cells/differential	Eosinophils	EOSLE	High
White blood cells/differential	Monocytes	MONOLE	High/Low

Shift tables based on the normal range from baseline to worst on-trial value (including scheduled and unscheduled assessments) will be produced with the following categories for all hematology and blood chemistry parameters (CTC gradable and non-CTC gradable):

- Baseline: Low/Normal/High/Missing/Overall
- Worst On-trial: Low/Normal/High/Missing/Overall

Normal category includes low values for high parameters and high values for low parameters.

Only subjects with post baseline laboratory values will be included in these analyses.

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

Listings will include at least the following items:

- Formulation
- Dose Level
- Subject identification number
- First / last dosing date

- Parameters
- Visit
- Date (Treatment day)
- Analysis value
- SI unit
- Change from baseline
- Reference range status (Low, Normal, High)
- CTC grade (with associated CTC name)
- Baseline flag (Yes/No)
- Worst value on-treatment flag (Yes/No)

In addition, a listing displaying parameters with at least one value with grade ≥ 3 will be provided. For each subject, only parameters where at least one value has Grade >=3 will be displayed (all visits for the corresponding parameter will be displayed).

Coagulation parameters

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

Urinalysis

A listing of urinalysis and microscopic analysis will be provided.

15.5 Vital Signs

Population: SAF analysis set

Boxplots will be produced for systolic blood pressure, diastolic blood pressure, heart rate, temperature and weight. These will be presented by visit. Only scheduled visits will be taken into account.

Vital signs data from "Vital Signs" eCRF pages will be listed.

15.6 Other Safety or Tolerability Evaluations

15.6.1 Macroscopic signs of bleeding

Population: SAF analysis set

The macroscopic signs of bleeding will be listed at baseline and after administration of M3814 using data from "Macroscopic Signs of Bleeding" eCRF page.

15.6.2 ECOG Performance Status

Population: SAF analysis set

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

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

15.6.3 ECG and QT/QTc evaluations

Population: SAF analysis set

Electrocardiogram values based on "Triplicate 12-Lead ECG" eCRF section will be used for summary statistics and shift tables.

The number of subjects with normal ECGs at baseline and abnormal ECGs under treatment will be calculated.

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

- The mean of the triplicate measurement will be used as summary of the quantitative parameters
- The worst Overall conclusion will be retained

Any unscheduled assessments that could be clearly identified as part of a triplicate measurement should be taken into account.

ECG parameters on-treatment will be presented by the following frequency table (by dose level and overall):

- Shift from normal baseline result to any abnormal post-baseline result
- Worst means absolute QTcF interval post-baseline
    - > 450 ms and ≤ 480 ms

- > 480 ms and ≤500 ms
- > 500 ms

- Worst means QTcF increase from baseline
  - > 30 ms and ≤ 60 ms
  - > 60 ms

Summary tables will be provided for each visit and time point by dose level and overall for the following ECG parameters

- Heart Rate
- R-R duration
- PQ/PR duration
- QT duration
- QR duration
- QTcF

ECG results (interpretation) will be summarized using a frequency table for each visit and time point by dose level and overall.

Visits and time points to be displayed in summary tables are:
- Baseline (corresponding to last measurement prior to the first dose of any trial treatment)
- Fraction day 1 post-dose (corresponding to ECG performed at 2 hours postdose for subjects enrolled under protocol V1.0 (collected in "ecg2" eCRF page) and at 2 to 3 hours postdose for subjects enrolled under protocol V1.0 or higher (collected in "ecg3" eCRF page))
- Fraction day 10

Two listings will display all the results as presented in "ECG" eCRF page, one on Qualitative Results and another one on Quantitative Results. All visits and time points will be included in listings.

15.6.4 Pregnancy Test

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

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Population: PK analysis set

Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Pharsight Corporation, a Certara Company, Princeton, New Jersey). The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary North Carolina), Windows version 9.2 or higher will be used to produce tables, listings and figures. Figures will be prepared with SAS Version 9.2, or higher.

Pharmacokinetic parameters will be calculated using standard non-compartmental methods and the actual administered dose.

For each subject with PK data, the following PK parameters will be calculated for M3814 and CCI as either single or multiple dose, as follows and as appropriate.

- FD1 – single dose
- CCI – single dose if it occurs on a Monday
- All other fraction days - multiple dose.

C_{max} Maximum observed concentration

C_{max}/Dose The Dose-normalized maximum observed concentration. Normalized using the actual dose, and the formula C_{max} /Dose.

AUC_{0-4} Area under the concentration-time curve (AUC) from time zero to time 4 hours postdose. AUC_{0-4} will be based on the estimated concentration at 4 hours and not the concentration at the actual observation time. For CCI in case no regression is available and a sample has been collected at 4 hours within the protocol-defined collection window (3.5 to 4.5 hours), actual time may be used.

AUC_{0-4}/Dose The Dose-normalized AUC from time zero to 4 hours postdose. Normalized using the actual dose, using the formula AUC_{0-4} /Dose.

AUC_{0-6} Area under the concentration-time curve (AUC) from time zero to time 6 hours postdose. AUC_{0-6} will be based on the estimated concentration at 6 hours and not the concentration at the actual observation time. In case no regression is available and a sample has been collected at 6 hours within the protocol-defined collection window (5.5 to 6.5 hours), actual time may be used.

AUC_{0-6}/Dose The Dose-normalized AUC from time zero to 6 hours postdose. Normalized using the actual dose, using the formula AUC_{0-6}/Dose.

AUC_{0-12} Area under the concentration-time curve (AUC) from time zero to time 12 hours postdose. AUC_{0-12} will be based on the estimated concentration at 12 hours based on the elimination rate constant.

AUC_{0-12}/Dose The Dose-normalized AUC from time zero to 12 hours postdose. Normalized using the actual dose, using the formula AUC_{0-12}/Dose.

t_{max} Time to reach the maximum observed concentration C_{max}

t_{last} The last sampling time at which the concentration is at or above the lower limit of quantification (LLOQ).

$R_{acc(Cmax)}$ Accumulation ratio for C_{max}, calculated as C_{max} CCI $C_{max,FD1}$ (all dose groups)

$F_{rel(Cmax)}$ Relative bioavailability for C_{max} of tablet compared to capsule formulation $C_{max,FD1}/C_{max}$ C (tablet testing group only)

$R_{acc(AUC0-4)}$ Accumulation ratio for AUC_{0-4} calculated as AUC_{0-4} CCI $AUC_{0-4,FD1}$ (all dose groups)

$F_{rel(AUC0-4)}$ Relative bioavailability for AUC_{0-4} of tablet compared to capsule formulation $AUC_{0-4,FD1}/AUC_{0-4}$ C (tablet testing group only)

$R_{acc(AUC0-6)}$ Accumulation ratio for AUC_{0-6} calculated as AUC_{0-6} CCI $AUC_{0-6,FD1}$ (all dose groups)

$R_{acc(AUC0-12)}$ Accumulation ratio for AUC_{0-12} calculated as AUC_{0-12} CCI $AUC_{0-12,FD1}$ (all dose groups)

$R_{acc(AUC0-24)}$ Accumulation ratio for AUC_{0-24} calculated as AUC_{0-24} CCI $AUC_{0-24,FD1}$ (all dose groups)

$F_{rel(AUC0-24)}$ Relative bioavailability for AUC_{0-24} of tablet compared to capsule formulation $AUC_{0-24,FD1}$/ AUC_{0-24} C (tablet testing group only)

AUC_{0-24} Area under the concentration-time curve (AUC) from time zero to time 24 hours. AUC_{0-24h} will be calculated after the first dose on Fraction Day 1 and after dosing on Fraction Day 6 (in tablet testing group only) and Fraction Day 10. AUC_{0-24} will be based on the estimated concentration at 24 hours, and not the concentration at the actual observation time. For FD1 and CCI in case no regression is available and a sample has been collected at 24 hours within the protocol-defined collection window (23.5 to 24.5 hours), actual time may be used. For CCI where available, the pre-dose concentration will be duplicated and used as the 24 hour concentration to allow AUC_{0-24} to be calculated (assuming steady state after multiple dosing).

AUC_{0-24}/Dose The Dose-normalized AUC from time zero to 24 hours. Normalized using the actual dose, using the formula AUC_{0-24}/Dose.

$C_{av,0-24}$	Average concentration from time zero to 24 hours. Formula: $AUC_{0-24}/24$.
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\ \lambda_z$; FD1, CCI (tablet testing group), single dose data.
$AUC_{0-\infty}$/Dose	The Dose-normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, and the formula $AUC_{0-\infty}$/Dose; FD1, CCI (tablet testing group), single dose data.
$t_{½}$	Apparent terminal half-life, $t_{½} = \ln 2/\lambda z$, where λz is defined as the terminal first order elimination rate constant
CL/f	Apparent total body predicted clearance of drug, calculated by Dose/$AUC_{0-\infty}$. FD1, CCI (tablet testing group), M3814 only.
V_z/f	Apparent predicted volume of distribution during the terminal phase. $V_{z/f}$ = Dose/($AUC_{0-\infty}$*λ_z) FD1, CCI (tablet testing group), M3814 only.
C_{trough}	Trough Concentration; predose concentration on FD2, CCI FD7 and CCI
CCI	[redacted]
[redacted]	[redacted]

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- Percentage of $AUC_{0-\infty}$ obtained by extrapolation (AUC_{extra}), calculated by (1-[$AUC_{0-t}/AUC_{0-\infty}$])×100.
- The time interval (h) of the log-linear regression to determine λ_z.
- Number of data points included in the log-linear regression analysis to determine λ_z.
- Goodness of fit statistic (Rsq,adj) for calculation of λ_z.

Plasma PK concentrations for M3814 and CCI will be listed and summarized by group (e.g. dose level, fraction day, analyte) using standard descriptive statistics. A listing of PK blood sample collection times as well as derived sampling time deviations will also be provided.

Individual concentration-time profiles showing all subjects by dose level, analyte and fraction day and profiles showing all subjects using the entire time course by dose level, analyte and formulation group will be created using the actual time points and the numeric concentration data. Arithmetic mean concentration-time profiles by group will be provided using scheduled (nominal)

time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean plots will include SD error bars when plotted on a linear scale.

The trough concentrations (C_{trough}) for FD2, CCI FD7, and CCI will be listed and summarized by group (e.g. dose level, fraction day, analyte), using standard descriptive statistics. Individual C_{trough} values will be plotted against actual time points on a linear scale, for all subjects by dose level. Arithmetic mean C_{trough} ±SD will also be plotted by dose level, on a linear scale.

The calculation of the AUC will be performed using the mixed log-linear trapezoidal method. The actual time of blood sampling will be used for PK parameter calculation. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time.

Partial areas AUC_{0-4} AUC_{0-6}, AUC_{0-12}, and AUC_{0-24} should be calculated using the scheduled dosing interval. The actual interval calculated from CRF time data should not be used.

Pre-dose samples will be considered as if they had been taken simultaneously with the administration, and will be assigned a time of 0 hours. Concentrations below the lower limit of quantification (LLOQ), will be taken as zero for summary statistics of PK concentration data, NCA and for graphical presentations.

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

AUC_{extra} should not be greater than 20%, the coefficient of correlation (R^2) should be ≥0.8000 and the observation period over which the regression line is estimated should be at least twofold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters (e.g.CL/f, and Vz/f etc.) will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags will be included in the study specific SDTM/ADaM.

Scatter plots and box plots of individual dose-normalized C_{max}, C_{av0-24} , AUC_{0-4}, AUC_{0-6}, AUC_{0-12}, AUC_{0-24}, and $AUC_{0-\infty}$ values versus dose will be presented graphically.

All descriptive summaries of PK data will be performed using the PK Analysis Set. Individual PK data will be listed using the Safety Analysis Set. The mean concentration-time profiles and PK parameter plots will be plotted using the PK Analysis Set and the individual subject concentration-time profiles will use the Safety Analysis Set. Exploratory dose proportionality analysis will be performed by visual inspection of the scatter plots and box plots of C_{max}/dose and AUC_{0-4}/dose against dose.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

CCI

[redacted]

CCI [redacted]

17 References

1. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: Efficient dose escalation with overdose control. Stat Med 1998;17(10):1103-20.

2. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to Phase I cancer trials. Stat Med 2008;27(13):2420-39.

3. Sweeting M, Mander A, Sabin T. Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials. J Stat Softw 2013;54:1-26.

18 Appendices

Appendix 1: Important Protocol Deviations

Protocol Deviation Category	Description of Protocol Deviation	Deviation Code	Clinically Important PD
1. Informed Consent Criteria	Subject did not sign Main ICF and was enrolled	PDEV1	N
1. Informed Consent Criteria	ICF is signed after study treatment was initiated	PDEV2	N
1. Informed Consent Criteria	ICF is signed after study procedure was done, but within the screening period	PDEV3	N
1. Informed Consent Criteria	Incorrect version of ICF signed	PDEV4	N
1. Informed Consent Criteria	Missing Date of Main ICF	PDEV5	N
1. Informed Consent Criteria	Subject withdrew consent from the study and the site does not inform Q2S(central lab) and IQVIA by updating the eCRF system and/or completing the subject withdrawal of consent form	PDEV6	N
2. Eligibility and Entry Criteria	Patient is Male or Female less than 18 years old	PDEV7	N

2. Eligibility and Entry Criteria	Phase Ia: Patient does not have advanced solid tumors or metastases including lymphoma localized in the head and neck region or thorax with an indication for fractionated palliative RT (Arm A); or is not treatment-naïve SCCHN eligible for fractionated curatively intended RT with concurrent cisplatin (Arm B) Phase Ib: patient is not treatment-naïve Stage III A/B NSCLC not eligible for surgical resection or concurrent chemoradiation (Arm A expansion cohort) or treatment-naïve SCCHN eligible for fractionated curatively intended RT with concurrent cisplatin (Arm B expansion cohort) cPoP: patient doesn't have tumor with at least 2 (sub)cutaneous tumor/metastases at least 2 cm apart which are RT naïve with an indication for high dose palliative RT	PDEV8	Y
2. Eligibility and Entry Criteria	ECOG PS > 1	PDEV9	N

2. Eligibility and Entry Criteria	Patient is not able to read, understand, and sign and date the Informed Consent Form (ICF); or fully understand the requirements of the trial and is not willing to comply with all trial visits and assessments	PDEV10	N
2. Eligibility and Entry Criteria	Life expectancy < 3 months	PDEV11	N
2. Eligibility and Entry Criteria	Subject does not have adequate hematological function, defined as absolute neutrophil count ≥ 1.0 × 109/L, platelet count ≥ 100 × 109/L, and hemoglobin ≥ 10 g/ dL, ie 5.7 mmol/L	PDEV12	N
2. Eligibility and Entry Criteria	Subject does not have an adequate liver function, defined by total bilirubin >1.5 × ULN or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2.5 × ULN (except for subjects with liver involvement, who can have AST/ALT >5 × ULN)	PDEV13	N
2. Eligibility and Entry Criteria	Subject does not have an adequate renal function, evidenced by serum creatinine >1.5 × upper limit of normal (ULN)	PDEV14	N

2. Eligibility and Entry Criteria	A male subject did not utilize a highly effective contraception (ie, methods with a failure rate of less than 1% per year) as detailed in Appendix II resulting in a pregnancy or donated sperm during the treatment period, and for at least 90 days after the last dose of study treatment	PDEV15	N
2. Eligibility and Entry Criteria	A female subjects did not utilize highly effective contraception which has resulted in a pregnancy during the treatment period or for at least 90 days aft ther last does of study treatment.	PDEV16	N
2. Eligibility and Entry Criteria	Use of other anticancer therapy, Chemotherapy, immunotherapy, hormonal therapy, biologic therapy within 28 days before the first dose of M3814	PDEV17	N
2. Eligibility and Entry Criteria	Residual toxicity due to previous anticancer therapy with no return to baseline or Grade ≤ 1 (except alopecia) according to CTCAE V4.03	PDEV18	N
2. Eligibility and Entry Criteria	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	PDEV19	N

2. Eligibility and Entry Criteria	Prior RT to the same region that would be irradiated in this study within 12 months (Arm A) or any time time previously (Arm B)	PDEV20	N
2. Eligibility and Entry Criteria	Surgical intervention within 28 days prior to the first dose of M3814 administration (except for diagnostic needle biopsy)	PDEV21	N
2. Eligibility and Entry Criteria	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	PDEV22	N
2. Eligibility and Entry Criteria	Hypertension uncontrolled by medication	PDEV23	N
2. Eligibility and Entry Criteria	Known CNS metastases unless previously treated by RT, stable by computed tomography (CT) scan for at least 3 months without evidence of cerebral edema and no requirement for corticosteroids or anticonvulsants	PDEV24	N
2. Eligibility and Entry Criteria	Known human immunodeficiency virus (HIV) positivity, known clinically significant history of hepatitis (e.g., Hepatitis B [HBV] or Hepatitis C [HCV] virus), current alcohol abuse, or cirrhosis. Screening for HIV to be performed according to	PDEV25	N

	local practice and local regulatory guidance. Testing for HIV and HBV/HCV should be repeated if the subject tested negative for the viruses more than 3 months before trial enrollment		
2. Eligibility and Entry Criteria	Ongoing active infection (requiring systemic treatment) or treatment with live or live attenuated vaccine within 30 days of dosing	PDEV26	N
2. Eligibility and Entry Criteria	History of difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the IMP, current use of percutaneous endoscopic gastrostomy (PEG) tubes	PDEV27	N
2. Eligibility and Entry Criteria	Subjects currently receiving H2-blocker or proton pump inhibitors (PPIs) (or unable to stop at least 5 days prior to the first treatment).	PDEV28	N
2. Eligibility and Entry Criteria	If the planned radiation field includes any part of the esophagus and the subject has symptoms of ongoing esophagitis, the subject is not eligible, unless an esophageal endoscopy rules out the presence of esophagitis.	PDEV29	N
2. Eligibility and Entry Criteria	Subjects where more than 10% of the total esophagus volume receives more than 50% of the prescribed RT dose	PDEV30	N

2. Eligibility and Entry Criteria	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	PDEV31	N
2. Eligibility and Entry Criteria	Known hypersensitivity or allergic reaction to the study treatments or to 1 or more of the excipients used	PDEV32	N
2. Eligibility and Entry Criteria	Pregnant or breast-feeding	PDEV33	N
2. Eligibility and Entry Criteria	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 M3814) or potent inducers of CYP3A or P-gp (must stop at least 3 weeks before treatment with M3814) or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior).	PDEV34	N
2. Eligibility and Entry Criteria	Legal incapacity or limited legal capacity.	PDEV35	N
3. Concomitant Medication Criteria	The subject was treated with a medicine forbidden by the protocol (section 6.5.2) while on treatment	PDEV39	N

3. Concomitant Medication Criteria	Any investigational or anticancer therapy given concomitantly while patient is on study treatment	PDEV40	N
4. Laboratory Assessment Criteria	Missed entire safety laboratory at the specified timepoint	PDEV41	N
4. Laboratory Assessment Criteria	Screening labs are not within 21 days before the start of the treatment	PDEV45	N
4. Laboratory Assessment Criteria	No post-dose PK sample collected	PDEV47	N
4. Laboratory Assessment Criteria	More than 2 PK timepoints missed	PDEV49	N
4. Laboratory Assessment Criteria	PK samples not in line with schedule of collection defined in the protocol and outside of windows, defined for minor PDs	PDEV51	N
4. Laboratory Assessment Criteria	Neither predose nor postdose sample for at least one biomarker assessment collected	PDEV52	N
5. Study Procedures Criteria	Screening tumor assessment (except CT scan, which is allowed up to 28 days) done outside of allowable 21 day window.	PDEV36	N

5. Study Procedures Criteria	Key screening tests/assessments not done: Tumor specimen not collected Pregnancy test not performed Complete vital signs and physical examination is missing Clinical evaluation of bleeding is missing Entire hematological panel is missing Entire chemistry panel is missing Entire coagulation panel is missing Missing urinalysis Missing ECG Esophageal endoscopy not performed, though no confirmation on absence of esophagitis (starting from Protocol v8.0/8.1)	PDEV37	N
5. Study Procedures Criteria	Physical exam, ECOG Performance, vital signs, ECG not performed at required time point—for 2 or more consecutive visits	PDEV53	N
5. Study Procedures Criteria	ECGs missing on 2 or more subsequent visits	PDEV57	N

5. Study Procedures Criteria	cPoP patients: biopsy done outside of the window, specified by protocol (2-4 hrs post RT) and more than +/-30 min	PDEV59	N
5. Study Procedures Criteria	Treatment not discontinued after withdrawal criteria defined at protocol section 5.5 are met: Patient withdrawal of consent at any time Any reason where the investigator considers that withdrawal is in the best interest of the patient Pregnancy Treatment delay for greater than 3 fraction days Lack of compliance with the study and/or study procedures (e.g. dosing instructions, study visits)	PDEV60	N
6. Serious Adverse Event Criteria	SAE(s) were not reported or not reported within 24 hours of site's awareness (discovered by CRAs during SDV)	PDEV61	N
6. Serious Adverse Event Criteria	Pregnancy was not repored (discovered by CRAs during SDV)	PDEV62	N
8. Visit Schedule Criteria	EOT Visit not done	PDEV63	N
8. Visit Schedule Criteria	Treatment Visits not performed/completed in absence of justifying AE/SAE	PDEV64	N
8. Visit Schedule Criteria	Visits performed outside of window during DLT period	PDEV65	N

8. Visit Schedule Criteria	Subject(s) lost to follow up within DLT period	PDEV67	N
8. Visit Schedule Criteria	Subject(s) lost to follow up outside of DLT period	PDEV68	N
9. IP Compliance	Treatment compliance: Patient not dosed per protocol. Dosed after RT IP was skipped, but RT continued in absence of AE justifying IP withdrawal IP was given, but RT skipped Actual dose different from planned dose on at least one fraction day IP formulation is different from assigned	PDEV69	N
9. IP Compliance	Treatment compliance: patient overdosed and not reported	PDEV70	N
9. IP Compliance	IP was given outside of protocol specified window before RT: The window exceeded allowed for minor PD window, i.e. less than 30 or more that 2.5 hrs before RT	PDEV72	N
9. IP Compliance	Treatment compliance: Patient did not receive at least 80% of planned dose in the overall treatment period for at least one treatment (i.e. RT and M3814.) Patients with this protocol deviation and with no DLT event will be excluded from DLT analysis. SPECIFY overall amount of doses	PDEV73	N

	administered in the 10 fraction days (Arm A) or 33-35 FDs (Arm B)		
9. IP Compliance	Event of temperature excursion of IP.	PDEV74	N
9. IP Compliance	Event of temperature excursion and study drug was administered to patient (priority if supply can confirm that drug should not have been used)	PDEV75	N
9. IP Compliance	Patient receives expired or damaged study drug	PDEV76	N
10. Efficacy Criteria	No baseline RECIST 1.1 assessment on or before date of first dose or outside the window allowed according to the protocol	PDEV77	N
10. Efficacy Criteria	1 or more consecutive tumor assessments not done	PDEV78	N
10. Efficacy Criteria	Tumor assessments not performed as per the schedule/ timepoint in the protocol (if exceeds window provided for minor PD)	PDEV81	N
11. Administrative Criteria	Staff performing study related procedures prior to having been delegated the responsibility on the Site Personnel Signature Delegation Log	PDEV82	N
12. Source Document Criteria	Medical records not provided to the monitor for SDV of SAEs	PDEV83	N

12. Source Document Criteria	Subject documents sent to study team/ outside of the institution with patient identifiers details	PDEV84	N
12. Source Document Criteria	Informed consent discussion and provision of copy of ICF to patient not documented in the Medical records	PDEV85	N
12. Source Document Criteria	Full medical records not provided to the monitor for SDV	PDEV86	N
13. Regulatory or Ethics Approvals Criteria	Treatment of subject before receipt of IRB approval	PDEV90	N
13. Regulatory or Ethics Approvals Criteria	New protocol not implemented or updated ICF not used after IRB/IEC and regulatory approval	PDEV91	N
13. Regulatory or Ethics Approvals Criteria	Other study specific documents (admin change, safety cards) and other patient specific documents used prior to IRB/IEC approval	PDEV92	N
13. Regulatory or Ethics Approvals Criteria	As per the site IRB's guidelines/policies, site did not report deviations to IRB in a timely manner	PDEV95	N
13. Regulatory or Ethics Approvals Criteria	As per the site IRB's guidelines/policies, site did not report SAEs to IRB in a timely manner	PDEV96	N

ELECTRONIC SIGNATURES

Document: ctp-emr100036-002-iap-ph1a-v3

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Business Approval	02-Sep-2020 09:31
PPD	Task Completed (Approval eSign): Approved	Business Approval	03-Sep-2020 14:42