Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors
Study Number:	MS201964-0001
Merck Compound:	MSB0010718C (avelumab), MSC2490484A (M3814)
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase I
Short Title:	Phase I Study of Avelumab-M3814 Combinations
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	For all countries except the US and Canada: **Merck KGaA** Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: **EMD Serono Research & Development Institute, Inc.** An affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike, Billerica, MA, USA.

	Medical Responsible: Name: Sarah Chennoufi, MD, PhD. General Merck Phone Number: +49 6151 72 58475 General Merck Fax Number: Not applicable
Regulatory Agency Identifying Numbers:	CCI [redacted]
Protocol Version:	PPD [redacted] /Version 3.0
Replaces Version:	26 June 2019/Version 2.0
Approval Date:	26 November 2020
Medical Monitor Name and Contact Information:	**US:** PPD [redacted] **Global:** PPD [redacted]

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	08 Aug 2018
2.0	Global Protocol Amendment	26 Jun 2019
3.0	Global Protocol Amendment	25 Nov 2020

Protocol Version 3.0 (25 November 2020)

Overall Rationale for the Amendment

The major purpose of this global protocol amendment is to revise upwards the number of participants planned for Part A (avelumab + M3814), and for Part B (avelumab + M3814 + radiotherapy) to accommodate the number of dose levels of M3814 which have been or will be assessed in Part A and Part B.

CCI [redacted]

However, over the course of this clinical trial, Safety Monitoring Committee (SMC) has decided, as a precautionary measure to introduce and assess in both Part A and Part B, the additional intermediate dose levels of M3814 in order to generate further safety and pharmacokinetic (PK) data, hence optimize the safety of participant who would be enrolled in the next dose level cohorts. As a result, the total number of participants that will be enrolled might exceed the number of participants initially planned. Therefore, as announced in the first version of the protocol, this protocol amendment has been developed to implement the change in number of study participants.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated the US Medical Monitor name and contact information.	To be consistent with current information.
1.3 Schedule of Activities Table 1 (Part A) and Table 4 (Part FE)	The frequency of urine dipstick analysis and physical examination updated. After Visit 3, the urine dipstick analysis and physical examination must be performed at Visit 6 and then every 8 weeks.	To avoid the on-site visit between two avelumab administrations.
1.3 Schedule of Activities Table 1 (Part A), Table 3 (Part B), and Table 4 (Part FE)	Clarified that safety follow-up period will be 30 days and 90 days after the last dose of avelumab.	For clarity and consistency with Section 4.1.1.3.
1.3 Schedule of Activities Table 2 and Table 3 (Part B) 8.2.5 Clinical Safety Laboratory Assessments	The name of laboratory test updated from "T4" (thyroxine) to "free T4" (free thyroxine).	For clarity and consistency with other sections.
1.3 Schedule of Activities Table 2 (Part B)	Specified that physical examination and dipstick urinalysis should be performed every 6 weeks starting from Visit 13. Specified that hematology and serum chemistry should be performed every 4 weeks starting from Visit 13. Specified that free T4 and thyroid-stimulating hormone (TSH) should be performed every 6 weeks starting from Visit 2.	To provide additional guidance regarding the assessment timepoints.
1.3 Schedule of Activities Table 7 (Pharmacokinetic and Biomarker Blood Sampling Schedule – Part FE)	PK sample collection timepoint shifted from Day 1 3-hour postdose to Day 22 4-hour postdose.	To better evaluate the effect of food on the PK of M3814. This change did not affect the total number of blood draws or total volume of blood collected or the duration of participant's visit.
CCI [redacted]	CCI [redacted]	CCI [redacted]
2.3.1 Summary of M3814 Data and Potential Benefits and Risks	Included the most recent safety data of M3814.	To align with the M3814 IB Version 8.0.
2.3.1 Summary of M3814 Data and Potential Benefits and Risks 2.3.1.1 Summary of M3814 Tablet Formulation and Potential Benefits and Risks 4.3 Justification for Dose (M3814)	The term used to specify the M3814 formulation updated from "powder in capsule (PiC)" to "capsule".	To align with the M3814 IB Version 8.0.
2.3.2 Summary of Potential Benefits and Risks of Avelumab	Included the most recent safety data of avelumab.	To align with the avelumab IB Version 10.0

Section # and Name	Description of Change	Brief Rationale
4.3.1 Justification for Dose (M3814)	CCI [redacted]	To align with the M3814 IB Version 8.0.
4.3.3 Justification for Dose (Avelumab)	The justification for avelumab dose selection was updated.	To align with the avelumab IB Version 10.0.
5.2 Exclusion Criteria 6.5.3 Prohibited Medicines 6.8 Special Precautions	Added that concomitant use of medications and/or herbal supplements known to be inhibitors or inducers of CYP2C9 is prohibited. Added that concomitant use of medications and/or herbal supplements known to be substrates of CYP2C9 is to be used with caution and safety should be monitored closely.	To keep consistency with other M3814 clinical trial protocols, this modification was added as requested by the Authorities for other M3814 clinical trial protocols. CCI [redacted] In addition, based on the available data, it is not predicted that M3814 directly inhibit CYP2C9 to a clinically relevant degree, but it cannot be excluded. Therefore, drugs metabolized by CYP2C9 are not prohibited. However, in case of concomitant treatment with M3814 and drugs metabolized by CYP2C9, participants should be closely monitored. Also, drugs metabolized by CYP2C9 with a narrow therapeutic index should be avoided if participants cannot be closely monitored.
6.6.2 Dose Selection (Part FE), 6.6.4 Dose Escalation Rules, 9.2 Sample Size Determination	Term "evaluable" deleted	For consistency with synopsis and to provide more clarity on the total number of participants that might be enrolled in each part of the study.
6.8 Special Precautions	Text added to specify that "Drugs which are substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or organic cation transporter 1 (OCT1) with a narrow therapeutic index are to be used with caution".	Based on a recent update of the drug-drug interaction assessment, BCRP, P-gp, and OCT1 substrates are not prohibited. However, participants treated with these substrates that have a narrow therapeutic index should be closely monitored due to a potential risk of increase in exposure of BCRP, P-gp, and OCT1 substrates.
CCI [redacted]	[redacted]	[redacted]
Appendix 2 Study Governance	Text updated to include definition of study start date, the first act of recruitment.	Mandatory change a per the protocol template Version 14.
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Adverse event of special interest (AESI) list of avelumab updated to include myasthenia gravis/myasthenic syndrome.	To align with the avelumab IB Version 10.0.

Section # and Name	Description of Change	Brief Rationale
Appendix 11 Coordinating Investigator Signature Page	E-mail address updated.	To be consistent with current information.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors

Short Title: Phase I Study of Avelumab-M3814 Combinations

Rationale: This study is part of a clinical development program which aims to evaluate the clinical utility of M3814, a DNA damage target agent with avelumab, an anti-programmed death-ligand 1 (PD-L1) therapy with and without radiotherapy (RT) in a broad range of cancers.

The first part of this study (Part A) will assess M3814 in combination with avelumab in participants with advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition.

The second part of this study (Part B) will assess M3814 in combination with avelumab and RT in participants with advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition and are amenable to receive RT.

The third part of this study (Part FE) will assess food effect (FE) on pharmacokinetics (PK) of M3814 when administered in combination with avelumab under fasted and fed conditions, in participants with advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition.

Objectives and Endpoints:

Part A

Objectives	Endpoints (Outcome Measures)
Primary	
To determine a safe, tolerable, RP2D and/or the MTD of M3814 when given in combination with avelumab	Occurrence of DLTs from first treatment to planned final assessment at the end of DLT period at 3 weeks
Secondary	
Safety	
To evaluate the safety profile and tolerability of M3814 in combination with avelumab	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS

Objectives	Endpoints (Outcome Measures)
Pharmacokinetics	
To characterize the pharmacokinetics of M3814 and avelumab when given as combination therapy	• Pharmacokinetic profile of avelumab in terms of pharmacokinetic parameter estimates, as feasible (e.g. C_{max}, C_{min}, Racc[C_{max}], Racc[AUC] and $t_{1/2}$) • Pharmacokinetic profile of M3814 in terms of pharmacokinetic parameter estimates (C_{max}, t_{max}, C_{min}, C_{avg}, fluctuation index, AUC_{0-t}, $AUC_{0-\infty}$, Racc[C_{max}], Racc[AUC], $t_{1/2}$, Vz/f, CL/f, and λ_z)
Immunogenicity	
To evaluate the immunogenicity of avelumab in combination with M3814	Immunogenicity as measured by ADA
Efficacy	
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab in participants with locally advanced or advanced solid tumors	• Confirmed BOR, DOR assessed from CR or PR until PD, death, or last tumor assessment, and PFS time according to RECIST v 1.1 as assessed by the Investigator • Tumor size measurement based on Investigator assessment according to RECIST v 1.1 from the first study interventions dose until confirmed PD or start of new cancer treatment • Overall Survival

ADA=antidrug antibody, BOR=best overall response, CR=complete response, DLT=dose-limiting toxicity, DOR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, MTD=maximum tolerated dose, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PD=progressive disease, PFS=progression-free survival, PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors, RP2D=recommended Phase II dose.

Part B

Objectives	Endpoints (Outcome Measures)
Primary	
To determine a safe, tolerable, RP2D and/or the MTD of M3814 when given in combination with avelumab and radiotherapy	Occurrence of DLTs from first treatment to planned final assessment at the end of DLT period at 4 weeks
Secondary	
Safety	
To evaluate the safety profile and tolerability of M3814 in combination with avelumab and radiotherapy	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS • Incidence, severity and outcomes of RT-induced toxicity

Objectives	Endpoints (Outcome Measures)
Pharmacokinetics	
To characterize the pharmacokinetics of M3814 and avelumab when given in combination with radiotherapy	• Pharmacokinetic profile of avelumab in terms of pharmacokinetic parameter estimates, as feasible (e.g. C_{max}, C_{min}, Racc[C_{max}], Racc[AUC] and $t_{1/2}$) • Pharmacokinetic profile of M3814 in terms of pharmacokinetic parameter estimates (C_{max}, t_{max}, C_{min}, C_{avg}, fluctuation index, AUC_{0-t}, $AUC_{0-\infty}$, Racc[C_{max}], Racc[AUC], $t_{1/2}$, Vz/f, CL/f, and λ_z)
Immunogenicity	
To evaluate the immunogenicity of avelumab in combination with M3814 plus radiotherapy	Immunogenicity as measured by ADA
Efficacy	
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab and radiotherapy in participants with locally advanced and advanced solid tumors	• Confirmed BOR, DOR assessed from CR or PR until PD, death, or last tumor assessment, and PFS time according to RECIST v 1.1 as assessed by the Investigator • Tumor size measurement based on Investigator assessment according to RECIST v 1.1 from the first study interventions dose until confirmed PD or start of new cancer treatment • Overall Survival

ADA=antidrug antibody, BOR=best overall response, CR=complete response, DLT=dose-limiting toxicity, DOR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, MTD=maximum tolerated dose, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PD=progressive disease, PFS=progression-free survival, PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors, RP2D=recommended Phase II dose, RT=radiotherapy.

Part FE

Objectives	Endpoints (Outcome Measures)
Primary	
To determine and compare the pharmacokinetic profile of M3814 under fasted and fed conditions	Area under the M3814 plasma concentration-time curve (AUC) from time zero to the last quantifiable sampling time (AUC_{0-t}) and maximum M3814 plasma concentration observed (C_{max})
Secondary	
Safety	
To evaluate the safety profile and tolerability of M3814 in combination with avelumab under fasted and fed conditions	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS
Immunogenicity	
To evaluate the immunogenicity of avelumab in combination with M3814 under fasted and fed conditions	Immunogenicity as measured by ADA

Objectives	Endpoints (Outcome Measures)
Efficacy	
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab in participants with locally advanced or advanced solid tumors, under fasted and fed conditions	• Confirmed BOR, DOR assessed from CR or PR until PD, death, or last tumor assessment, and PFS time according to RECIST v 1.1 as assessed by the Investigator • Tumor size measurement based on Investigator assessment according to RECIST v 1.1 from the first study interventions dose until confirmed PD or start of new cancer treatment • Overall Survival

ADA=antidrug antibody, BOR=best overall response, CR=complete response, DOR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PD=progressive disease, PFS=progression-free survival, PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors.

Overall Design:

This is a Phase I, multicenter study consisting of 3 parts (Part A, Part B, and Part FE).

- Part A aims to determine the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) of M3814 when given in combination with avelumab.
- Part B aims to determine the MTD and/or the RP2D of M3814 when given in combination with avelumab and RT.
    - Part B will be initiated once a first dose level of Part A has been declared as safe and tolerable by the Safety Monitoring Committee (SMC).
- Part FE aims to evaluate the FE on PK of M3814 following administration of M3814 in combination with avelumab under fasted and fed conditions. Only doses of M3814 already declared as safe and tolerable in Part A by the SMC will be investigated in this part of the study.
- The tablet formulation of M3814 will be used in this study.
- Additional dosing regimens of M3814 and avelumab (Part A and Part FE) or M3814, avelumab, and RT (Part B) may be introduced by protocol amendment to be explored.
- An increase in the sample size for Part A, Part B, and/or Part FE of the study to accommodate additional dose levels may be added by protocol amendment.
- In addition, expansion cohorts in defined advanced solid tumor indications may be added by amendment to explore preliminary efficacy of the combination regimens studied in Part A and/or Part B.

Number of Participants:

In this study, for each part (A and B) the sample size will depend on the number of dose-limiting toxicities (DLTs) observed at the different dose levels and the number of tested or expanded dose levels for M3814 as dose escalation will be guided by a Bayesian logistic regression model with overdose control.

A two-parameter logistic model will be used to describe the dose-toxicity relation for M3814. CCI clinical data of M3814 are used to set up the model. It is anticipated that 6 to 30 participants in Part A (3 to 6 participants at each dose level) and 6 to 24 participants in Part B (3 to 6 participants at each dose level) may be needed. In addition, 6 to 12 participants will be enrolled in Part FE to assess the FE on PK of M3814. Thus, the total number of participants may be 18 to 66.

Study Intervention Groups and Duration:

Part A: M3814 will be administered twice daily (BID) continuously, in combination with avelumab 800 mg once every 2 weeks (Q2W) starting on Day 1 until progressive disease (PD) or unacceptable toxicity. The starting dose of M3814 in Part A will be 100 mg BID. Subsequent doses and schedules will be determined by the SMC.

Part B: M3814 will be administered once daily (QD). Radiotherapy will be given at the dose of 3 Gy per day. M3814 and RT will both be given starting Day 1 for 5 days/week for 2 weeks. Avelumab 800 mg will be administered Q2W starting on Day 1 until PD or unacceptable toxicity. The starting dose of M3814 in the first cohort of Part B will be 100 mg total daily dose. However, this starting dose might be adjusted by the SMC based on safety, PK, and pharmacodynamic (Pd) data generated during the first dose level in Part A and/or emerging data from the ongoing clinical studies involving M3814.

Part FE: M3814 will be administered BID continuously, in combination with avelumab 800 mg Q2W starting on Day 1 until PD or unacceptable toxicity. The starting dose of M3814 will be 100 mg BID. Subsequent doses and schedules will be determined based on the PK and safety data generated in previous cohorts of both of Part A and Part FE.

Involvement of Special Committee(s): Yes (SMC)

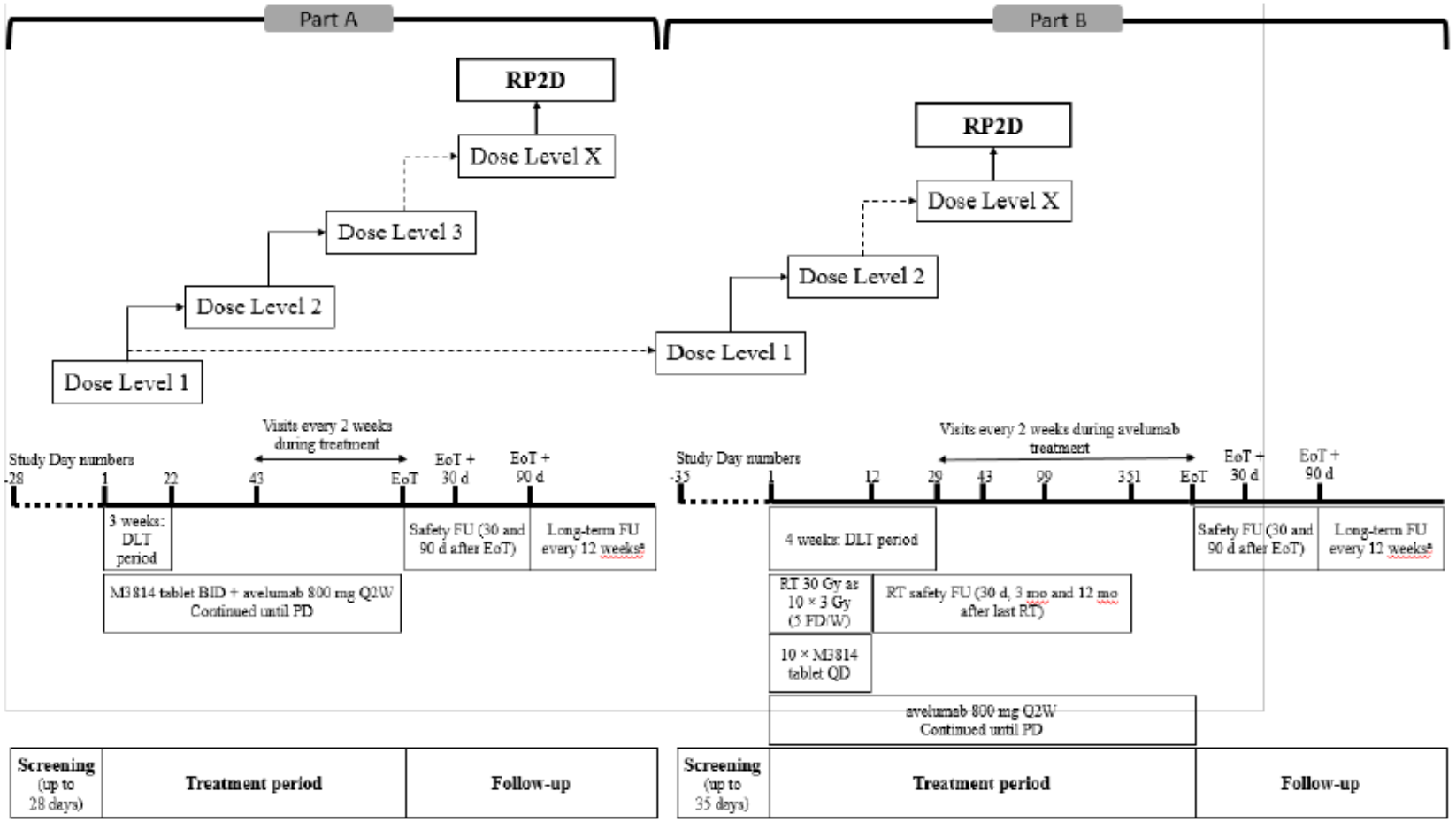
The SMC consists of core (voting) members from the Sponsor (Global Patient Safety Product Leader [Chair], Medical Responsible, Clinical Pharmacologist and Biostatistician), the Coordinating Investigator, and (if applicable) the Medical Monitor of the Contract Research Organization (CRO). Ad hoc members may be invited as needed (if deemed necessary).

The SMC will regularly review the safety data of participants enrolled in any part of this study. It will decide on relevant DLT based on criteria defined in the protocol and will provide recommendation by consensus on dose escalation, dose de-escalation, or suspension of enrollment and/or declaration of the MTD and/or the RP2D.

CCI

1.2 Schema

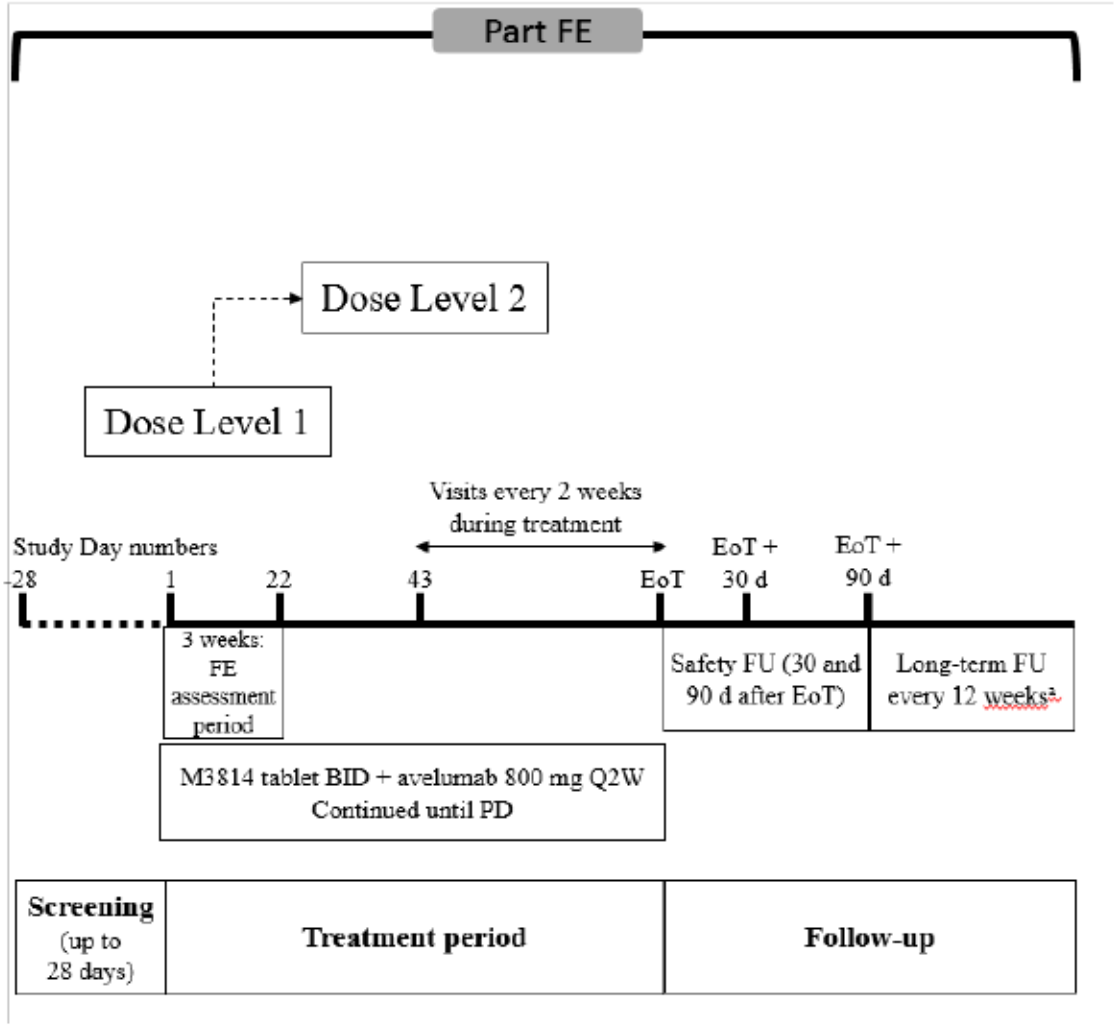
Figure 1 Study Design Schema - Part A and B



BID=twice daily, d=day, DLT=dose-limiting toxicity, EoT=End of Treatment, FD/W=fraction days/week, FU=follow-up, mo=months, PD=Progressive Disease, Q2W=every 2 weeks, QD=once daily, RP2D=recommended Phase II dose, RT=radiotherapy.

[a] All participants will be followed up for survival and use of subsequent anticancer treatment by phone every 3 mo until 12 mo after last participant has received the last dose of study interventions or dies, whichever comes first.

Figure 2 **Study Design Schema - Part FE**



BID=twice daily, d=day, DLT=dose-limiting toxicity, EoT=End of Treatment, FU=follow-up, mo=months, PD=Progressive Disease, Q2W=every 2 weeks.
[a] All participants will be followed up for survival and use of subsequent anticancer treatment by phone every 3 mo until 12 mo after last participant has received the last dose of study interventions or dies, whichever comes first.

1.3 Schedule of Activities

Table 1 Schedule of Activities - Part A (M3814 + Avelumab)

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Signed Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Demography	X											
Medical History	X											
β-HCG Pregnancy Test (if applicable)	X	X			X		Q4W		X			Serum β-HCG at Screening (can be up to 28 days prior to the first administration of study interventions); urine β-HCG thereafter for WOCBP. Results of most recent pregnancy test should be available prior to administration of study intervention.
FSH (if applicable)	X											See Section 8.2.5, Appendix 3 and Appendix 6.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Infection Screen (Hepatitis B and C), Optional HIV Test	X											Hepatitis B and C test at Screening (can be up to 28 days prior to the first study interventions) unless done ≤ 3 mo prior to Screening. HIV test per local practice and local regulatory guidance.
Vital Signs	X	X	X	X	X	X	X	X	X			All timepoints: weight, temperature, diastolic and systolic BP, pulse, pulse oximetry, and respiratory rate. Screening only: height. To be performed prior to the administration of study intervention on Day 1. Only required at EoT if participant has not started a new antitumor treatment. Screening period: can be up to 28 days prior to the first study interventions.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Physical Exam (PE)	X	X		X			Perform at Visit 6 (Week 8) and then Q8W	X	X			Complete PE at Screening (can be up to 28 days prior to the first study interventions), Day 1 prior to the first administration of study interventions, and Day 22. A PE only required at EoT if participant has not started a new antitumor treatment. Symptom-oriented PE at each visit if deemed necessary by the Investigator.
ECOG Performance Status	X		X	X	X	X	X	X	X			
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	Continuously, at EoT, and Safety FU, ongoing treatment-emergent AEs should be evaluated. At Long-term FU, only needed if participant has not started a new antitumor treatment.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Hematology, Serum Chemistry	X	X		X	X		Q4W	X	X			Baseline complete hematology and core serum chemistry analyses could be performed within the Screening period (can be up to 28 days prior to the first administration of study interventions). Prior to the administration of study interventions, the most recent complete hematology and core serum chemistry results must be available and reviewed. See Appendix 6.
Dipstick Urinalysis	X	X		X			Perform at Visit 6 (Week 8) and then Q8W	X				Full urinalysis (dipstick + microscopic analysis) should be performed only at Screening and EoT. If dipstick urinalysis at other assessments is abnormal, full analysis should be performed. See Appendix 6.
Free T4, TSH	X	X				X	Q6W		X			

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
12-Lead ECG (including QTcF)	X	X	X	X				X				PK-matched digital 12-lead resting ECG will be performed in triplicate at predose,1, 2 and 6 h post-M3814 administration before blood collection for PK, CCI sampling, followed by vital signs after the morning dose only. The assessment should be performed after the participant has been in supine position breathing quietly for ≥ 5 min at predose and all postdose sampling times.
Tumor Assessment (RECIST v 1.1)	X						Day 56, Day 112, Day 168, then Q12W	X	X		X	Tumor imaging by CT or MRI at Baseline to document tumor lesion burden. Can be up to 28 days prior to first study intervention. Then at D56, D112, D168 and then Q12W, until confirmed PD, the start of subsequent systemic anticancer therapy, or the end of the study. At EoT/Long-term FU, tumor response assessment is only required if participant has not progressed or has not started a new treatment.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Tumor Material	X	See Notes										CCI [redacted]
Survival	X	X	X	X	X	X	X	X	X	X	X	All participants will be followed up for survival and use of subsequent anticancer treatment (by phone after EoT) every 12 wks until 1 year after last participant has received the last dose of study interventions or dies, whichever comes first.

☎: phone call visit.

AE=adverse event, β-HCG=beta human chorionic gonadotropin, BID=twice daily, BP=blood pressure, CT=computed tomography, ctDNA=circulating tumor DNA, d=days, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EoT=End of Treatment Visit, FSH=follicle-stimulating hormone, FU=follow-up, HIV=human immunodeficiency virus, mo=months, MRI=magnetic resonance imaging, PE=physical examination; PK=pharmacokinetic, PD=progressive disease, CCI [redacted], QTcF= Fridericia's Correction Formula, QxW=every x weeks, RECIST=Response Evaluation Criteria in Solid Tumors, free T4=free thyroxine, TSH=thyroid-stimulating hormone, wk=week, WOCBP=women of childbearing potential.

Table 2 **Schedule of Activities – Dose-Limiting Toxicity Evaluation Period – Part B (M3814 + Radiotherapy + Avelumab)**

Study Period	Screening	DLT Evaluation Period Week 1 to 4 (M3814 + RT + avelumab)						Notes
Study Visit	1	2	3-6	7-10	11	12	13	
Study Day *(± Visit window)*	-35 to -1	1	2-5 *(± 1)*	8-11 *(± 1)*	12	15 *(± 1)*	29 *(± 1)*	
M3814		X	X	X	X			M3814 QD 5 d/wk (only on days of radiation). See Section 6.6.5.2.
RT 3 Gy × 10 (5 FD/W)		X	X	X	X			RT 3 Gy/fraction, 5 FD/wk. RT to be given 1.5 h (± 30 min) after M3814.
Premedication Avelumab		X				X	X	Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X				X	X	800 mg iv Q2W until PD; on Day 1 avelumab will be given prior to M3814. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Signed Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Demography	X	X						
Medical History	X							
β-HCG Pregnancy Test (if applicable)	X	X					X	Serum β-HCG at Screening; urine β-HCG thereafter for WOCBP. Results of most recent pregnancy test should be available prior to administration of study intervention.
FSH (if applicable)	X							See Section 8.2.5, Appendix 3 and Appendix 6

Study Period	Screening	DLT Evaluation Period Week 1 to 4 (M3814 + RT + avelumab)						Notes
Study Visit	1	2	3-6	7-10	11	12	13	
Study Day *(± Visit window)*	-35 to -1	1	2-5 *(± 1)*	8-11 *(± 1)*	12	15 *(± 1)*	29 *(± 1)*	
M3814		X	X	X	X			M3814 QD 5 d/wk (only on days of radiation). See Section 6.6.5.2.
RT 3 Gy × 10 (5 FD/W)		X	X	X	X			RT 3 Gy/fraction, 5 FD/wk. RT to be given 1.5 h (± 30 min) after M3814.
Premedication Avelumab		X				X	X	Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X				X	X	800 mg iv Q2W until PD; on Day 1 avelumab will be given prior to M3814. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Infection Screen (Hepatitis B and C); Optional HIV Test	X							Hepatitis B and C test at Screening unless done ≤ 3 mo prior to Screening. HIV test per local practice and local regulatory guidance.
Vital Signs	X	X	X	X	X	X	X	Height at Screening only, weight at Screening and Day 29. Temperature, diastolic and systolic blood pressure, pulse, pulse oximetry, and respiratory rate at each visit. Screening period: can be up to 35 days prior to the first administration of study interventions.
Physical Exam (PE)	X	X	X (D5)		X		X Q6W Starting Visit 13	A complete PE at Screening (can be up to 35 days prior to the first administration of study interventions), D1 prior the start of study intervention, D5 (RT fraction 5), D12 (RT fraction 10) and D29. PE will report findings in the irradiated area. Symptom-oriented PE whenever deemed necessary by the Investigator.
Esophageal endoscopy (if relevant)	X							Only required in case of active esophagitis or clinical signs of esophagitis and if it is estimated that the radiation fields will involve any portion of the esophagus.
Clinical Examination of Tissues in RT Area			X	X		X	X	Required on each day of RT schedule.
ECOG PS	X	X	X	X		X	X	
Adverse Event Assessment	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	

Study Period	Screening	DLT Evaluation Period Week 1 to 4 (M3814 + RT + avelumab)						Notes
Study Visit	**1**	**2**	**3-6**	**7-10**	**11**	**12**	**13**	
Study Day *(± Visit window)*	**-35 to -1**	**1**	**2-5** *(± 1)*	**8-11** *(± 1)*	**12**	**15** *(± 1)*	**29** *(± 1)*	
M3814		X	X	X	X			M3814 QD 5 d/wk (only on days of radiation). See Section 6.6.5.2.
RT 3 Gy × 10 (5 FD/W)		X	X	X	X			RT 3 Gy/fraction, 5 FD/wk. RT to be given 1.5 h (± 30 min) after M3814.
Premedication Avelumab		X				X	X	Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X				X	X	800 mg iv Q2W until PD; on Day 1 avelumab will be given prior to M3814. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Hematology and Serum Chemistry	X	X	X (D5)		X		X Q4W Starting Visit 13	Baseline complete hematology and core serum chemistry analyses could be performed within Screening period (can be up to 35 days prior to the first administration of study interventions). Prior to the administration of study interventions, the most recent complete hematology and core serum chemistry results must be available and reviewed. See Appendix 6.
Dipstick Urinalysis	X	X					X Q6W Starting Visit 13	Full urinalysis (dipstick + microscopic analysis) should be performed only at Screening (can be up to 35 days prior to the first administration of study interventions). If dipstick urinalysis at other assessments is abnormal, full analysis should be performed. See Appendix 6.
Free T4, TSH	X	X Q6W Starting Visit 2						
12-Lead resting ECG	X	X					X	The assessment should be performed after the participant has been in supine position breathing quietly for ≥ 5 min.
Tumor Assessment (RECIST v 1.1)	X							Tumor imaging by CT or MRI at Baseline to document tumor lesion burden. Can be up to 35 days prior to treatment start.

Study Period	Screening	DLT Evaluation Period Week 1 to 4 (M3814 + RT + avelumab)						Notes
Study Visit	1	2	3-6	7-10	11	12	13	
Study Day *(± Visit window)*	-35 to -1	1	2-5 *(± 1)*	8-11 *(± 1)*	12	15 *(± 1)*	29 *(± 1)*	
M3814		X	X	X	X			M3814 QD 5 d/wk (only on days of radiation). See Section 6.6.5.2.
RT 3 Gy × 10 (5 FD/W)		X	X	X	X			RT 3 Gy/fraction, 5 FD/wk. RT to be given 1.5 h (± 30 min) after M3814.
Premedication Avelumab		X				X	X	Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X				X	X	800 mg iv Q2W until PD; on Day 1 avelumab will be given prior to M3814. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Tumor Material	X							CCI [redacted]

β-HCG=beta human chorionic gonadotropin, CR=complete response, CT=computed tomography, d=days, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EoT=End of Treatment Visit, FSH=follicle-stimulating hormone, FD/W=fraction days/week, Gy=Grays, HIV=human immunodeficiency virus, iv=intravenous, mo=months, MRI=magnetic resonance imaging, PE=physical examination, PK=pharmacokinetic, PD=progressive disease, QD=once daily, QxW=every x weeks, RECIST=Response Evaluation Criteria in Solid Tumors, RT=radiotherapy, free T4=free thyroxine, TSH=thyroid-stimulating hormone, wk=week, WOCBP=women of childbearing potential.

Table 3 Schedule of Activities – Safety Follow-up Period - Part B (M3814 + Radiotherapy + Avelumab)

Study Period	RT Safety FU Visits and Avelumab Treatment				End of Treatment (EoT)/FU				Notes
	RT Short-term Safety FU	RT Mid-term Safety FU	RT Long-term Safety FU	Avelumab Treatment	EoT	30-Day Safety FU	90-Day Safety FU ☎	Long-term FU	If participant discontinues avelumab prior to RT Long-term Safety FU, RT Long-term Safety FU can be performed by telephone.
Study Day *(± Visit window)*	43 *(± 7)*	99 *(± 7)*	351 *(± 2)*	n+14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 days *(± 5)*	90 days *(± 5)*	*(Q12W)*	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo an EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
Premedication avelumab	X								Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab	X	X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
β-HCG Pregnancy Test (if applicable)				Q4W		X			Urine β-HCG for WOCBP. Results of most recent pregnancy test should be available prior to administration of study intervention.
Vital Signs	X	X	X	X	X	X			Weight, temperature, diastolic and systolic blood pressure, pulse, pulse oximetry, and respiratory rate Q2W, at the EoT Visit, and at 30-day Safety FU. Only required at EoT if participant has not started a new antitumor treatment.
Physical Exam (PE)	X	X	X	Q6W	X	X			A complete PE will report findings in the irradiated area during all FU periods.
Evaluation of all Tissues in RT Area	X	X	X						

Study Period	RT Safety FU Visits and Avelumab Treatment				End of Treatment (EoT)/FU				Notes
	RT Short-term Safety FU	RT Mid-term Safety FU	RT Long-term Safety FU	Avelumab Treatment	EoT	30-Day Safety FU	90-Day Safety FU ☎	Long-term FU	If participant discontinues avelumab prior to RT Long-term Safety FU, RT Long-term Safety FU can be performed by telephone.
Study Day *(± Visit window)*	43 *(± 7)*	99 *(± 7)*	351 *(± 2)*	n+14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 days *(± 5)*	90 days *(± 5)*	*(Q12W)*	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo an EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
Premedication avelumab	X								Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab	X	X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
ECOG PS	X	X	X	X	X	X			
Adverse Event Assessment	X	X	X	X	X	X	X	X	Continuously, at all RT safety FU, EoT, and Safety FU, ongoing treatment-emergent AEs should be evaluated. At Long-term FU, only needed if participant has not started a new antitumor treatment.
Concomitant Medication	X	X	X	X	X	X	X	X	
Hematology and Serum Chemistry	X	X	X	Q4W	X	X			Most recent complete hematology and core serum chemistry results must be available and reviewed prior to the administration of study interventions. See Appendix 6.
Dipstick Urinalysis				Q6W	X				Full urinalysis (dipstick + microscopic analysis) should be performed only at EoT. Otherwise, dipstick urinalysis Q6W. If dipstick urinalysis is abnormal, a full analysis should be performed.

Study Period	RT Safety FU Visits and Avelumab Treatment				End of Treatment (EoT)/FU				Notes
	RT Short-term Safety FU	RT Mid-term Safety FU	RT Long-term Safety FU	Avelumab Treatment	EoT	30-Day Safety FU	90-Day Safety FU ☎	Long-term FU	If participant discontinues avelumab prior to RT Long-term Safety FU, RT Long-term Safety FU can be performed by telephone.
Study Day *(± Visit window)*	**43** *(± 7)*	**99** *(± 7)*	**351** *(± 2)*	**n+14 d** *(± 2)*	*(Within 7 days of decision to discontinue)*	**30 days** *(± 5)*	**90 days** *(± 5)*	*(Q12W)*	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo an EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
Premedication avelumab	**X**								Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab	**X**	**X**	**X**	**X**					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Free T4, TSH	X			Q6W		X			Q6W until PD.
12-Lead ECG					X				
Tumor assessment (RECIST v 1.1)				Day 56, Day 112, Day 168, then Q12W	X	X		X	At D56, D112, D168 and then Q12W, until confirmed PD, the start of subsequent systemic anticancer therapy, or the end of the study. At EoT/Long-term FU, tumor response assessment is only required if participant has not progressed or has not started a new treatment.

Study Period	RT Safety FU Visits and Avelumab Treatment				End of Treatment (EoT)/FU				Notes
	RT Short-term Safety FU	RT Mid-term Safety FU	RT Long-term Safety FU	Avelumab Treatment	EoT	30-Day Safety FU	90-Day Safety FU ☎	Long-term FU	If participant discontinues avelumab prior to RT Long-term Safety FU, RT Long-term Safety FU can be performed by telephone.
Study Day *(± Visit window)*	43 *(± 7)*	99 *(± 7)*	351 *(± 2)*	n+14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 days *(± 5)*	90 days *(± 5)*	*(Q12W)*	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo an EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3.
Premedication avelumab	X								Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab	X	X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Tumor Material	See notes								CCI [redacted]
Survival	X	X	X	X	X	X	X	X	All participants will be followed up for survival and use of subsequent anticancer therapy by phone every 12 wks until 1 year after last participant has received the last dose of study interventions or the last participant dies, whichever comes first.

☎: phone call visit.

AE=adverse event, β-HCG=beta human chorionic gonadotropin, d=days, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EoT=End of Treatment Visit, FU=follow-up, iv=intravenous, mo=months, PD=progressive disease, QxW=every x weeks, RECIST=Response Evaluation Criteria in Solid Tumors, RT=radiotherapy, free T4=free thyroxine, TSH=thyroid-stimulating hormone, wk=week, WOCBP=women of childbearing potential.

Table 4 Schedule of Activities – Part FE (M3814 + Avelumab)

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Breakfast at site		X		X								See Section 6.6.5.3 for details on breakfast composition.
Signed Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Demography	X											
Medical History	X											
β-HCG Pregnancy Test (if applicable)	X	X			X		Q4W		X			Serum β-HCG at Screening (can be up to 28 days prior to the first administration of study interventions); urine β-HCG thereafter for WOCBP. Results of most recent pregnancy test should be available prior to administration of study intervention.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
FSH (if applicable)	X											See Section 8.2.5, Appendix 3 and Appendix 6.
Infection Screen (Hepatitis B and C), Optional HIV Test	X											Hepatitis B and C test at Screening (can be up to 28 days prior to the first study interventions) unless done ≤ 3 mo prior to Screening. HIV test per local practice and local regulatory guidance.
Vital Signs	X	X	X	X	X	X	X	X	X			All timepoints: weight, temperature, diastolic and systolic BP, pulse, pulse oximetry, and respiratory rate. Screening only: height. To be performed prior to the administration of study intervention on Day 1. Only required at EoT if participant has not started a new antitumor treatment. Screening period: can be up to 28 days prior to the first study interventions.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Physical Exam (PE)	X	X		X			Perform at Visit 6 (Week 8) and then Q8W	X	X			Complete PE at Screening (can be up to 28 days prior to the first study interventions), Day 1 prior to the first administration of study interventions, and Day 22. A PE only required at EoT if participant has not started a new antitumor treatment. Symptom-oriented PE at each visit if deemed necessary by the Investigator.
ECOG Performance Status	X		X	X	X	X	X	X	X			
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	Continuously, at EoT, and Safety FU, ongoing treatment-emergent AEs should be evaluated. At Long-term FU, only needed if participant has not started a new antitumor treatment.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Hematology, Serum Chemistry	X	X		X	X		Q4W	X	X			Baseline complete hematology and core serum chemistry analyses could be performed within the Screening period (can be up to 28 days prior to the first administration of study interventions). Prior to the administration of study interventions, the most recent complete hematology and core serum chemistry results must be available and reviewed. See Appendix 6.
Dipstick Urinalysis	X	X		X			Perform at Visit 6 (Week 8) and then Q8W	X				Full urinalysis (dipstick + microscopic analysis) should be performed only at Screening and EoT. If dipstick urinalysis at other assessments is abnormal, full analysis should be performed. See Appendix 6.
Free T4, TSH	X	X				X	Q6W		X			

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
12-Lead ECG (including QTcF)	X	X	X	X				X				PK-matched digital 12-lead resting ECG will be performed in triplicate at predose,1, 2 and 6 h post-M3814 administration before blood collection for PK, CCI sampling, followed by vital signs after the morning dose only. The assessment should be performed after the participant has been in supine position breathing quietly for ≥ 5 min at predose and all postdose sampling times.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT. All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Tumor Assessment (RECIST v 1.1)	X						Day 56, Day 112, Day 168, then Q12W	X	X		X	Tumor imaging by CT or MRI at Baseline to document tumor lesion burden. Can be up to 28 days prior to first study intervention. Then at D56, D112, D168 and then Q12W, until confirmed PD, the start of subsequent systemic anticancer therapy, or the end of the study. At EoT/Long-term FU, tumor response assessment is only required if participant has not progressed or has not started a new treatment.
Tumor Material	X	See Notes										Archival tumor materials sampled before start of treatment not older than 6 mo can be collected if available; if no archival tumor material available, no fresh biopsy is required. However, approximately 10 mL whole blood sample for plasma ctDNA must be taken prior to the first dose of study treatment.

Study Period	Screening	Treatment Period: M3814+avelumab						End of Treatment (EoT)/FU				Notes
		DLT Period						EoT	Safety FU		Long-term FU	
Visit	-1	1	2	3	4	5	n				Q12W	During on-treatment period, after Day 29, visits will be every 2 wks on days of avelumab infusions until EoT.
Study Day *(± Visit window)*	-28 to -1	1	15 *(± 1)*	22 *(± 1)*	29 *(± 1)*	43 *(± 1)*	n + 14 d *(± 2)*	*(Within 7 days of decision to discontinue)*	30 d *(± 5)*	☎ 90 d *(± 5)*	*(± 7)*	All participants discontinuing study interventions for any reason must undergo EoT Visit within 7 days after decision to discontinue study interventions, but (if possible) before any new antineoplastic therapy is started. The safety follow-up period will be 30 days (± 5 days) and 90 days (± 5 days) after the last dose of avelumab, see Section 4.1.1.3
M3814		Continuous BID dosing (7 days/wk)										See Section 6.6.5.1 for details.
Premedication (avelumab)		X	X		X	X						Required only for first 4 avelumab infusions, as needed thereafter. See Section 6.5.5.
Avelumab		X	X		X	X	X					800 mg iv Q2W until PD. For post-PD treatment, see Section 6.6.6. For post-CR treatment, see Section 4.1.1.2.
Survival	X	X	X	X	X	X	X	X	X	X	X	All participants will be followed up for survival and use of subsequent anticancer treatment (by phone after EoT) every 12 wks until 1 year after last participant has received the last dose of study interventions or dies, whichever comes first.

☎: phone call visit. AE=adverse event, β-HCG=beta human chorionic gonadotropin, BID=twice daily, BP=blood pressure, CT=computed tomography, ctDNA=circulating tumor DNA, d=days, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EoT=End of Treatment Visit, FSH=follicle-stimulating hormone, FU=follow-up, HIV=human immunodeficiency virus, mo=months, MRI=magnetic resonance imaging, PE=physical examination; PK=pharmacokinetic, PD=progressive disease, CCI QTcF= Fridericia's Correction Formula, QxW=every x weeks, RECIST=Response Evaluation Criteria in Solid Tumors, free T4=free thyroxine, TSH=thyroid-stimulating hormone, wk=week, WOCBP=women of childbearing potential.

Table 5 Pharmacokinetic and Biomarker Blood Sampling Schedule – Part A (M3814 + Avelumab)

		M3814 and Avelumab				M3814		Avelumab	
Week (Day)	Time (h)	CCI	Soluble Factors	Immune phenotyping	CCI	PK	CCI	PK	CCI
	Blood Volume (approximate)	CCI	8.5 mL	9 mL	CCI	2 mL	CCI	3.5 mL	CCI
Week 1 (Day 1)	Predose (approximate)	CCI	X	X	X CCI)	X	X CCI)	X	X
	1					X			
	EoI							X	
	2					X	X		
	3					X			
	4					X	X		
	6					X	X		
Week 3 (Day 15)	predose		X	X	X	X		X	X
	1					X			
	2					X			
	3					X			
	4					X			
	6					X			
Week 4 (Day 22)	predose					X			
	2					X			
	6					X			
Week 5 (Day 29)	predose		X	X		X		X	X
	EoI							X	
Week 9 (Day 57)	predose		X	X	X			X	X
Week 13 (Day 85)	predose		X		X			X	X
Weeks 25, 37, 49	predose				X			X	X

		M3814 and Avelumab				M3814		Avelumab	
Week (Day)	**Time (h)**	CCI	**Soluble Factors**	**Immune phenotyping**	CCI	**PK**	CCI	**PK**	CCI
EoT for M3814 (only applies if M3814 treatment is stopped. If avelumab and M3814 treatment are stopped at the same time prior to Week 49, only 1 sample for immune phenotyping and plasma ctDNA should be collected).				X	X	X			
EoT for avelumab (if prior to Week 49)			X	X	X			X	
30-Day Safety FU (if prior to Week 49)								X	X

CCI , EoI=end of infusion; EoT=End of treatment, FU=follow-up, CCI , PK=pharmacokinetic, CCI .

Table 6 Pharmacokinetic and Biomarker Blood Sampling Schedule – Part B (M3814 + Radiotherapy + Avelumab)

		M3814 and Avelumab				M3814		Avelumab		Notes
Week (Day)	Time (h)	CCI	Soluble Factors	Immune phenotyping	CCI	PK	CCI	PK	CCI	PK and/or Pd sampling collection times may be modified based on emerging data from prior dose levels by the SMC. M3814 PK sampling should be performed within ± 10 min for the first 2 h postdose sample collections, and within ± 20 min for subsequent sampling at each sampling day. The M3814 predose sample should be taken within 1 h before dosing at each sampling day. Avelumab PK and ADA sampling should be performed within 120 minutes prior to dose and within 15 minutes before EoI.
	Blood volume (approximate)	CCI	8.5 mL	9 mL	CCI	2 mL	CCI	3.5 mL	CCI	
Week 1 (Day 1; FD1)	Predose (approximate)	CCI	X	X	CCI	CCI	CCI	CCI	CCI	
	1					X				Post M3814 administration.
	EoI							X		
	2					X	X			Post M3814 administration.
	4					X	X			Post M3814 administration.
	6					X	X			Post M3814 administration.
Week 1 Day 2 (FD2)	Predose					X	X			For M3814 parameter calculations, the predose value will serve as an estimate for the 24 h postdose concentrations of the previous fraction day.
	2					X				Post M3814 administration.

		M3814 and Avelumab				M3814		Avelumab		Notes
Week (Day)	**Time (h)**	CCI	**Soluble Factors**	**Immune phenotyping**	CCI	**PK**	CCI	**PK**	CCI	PK and/or Pd sampling collection times may be modified based on emerging data from prior dose levels by the SMC. M3814 PK sampling should be performed within ± 10 min for the first 2 h postdose sample collections, and within ± 20 min for subsequent sampling at each sampling day. The M3814 predose sample should be taken within 1 h before dosing at each sampling day. Avelumab PK and ADA sampling should be performed within 120 minutes prior to dose and within 15 minutes before EoI.
Week 2 (Day 8; FD6)	Predose		X			X				For M3814 PK parameter calculations, the predose value will serve as an estimate for the 24 h postdose concentrations of the previous fraction day.
	2					X				post M3814 administration.
Week 2 (Day 12; FD10)	Predose		X	X	X	X	X			For M3814 PK parameter calculations, the predose value will serve as an estimate for the 24 h postdose concentrations of the previous fraction day. If Day 12 (FD10) is a Friday, PK and Pd sampling must be done on Day 11 (FD9). Following Day 12 (FD 10), avelumab predose PK should be collected prior to next infusion, every 6 wks until wk 25 and then at 12-wk intervals while on avelumab treatment.
	2					X	X			Post M3814 administration.
	4					X	X			Post M3814 administration.
	6					X				Post M3814 administration.
Week 3 (Day 15)	predose		X	X	X			X	X	
Week 5 (Day 29)	predose		X	X				X	X	

		M3814 and Avelumab				M3814		Avelumab		Notes
Week (Day)	**Time (h)**	CCI	**Soluble Factors**	**Immune phenotyping**	CCI	**PK**	cci	**PK**	CCI	PK and/or Pd sampling collection times may be modified based on emerging data from prior dose levels by the SMC. M3814 PK sampling should be performed within ± 10 min for the first 2 h postdose sample collections, and within ± 20 min for subsequent sampling at each sampling day. The M3814 predose sample should be taken within 1 h before dosing at each sampling day. Avelumab PK and ADA sampling should be performed within 120 minutes prior to dose and within 15 minutes before EoI.
	EoI							X		
Week 9 (Day 57)	predose		X	X	X			X	X	
Week 13 (Day 85)	predose				X			X	X	
Week 25, 37, 49	predose				X			X	X	
EoT for M3814						X				
EoT for avelumab			X	X	X			X		If prior to W49.
30-day Safety FU								X	X	If prior to W49.

CCI
CCI
, EoI=end of infusion, EoT=End of Treatment, F=fractions, FD=fraction day, FU=follow-up, PK=pharmacokinetics, SMC=Safety Monitoring Committee.

Table 7 Pharmacokinetic and Biomarker Blood Sampling Schedule – Part FE (M3814 + Avelumab)

		M3814 and Avelumab				M3814		Avelumab	
Week (Day)	**Time (h)**	CCI	**Soluble Factors**	**Immune phenotyping**	CCI	**PK**	CCI	**PK**	CCI
	Blood Volume (approximate)	CCI	8.5 mL	9 mL	CCI	2 mL	CCI	3.5 mL	CCI
Week 1 (Day 1)	Predose (approximate)	CCI	X	X	CCI				
	1					X			
	EoI							X	
	2					X	X		
	4					X	X		
	6					X	X		
Week 3 (Day 15)	predose		X	X	X	X		X	X
	1					X			
	2					X			
	3					X			
	4					X			
	6					X			
Week 4 (Day 22)	predose					X			
	2					X			
	4					X			
	6					X			
Week 5 (Day 29)	predose							X	X
Week 13 (Day 85)	predose							X	X
Weeks 25, 37, 49	predose							X	X
EoT for M3814						X			
30-Day Safety FU (if prior to Week 49)								X	X

CCI
CCI
, CCI
EoI=end of infusion; EoT=End of treatment, FU=follow-up, CCI
PK=pharmacokinetic,

2 Introduction

Complete information on the chemistry, pharmacology, efficacy, and safety of avelumab and M3814 is in the respective Investigator's Brochures (IB) and in the avelumab (Bavencio®) US Product Information.

2.1 Study Rationale

This study is part of a clinical development program which aims to evaluate the clinical utility of M3814, a DNA damage target agent, with avelumab, an anti-PD-L1 therapy, with and without RT in a broad range of cancers.

In addition, the food effect (FE) on PK of M3814 will be investigated to evaluate the effects of prandial state and fat content of meals on the pharmacokinetic (PK) parameters of M3814.

The first part of this study (Part A) will assess M3814 in combination with avelumab in participants with advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition.

The second part of this study (Part B) will assess M3814 in combination with avelumab and RT in participants with advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition and are amenable to receive RT.

The third part of this study (Part FE) will assess the FE on PK of M3814 when administered in combination with avelumab under fasted and fed conditions in participants with advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition. Only doses of M3814 already declared safe and tolerable in Part A by the Safety Monitoring Committee (SMC) will be introduced in this part of the study.

2.1.1 Combining a DNA Damage Agent with M3814, a DNA Repair-Targeted Therapy

M3814 is a DNA-PK inhibitor which targets tumor cell growth and survival by inhibiting a critical double-strand break (DSB) DNA damage repair (DDR) mechanism. The antitumor effect of M3814 is dependent on the functionality of DNA repair and checkpoint signaling in cancer cells, which have a lowered ability to cope with DSBs, leading to cell death. Hence, the rationale of DNA-PK inhibition is to increase the amount of DSB DNA damage generated by DNA-damaging agents including direct DNA-damaging chemotherapy agents or Ionizing Radiation (IR). CCI [redacted] In combination with etoposide and cisplatin in the NCI-H526 xenograft model, M3814 showed a better tumor control compared to etoposide + cisplatin or M3814 alone. CCI [redacted]

CCI [redacted]

2.1.2 Combining Radiation, a DNA Damage Agent with M3814, a DNA Repair-Targeted Therapy and Immunotherapy

In addition to the potential of using DDR inhibitors in combination regimens with other DDR inhibitors or with DDR damaging agents such as standard-of-care chemotherapy or RT treatments, it is increasingly recognized that some consideration might be given to identifying optimized approaches to using DDR inhibitors alongside immunotherapy agents including immune checkpoint inhibitors. While many mechanisms by which DDR damaging agents can elicit antitumor immunity have been identified, the mechanisms by which DNA repair-directed agents (such as ATM, ATR, or DNA-PK catalytic subunit [DNA-PKcs] inhibitors) modulate the tumor immune environment and affect sensitivity to immune checkpoint inhibitors still need to be fully elucidated. However, it is reasonable to hypothesize that genomic instability induced by disruption of normal DNA repair pathway function could result in increased tumor mutational burden, neoantigens, and/or STING pathway activation, all of which could contribute to heightened immune checkpoint inhibitors sensitivity (McGranahan 2016; Mouw 2017).

Teo 2018 reported in subjects with metastatic urothelial cancer and treated with anti-PD-1/anti-PD-L1 antibodies atezolizumab and nivolumab, that the presence of DDR alterations was strongly associated with a higher objective response rate than those without any DDR alterations (67.9% versus 18.8%; $p < 0.001$). The median overall survival (OS) was not reached for subjects with deleterious DDR alterations, with 71.5% alive at 12 months, whereas the median OS for those with DDR alterations of unknown significance or no detectable DDR alterations were 23.0 and 9.3 months, respectively.

Several clinical studies are now under way to test the safety and efficacy of combinations of DNA repair-targeted agents with immune checkpoint inhibitors in both DNA repair-deficient and DNA repair-proficient settings (Yap 2015).

CCI [redacted]

The interaction between the immune system and IR has been appreciated for many decades. Therapeutic radiation creates numerous types of DNA damage, including DSBs and the immune system can impact radiation-associated tumor control both locally (within the radiation field) and distantly (at unirradiated tumor sites). CCI [redacted] Radiation increases PD-L1 expression on tumor cells, and this inhibitory effect can be overcome with PD-L1/PD-1 blockade resulting in a better tumor control

and improvement of survival compared to each treatment regimen alone (Deng 2014; Dovedi 2014).

Another study showed that radiation, anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4), and anti-PD-1/PD-L1 agents function in nonredundant ways to activate the immune system. Data from melanoma patients CCI suggest that although radiation diversifies the T cell repertoire and anti-CTLA4 therapy inhibits regulatory T cells, anti-PD-L1 therapy is necessary to overcome resistance driven by increased PD-L1 expression on tumor cells (Twyman-Saint Victor 2015).

Furthermore, clinical case reports and retrospective analyses suggest that a treatment regimen combining immune checkpoint blockade treatment and RT in a variety of solid tumors may result in a better disease control and longer survival than that seen with immune checkpoint blockade treatment alone, with an acceptable safety profile (Hiniker 2016, Ahmed 2017, Olson 2015, Shaverdian 2017). Based on these findings, clinical studies combining radiation and immune checkpoint therapies are ongoing in a variety of tumors in different clinical settings.

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Taken together, the emerging experimental and clinical evidence suggests that DNA lesions arising from different backgrounds (increased DNA damage exposure [i.e. RT as exogenous source of damage and/or decreased DNA repair capacity {DDR inhibitor agent}]) often leads to increased mutational load and neoantigen burden, both of which have been correlated with immune checkpoint blockade response in a variety of settings. Therefore, combining an immune checkpoint inhibitor such as avelumab with a DNA-damaging agent such as RT and a DNA repair-targeted agent such as a CCI may be a useful therapeutic strategy in patients suffering from cancer.

The purpose of this Phase I study is to evaluate the safety, tolerability, PK/Pd profile and preliminary clinical activity of M3814, in combination with avelumab with and without RT in participants with advanced or metastatic select solid tumors. Part A of the dose escalation will establish the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of M3814 when administered in combination with avelumab, while Part B will define the MTD and/or RP2D of M3814 when administered in combination with avelumab and RT. In addition, the Part FE will assess FE on PK of M3814 when administered in combination with avelumab under fasted and fed conditions.

2.2 Background

2.2.1 Clinical Response and Resistance to Immune Checkpoint Inhibitors

Immune checkpoint inhibitors targeting CTLA4 and the PD-1/PD-L1 axis have shown unprecedented clinical activity in several types of cancer and are rapidly transforming the practice of medical oncology (Pardoll 2012; Topalian 2015; Sharma 2017).

Programmed death 1 (PD-1) is a negative regulator of T cell activity that limits the activity of T cells at a variety of stages of the immune response when it interacts with its 2 ligands, PD-L1 and PD-L2 (Ishida 1992; Keir 2006; Freeman 2000). When engaged by a ligand, through phosphatase activity, PD-1 inhibits kinase-signaling pathways that normally lead to T cell activation. A number of antibodies that disrupt the PD-1 axis have entered clinical development. PD-L1 is also considered to exert negative signals on T cells by interacting with PD-1 (Butte 2007), and PD-L1-blocking antibodies prevent this interaction. Immune checkpoint inhibitors also enhance the function of tumor-infiltrating lymphocytes (TILs), and more specifically cytotoxic T cells, which augments antitumor immunity within the tumor microenvironment. The presence of TILs has been correlated to improved prognosis in many cancer types, including bladder (Lipponen 1993; Tsujihashi 1988; Sharma 2007), lung (Geng 2015), breast (Adams 2014), colorectal (Maby 2015), and esophageal (Jiang 2017) carcinomas. Moreover PD-1 positive expression as well as TILs have been shown to be predictive biomarkers of response to immune checkpoint blockade (Curran 2010; Herbst 2014). Several antibodies that disrupt the PD-1 or PD-L1 axis including avelumab are approved and/or are in clinical development for several tumor indications.

Despite robust and durable responses to immune checkpoint inhibitors in a subset of tumors (Wolchok 2013; Postow 2015a; Postow 2015b; Herbst 2016; Brahmer 2015), efficacy of immune checkpoints inhibitors varies widely. Even among tumor types such as melanoma and non-small

cell lung cancer for which many of the first immune checkpoint inhibitors studies were conducted, only a subset of patients responds to therapy (Brahmer 2012; Teo 2018). As evidence for immune checkpoint inhibitor use across clinical settings continues to grow, a major unmet need is the identification of reliable biomarkers that predict response to immune checkpoint inhibitors and/or treatment combinations which allow to achieve clinical benefit in a larger proportion of patients. Numerous lines of evidence now suggest that the DNA repair landscape has an important role in driving sensitivity and response to immune checkpoint blockade.

2.2.2 DNA Repair Pathways Alterations are Cancer Drivers and Affect Response to Immunotherapy

DNA damage arises either because of a failure to repair endogenous DNA damage in cells or due to cellular exposure to exogenous sources of damaging agents such as chemotherapy or RT (Jackson and Bartek 2009). Radiotherapy (RT) is widely used as standard-of-care treatment across a range of tumor types with either a curative intent in the nonmetastatic setting or to alleviate symptoms in patients with metastatic cancers. However, for most patients, DNA-damaging agents provide only modest and limited benefit over time due to highly proficient cellular processes that can detect and repair the damaged DNA. Therefore, inhibiting the repair of endogenous or exogenous DNA damage is also an attractive anticancer strategy and several different DNA repair inhibitors are in nonclinical and clinical development (Brown 2017).

Among types of DNA damage, DSBs are one of the most harmful lesions to a cell. Failure in DSB repair could lead to genomic instability and cancer. Homologous recombination (HR) and nonhomologous end joining are major DSB repair pathways in higher eukaryotes. It is known that expression of DSB repair genes is altered in various cancers. Also, the activation of DSB repair genes is one of the reasons for chemo- and radioresistance.

Furthermore, erroneous or deregulated DNA repair results in chromosomal translocations, genomic rearrangements, higher mutation rates, and/or immunogenic cell death which lead to promoting immunogenicity and may provide survival advantages to cancer cells (Lieberman 2008; Powell and Bindra 2009). Therefore, patients with tumors deficient in DNA damage or mismatch repair may respond to treatment with immune checkpoint inhibitors (Le 2015; Strickland 2016). In addition, there is increasing evidence that DDR inhibiting agents combined with immune-checkpoint inhibitors may exert a pronounced antitumor activity (Mouw 2017).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of M3814 and avelumab may be found in Section **Error! Reference source not found.** (Scientific Rationale for Study Design) and the respective IBs and US Product Information for avelumab.

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

2.3.1 Summary of M3814 Data and Potential Benefits and Risks

M3814 is a potent and selective inhibitor of the ATP binding site of DNA-PK that targets tumor cell growth and survival by inhibiting the critical DDR mechanism in solid and hematological malignancies.

M3814 potentiates the growth inhibitory activity of DNA-damaging agents such as etoposide and RT. CCI

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A number of measures have been implemented in this study to minimize the potential safety risk related to study interventions and enhance the safety of participants, including additional exclusion criteria, Screening assessments in participants with potential risk factors, additional constraint to the volume and dose of irradiation to be delivered to the esophagus, and a Long-term Follow-up of participants at 1 year after the last dose of RT to enable the detection and the management of potential late toxicities. Also, clear information about potential late toxicities related to study interventions will be provided to participants and Investigators. The Sponsor considers that the overall benefit-risk-balance of M3814 in combination with fractioned RT (3 Gy x 10; 5 fractions per week for 2 weeks in total) remains positive.

CCI [redacted]

M3814 was also evaluated in combination with cisplatin and etoposide in 2 participants with extensive stage small cell lung cancer in a Phase Ib (open-label dose escalation)/Phase II (placebo-controlled, randomized) study (MS100036-0022). Enrollment in the study was prematurely terminated due to recruitment challenges and not due to concerns of safety for the participants.

CCI [redacted]

2.3.2 Summary of Potential Benefits and Risks of Avelumab

Avelumab (MSB0010718C) is a fully human immunoglobulin G1 (IgG1) anti-PD-L1 monoclonal antibody that inhibits PD-L1/PD-1 interactions but leaves intact the PD-L2/PD-1 pathway (Boyerinas 2015; Gulley 2015; Heery 2014; Heery 2015).

To date, avelumab has been administered at the clinically active tolerable dose of 10 mg/kg Q2W to more than 1800 participants across multiple indications. It has been approved by FDA for adults and pediatric patients 12 years and older with metastatic Merkel Cell Carcinoma and for adults with locally advanced or metastatic urothelial carcinoma and is currently being evaluated as monotherapy or in combination with chemotherapy and targeted agents across a wide range of cancers.

Most of the observed AEs were either in line with those expected in participants with advanced solid tumors or with class effects of monoclonal antibody blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-related adverse events (irAEs; immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, Type I diabetes mellitus, pituitary disorders], immune-related nephritis and renal dysfunction and other irAEs [myositis, myocarditis, Guillain-Barrésyndrome, uveitis, pancreatitis, and myasthenia gravis/myasthenic syndrome]) have been identified as important risks for avelumab. Guidelines for the management of irAEs and infusion-related reactions are implemented in all ongoing clinical studies with avelumab (avelumab IB Version 10.0, 29 May 2020).

2.3.3 Summary of Potential Benefits and Risks of Radiotherapy

Radiotherapy is an integral part of the multidisciplinary treatment of cancer, both in the curative and palliative setting. It is estimated that over 60% of patients with solid tumors will have RT as part of their total course of treatment (Halperin 2008).

Palliative RT is frequently used for patients with advanced or metastatic diseases. It offers a quick, inexpensive, and effective way of reducing many of the focal symptoms of advanced, incurable cancer, whether these arise from the primary tumor or from metastatic lesions. It can improve quality of life while being associated with limited treatment burden in terms of both hospital attendances and side effects (Lutz 2014).

In order to achieve optimal patient care outcomes, a major goal of radiation therapy is the delivery of the desired dose distribution of IR to target tissue while limiting the radiation dose to the surrounding normal tissues to an acceptable level. With the introduction of intensity-modulated radiation therapy (IMRT) in the early 1990s, it was recognized that dose distributions could be significantly improved to better handle this class of treatment planning problems (ACR Practice Parameter for IMRT 2016).

Intensity-modulated radiation therapy has become widely used for a variety of clinical indications, such as tumors of the central nervous system, head and neck, breast, prostate, gastrointestinal tract, lung, and gynecologic system, as well as sites previously irradiated (Bittner 2015; Bauman 2012). In general, the ability of IMRT to deliver dose preferentially to target structures in close proximity

to organs at risk and other nontarget tissues makes it a valuable tool enabling the radiation oncologist to deliver dose to target volumes while minimizing dose to adjacent normal tissues.

Although curative treatment schemes have been developed to deliver daily fraction sizes of 1.8 to 2.0 Gy to doses totaling between 40 and 80 Gy (depending on tumor histology), palliative courses are designed to minimize time and effort spent in travel and treatment for patients suffering from incurable diseases. In addition, although hypo fractionated treatments may correlate with a higher risk of late toxicity, careful selection of palliative patients with limited life expectancies minimizes those risks. Thus, palliative treatment courses of 8 to 30 Gy given in 1 to 10 fractions have been shown to be useful for a wide range of scenarios (Lutz 2014). Also, the technique of simultaneous multisite palliative RT provides cost benefits to patients when analyzed in terms of cost per treated site (Wendt 2016).

Therefore, in an attempt to minimize RT related toxicities and improve participant convenience in this study, IMRT has been chosen as a RT technique and 30 Gy total dose delivered as 3 Gy daily fraction for 10 days total treatment duration has been adopted as a treatment scheme.

2.3.4 Summary of Potential Benefits and Risks of the Treatment Combinations

The risk-benefit relationship has been carefully considered in the planning of the study. CCI [redacted]

Based on the mechanisms of action of avelumab and M3814, which are well separated, and the safety profile of M3814 and avelumab monotherapy, there are no major overlapping toxicities expected when the agents are given in combination. Yet Part A of this first in human (FIH) study is proposed to allow for a detailed evaluation by an SMC of the safety and tolerability of the combination of M3814 and avelumab, and to generate safety, Pd, and PK data on this combination, which will be used to help define the starting dose of M3814 in combination with avelumab and RT in Part B.

The clinical activity and safety of anti-PD-1 and anti-PD-L1 in combination with RT have been investigated retrospectively in a variety of solid tumors including lung cancer, and the results show a clinical benefit in OS and progression-free survival (PFS) without an increase in toxicities. Thus, numerous prospective clinical studies that combine radiation with anti-PD-1 and anti-PD-L1 including avelumab, are now under way in both the early and metastatic settings to confirm these results.

CCI [redacted] Hence, for Part B of the current study, where the triplet of avelumab, M3814 and RT is to be investigated, available safety data from Part A of this study CCI [redacted]

2.3.5 Summary Benefit/Risk Statement

In summary, the potential for clinical benefit associated with the combination of the PD-1/PD-L1 pathway inhibitor (avelumab), DNA-damaging repair inhibitor (M3814) with and without a DNA-damaging agent (RT), CCI [redacted] and outweighs the potential risks based on the AEs reported in participants treated either with M3814 monotherapy or in combination with RT as well as the well-known safety profile of avelumab. Thus, the benefit/risk assessment favors the conduct of this proposed study.

3 Objectives and Endpoints

The objectives and endpoints of Part A and Part FE (M3814 in combination with avelumab) are shown in Table 8 and Table 10 and of Part B (M3814 in combination with avelumab and RT) in Table 9.

3.1 Part A

Table 8 Study Objectives and Endpoints – Part A

Objectives	Endpoints (Outcome Measures)
Primary	
To determine a safe, tolerable, RP2D and/or the MTD of M3814 when given in combination with avelumab	Occurrence of DLTs from first treatment to planned final assessment at the end of DLT period at 3 weeks
Secondary	
Safety	
To evaluate the safety profile and tolerability of M3814 in combination with avelumab	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS
Pharmacokinetics	
To characterize the pharmacokinetics of M3814 and avelumab when given as combination therapy	• Pharmacokinetic profile of avelumab in terms of pharmacokinetic parameter estimates, as feasible (e.g. C_{max}, C_{min}, Racc[C_{max}], Racc[AUC] and $t_{1/2}$) • Pharmacokinetic profile of M3814 in terms of pharmacokinetic parameter estimates (C_{max}, t_{max}, C_{min}, C_{avg}, fluctuation index, AUC_{0-t}, $AUC_{0-\infty}$, Racc[C_{max}], Racc[AUC], $t_{1/2}$, Vz/f, CL/f, and λ_z)
Immunogenicity	
To evaluate the immunogenicity of avelumab in combination with M3814	Immunogenicity as measured by ADA

Objectives	Endpoints (Outcome Measures)
Efficacy	
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab in participants with locally advanced or advanced solid tumors	• Confirmed BOR, DOR assessed from CR or PR until PD, death, or last tumor assessment, and PFS time according to RECIST v 1.1 as assessed by the Investigator • Tumor size measurement based on Investigator assessment according to RECIST v 1.1 from the first study interventions dose until confirmed PD or start of new cancer treatment • Overall Survival
Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ADA=antidrug antibody, ADME=absorption, distribution, metabolism, and excretion, BOR=best overall response, CR=complete response, DLT=dose-limiting toxicity, DNA-PK=DNA-dependent protein kinase, DOR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, FcγR=Fc receptors for IgG, MTD=maximum tolerated dose, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PD=progressive disease, CCI [redacted] PFS=progression-free survival, CCI [redacted] PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors, RP2D=recommended Phase II dose.

3.2 Part B

Table 9 Study Objectives and Endpoints – Part B

Objectives	Endpoints (Outcome Measures)
Primary	
To determine a safe, tolerable, RP2D and/or the MTD of M3814 when given in combination with avelumab and radiotherapy	Occurrence of DLTs from first treatment to planned final assessment at the end of DLT period at 4 weeks

Objectives	Endpoints (Outcome Measures)
Secondary	
Safety	
To evaluate the safety profile and tolerability of M3814 in combination with avelumab and radiotherapy	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS • Incidence, severity and outcomes of RT-induced toxicity
Pharmacokinetics	
To characterize the pharmacokinetics of M3814 and avelumab when given in combination with radiotherapy	• Pharmacokinetic profile of avelumab in terms of pharmacokinetic parameter estimates, as feasible (e.g. C_{max}, C_{min}, Racc[C_{max}], Racc[AUC] and $t_{1/2}$) • Pharmacokinetic profile of M3814 in terms of pharmacokinetic parameter estimates (C_{max}, t_{max}, C_{min}, C_{avg}, fluctuation index, AUC_{0-t}, $AUC_{0-\infty}$, Racc[C_{max}], Racc[AUC], $t_{1/2}$, Vz/f, CL/f, and λ_z)
Immunogenicity	
To evaluate the immunogenicity of avelumab in combination with M3814 plus radiotherapy.	Immunogenicity as measured by ADA
Efficacy	
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab and radiotherapy in participants with locally advanced and advanced solid tumors	• Confirmed BOR, DOR assessed from CR or PR until PD, death, or last tumor assessment, and PFS time according to RECIST v 1.1 as assessed by the Investigator • Tumor size measurement based on Investigator assessment according to RECIST v 1.1 from the first study interventions dose until confirmed PD or start of new cancer treatment • Overall Survival
Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints (Outcome Measures)
CCI [redacted]	[redacted]

ADA=antidrug antibody, ADME=absorption, distribution, metabolism, and excretion, BOR=best overall response, CR=complete response, DLT=dose-limiting toxicity, DNA-PK=DNA-dependent protein kinase, DOR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, FcγR=Fc receptors for IgG, MTD=maximum tolerated dose, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PD=progressive disease, CCI [redacted] PFS=progression-free survival, CCI [redacted], PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors, RP2D=recommended Phase II dose, RT=radiotherapy.

3.3 Part FE

Table 10 Study Objectives and Endpoints – Part FE

Objectives	Endpoints (Outcome Measures)
Primary	
To determine and compare the pharmacokinetic profile of M3814 under fasted and fed conditions	Area under the M3814 plasma concentration-time curve (AUC) from time zero to the last quantifiable sampling time (AUC_{0-t}), and maximum M3814 plasma concentration observed (C_{max})
Secondary	
Safety	
To evaluate the safety profile and tolerability of M3814 in combination with avelumab under fasted and fed conditions	• Occurrence of treatment-emergent adverse events and treatment-related adverse events according to the NCI-CTCAE v 5.0, and serious adverse events • Occurrence of abnormalities (Grade ≥ 3) in laboratory test values, markedly abnormal vital sign measurements, markedly abnormal physical examination measurements, clinically significant abnormal ECG, marked changes in ECOG PS
Immunogenicity	
To evaluate the immunogenicity of avelumab in combination with M3814 under fasted and fed conditions	Immunogenicity as measured by ADA
Efficacy	
To evaluate the preliminary antitumor activity of M3814 when given in combination with avelumab in participants with locally advanced or advanced solid tumors, under fasted and fed conditions	• Confirmed BOR, DOR assessed from CR or PR until PD, death, or last tumor assessment, and PFS time according to RECIST v 1.1 as assessed by the Investigator • Tumor size measurement based on Investigator assessment according to RECIST v 1.1 from the first study interventions dose until confirmed PD or start of new cancer treatment • Overall Survival
Exploratory	
CCI [redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints (Outcome Measures)
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ADA=antidrug antibody, ADME=absorption, distribution, metabolism, and excretion, BOR=best overall response, CR=complete response, DOR=duration of response, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, FcγR=Fc receptors for IgG, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PD=progressive disease, CCI [redacted] PFS=progression-free survival, CCI [redacted] PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors.

4 Study Design

4.1 Overall Design

This is a Phase I, multicenter study consisting of 3 parts (Part A, Part B, and Part FE) as shown in Figure 1 and Figure 2.

- Part A aims to determine the MTD and/or the RP2D of M3814 when given in combination with avelumab.
- Part B aims to determine the MTD and/or the RP2D of M3814 when given in combination with avelumab and RT.
    - Part B will be initiated once a first dose level of Part A has been declared as safe and tolerable by the SMC
- Part FE aims to evaluate the FE on PK of M3814 following administration of M3814 in combination with avelumab under fasted and fed conditions. Only doses of M3814 already declared as safe and tolerable in Part A by the SMC will be investigated in this part of the study.
- The tablet formulation of M3814 will be used in this study. Treatment after the study ends is described in Section 6.7.
- Additional dosing regimens of M3814 and avelumab (Part A and Part FE) or M3814, avelumab, and RT (Part B) may be introduced by protocol amendment to be explored.
- An increase in the sample size for Part A, Part B, and/or Part FE of the study to accommodate additional dose levels may be added by protocol amendment.
- In addition, expansion cohorts in defined advanced solid tumor indications may be added by amendment to explore preliminary efficacy of the combination regimens studied in Part A

and/or Part B.

4.1.1 Study Periods

Each part of the study (Part A, Part B, and Part FE) will comprise 3 study periods: a Screening period, a Treatment period, and a Follow-up period.

4.1.1.1 Screening Period

After providing informed consent for the study, the eligibility of study participants will be established according to the protocol-defined inclusion (Section 5.1) and exclusion criteria (Section 5.2) during a maximum 28-day Screening period (Screening and Baseline evaluations) for Part A and FE and a maximum 35-day Screening period for Part B.

4.1.1.2 Treatment Period

The treatment period will begin at the first dose of M3814 which will be administered continuously in combination with avelumab for Part A and Part FE, and with avelumab and RT for Part B.

Part A and Part FE: M3814 will be administered BID continuously, in combination with avelumab Q2W starting on Day 1 until PD or unacceptable toxicity.

Part B: M3814 will be administered QD. Radiotherapy will be given at the dose of 3 Gy per day. M3814 and RT will both be given starting Day 1 for 5 days/week for 2 weeks. Avelumab will be administered Q2W starting on Day 1 until PD or unacceptable toxicity.

Part A and Part B:

- Dose-limiting toxicity (DLT) Assessment Period: will last **3 weeks** in Part A and **4 weeks** in Part B (after the first administration of study intervention) for the evaluation of acute systemic and local toxicity in all participants. The DLT assessment period in Part B will be longer than for Part A because toxicities related to radiation including Radiation-Induced Lung Toxicities (RILT) might occur within a few weeks to months after radiation. Therefore, additional RT Safety Follow-ups are scheduled at 1, 3, and 12 months after the end of RT to investigate these potential late toxicities.

Part FE:

- FE Assessment Period: will last **3 weeks** (after the first administration of study intervention) for the evaluation of the effect of food conditions (fasted/fed) on M3814 PK.

Part A, Part B, and Part FE:

- Participants who have experienced a confirmed complete response (CR) should be treated for a minimum of 12 months with avelumab + M3814 in Part A and Part FE or avelumab in Part B based on clinical judgment of benefit and/or until disease progression, unacceptable toxicity, after confirmation of response as specified in the protocol. Where a participant with a confirmed CR relapses after stopping treatment, during Long-term Follow-up, but prior to the End-of-Trial, 1 reinitiation of treatment is allowed at the discretion of the Investigator and

agreement of the Medical Monitor. To be eligible for retreatment, the participant must not have experienced any toxicity that led to treatment discontinuation of the initial avelumab or M3814 therapy in Part A and Part FE or avelumab in Part B. Participants who reinitiate treatment will stay on the study and will be treated and monitored according to the protocol and the "until progression" schedule in the Schedule of Activities (Table 1, Table 2, Table 3, and Table 4). Participants who reinitiate treatment will not have to undergo a second Screening Visit.

4.1.1.3 Follow-Up Periods

Safety Follow-up

- **Part A, Part B, and Part FE**

The Safety Follow-up period will be 30 days and 90 days after the last dose of avelumab for safety evaluation of the combination of study interventions.

- **Part B**

In addition to the Safety Follow-up relating to the combination of study interventions after the last dose of avelumab, for Part B, the following RT Safety Follow-up periods are defined to assess potential toxicity of RT when administered in combination with M3814 and avelumab:

1. Short-term RT Safety Follow-up: 30 days after the end of RT for evaluation of safety.
2. Mid-term RT Safety Follow-up: 3 months after the end of RT to evaluate late signs of RT-induced toxicity on normal surrounding tissues.
3. Long-term RT Safety Follow-up: 12 months after the end of RT, to evaluate RT-induced toxicities, by telephone call.

Long-Term Follow-up

- **Part A, Part B, and Part FE**

Participants will be followed for survival and use of subsequent anticancer therapy until the end of the study. Participants without PD who are not receiving subsequent anticancer therapy after the End of Treatment Visit, will be followed every 8 weeks with radiographic disease evaluation for the first 6 months of the study and then every 12 weeks thereafter until PD according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v 1.1), and for survival and use of subsequent anticancer therapy until the end of the study.

4.2 Scientific Rationale for Study Design

The dose escalation design proposed for this Phase I study is deemed appropriate to define the MTD and/or RP2D of M3814 (Part A and Part B) and further investigate its safety, tolerability, PK/Pd profile, preliminary antitumor activity and the effect of high-fat meal on PK of M3814 when given in combination with avelumab in participants with metastatic or advanced solid tumors (Part A and Part FE) and with avelumab and RT in participants with selected advanced or

metastatic solid tumors (Part B). An open-label design is considered appropriate for a dose escalation study.

The decision to start Part B once the first dose level in Part A is declared safe and tolerable, along with using a 2-fold lower starting dose of M3814 compared with the starting dose level in Part A, aims to mitigate a potential increase in severity or frequency of radiation toxicity which could be related to the combination of RT with avelumab and/or M3814. This conservative approach aims to minimize risk to study participants in the initial cohort of Part B.

The starting dose in Part FE will be 100 mg BID since this dose has been assessed in 4 participants in Part A and already declared safe and tolerable. Subsequent doses will be defined based on PK and safety data generated in previous cohorts of Part A and Part FE and will be within the range of doses determined as safe in Part A. Data collected from participants in Part FE will primarily be used to investigate the FE on M3814 PK. In addition, the effects of prandial state on the safety profile of M3814 along with, tolerability, Pd profile, and preliminary antitumor activity of escalating doses of M3814 when given in combination with avelumab will also be evaluated.

Additional dosing regimens of M3814 and avelumab (Part A and Part FE) or M3814, avelumab, and RT (Part B) may be introduced by protocol amendment to be explored.

An increase in the sample size for Part A, Part B, and/or Part FE of the study to accommodate additional dose levels may be added by protocol amendment.

Future dose expansion cohorts may be included by amendment to explore efficacy in selected tumor indications in Part A and/or Part B.

Part A and Part B:

The primary endpoints of occurrence of DLTs as well as the secondary endpoint of occurrence, severity and duration of treatment-emergent adverse events (TEAEs) and treatment-related AEs according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.0 are standard objective measures of safety. A 3-week (Part A) and 4-week (Part B) period has been defined as the DLT assessment period to monitor DLT over 42 doses of M3814 and 2 administrations of avelumab for Part A and 10 administrations of M3814 and 8 fractions of RT (3 Gy each) and 3 administrations of avelumab for Part B. Secondary endpoints relating to PK, immunogenicity, and confirmed objective response as assessed by the Investigator using RECIST v1.1 criteria are also standard measurements. Duration of response, PFS and OS will also be determined as secondary endpoints and will serve to assess whether the objective response is associated with lasting clinical and survival benefit.

Part FE:

The primary endpoint is to evaluate the FE (fasted/fed state) on PK of M3814. A 3-week period has been defined as the FE Assessment Period to monitor the exposure both after single and repeated administration of M3814 over 42 doses of M3814 and 2 administrations of avelumab. Secondary endpoints relating to the effects of prandial state on the safety profile of M3814 along with immunogenicity and confirmed objective response as assessed by the Investigator using RECIST v 1.1 criteria are also standard measurements. Duration of response, PFS, and OS will

also be determined as secondary endpoints and will serve to assess whether the objective response is associated with lasting clinical and survival benefit.

Part A, Part B, and Part FE:

The exploratory pharmacodynamic assessments were selected based on the known mechanism of action and effects of M3814 and are relevant to the response, safety, or resistance to the combination. These assessments will contribute to the understanding of AEs and help in the determination of the RP2D.

Participants must have histologically or cytologically proven advanced or metastatic solid tumors (Part A and Part FE) and advanced or metastatic solid tumors eligible for fractionated RT (Part B) for which no standard therapy exists, standard therapy has failed, or the participant is intolerant to or has rejected established therapy known to provide clinical benefit for their condition. Section 5.1 and Section 5.2 provide detailed inclusion and exclusion criteria, respectively.

4.3 Justification for Dose

4.3.1 M3814

CCI

[redacted]

[redacted]

Part A

The selection of 200 mg as the starting total daily dose of the M3814 tablet formulation given as 100 mg BID concurrently with avelumab 800 mg Q2W takes into account the biologically effective dose (BED) of M3814 monotherapy which is estimated, based on modeling and simulation results, to be in the dose range of 200 to 800 mg total daily dose using the capsule formulation. CCI [redacted]

Furthermore, the mechanism of action of M3814 (potent and selective small-molecule adenosine triphosphate-competitive inhibitor of DNA-PK) and avelumab (a human anti-PD-L1 monoclonal antibody) are distinct and their acceptable safety profiles when given as single agents do not predict major additional safety toxicities if combined. CCCI [redacted]

However, as this is a novel combination of an immune-oncology agent and a small-molecule kinase inhibitor, an additional safety factor of 2-fold has been considered to account for any unexpected toxicities when M3814 is given in combination with avelumab.

CCI [redacted]

CCI [redacted]

Part B

The starting dose of M3814 in the first cohort of participants is expected to be 100 mg total daily dose (i.e. 2-fold lower than in Part A), as recommended by the SMC based on safety, PK, and Pd data generated during the first dose level in Part A and/or emerging safety and pharmacology data from the ongoing clinical studies involving M3814 in combination with RT (e.g. CCI [redacted]. In Part B, M3814 will be administered QD. M3814 and RT will both be given starting Day 1 for 5 days/week for 2 weeks.

CCI [redacted] in the dose range of

50 to 400 mg daily with capsule formulation. CCI [redacted]
Therefore, a starting dose of 100 mg QD using the tablet formulation has been defined to allow the BED to be achieved while taking into account the safety of participants in the first cohort.

In the context of this treatment combination FIH clinical study, the decision to conduct the 2 study parts (Part A and Part B) sequentially (i.e. Part B starting once the first dose in Part A is declared safe) and in overlapping fashion (i.e. dose escalation in Part A continuing once Part B has started) will enable the integration of safety, PK, and Pd data generated during the first dose level in Part A along with emerging safety and pharmacology data from the ongoing clinical studies involving M3814 and RT in the decision-making of starting dose which is either confirming the selected starting dose of 100 mg total daily dose of M3814 or informing the selection of another dose of M3814 to be evaluated as a starting dose level, if deemed appropriate and safe by the SMC.

Therefore, CCI [redacted] and clinical experience with M3814, as well as the study design, justify the starting dose approach adopted in Part B of this study.

In Part B, the QD administration starting 1.5 hours (± 30 minutes) before RT and only during days when RT is delivered is justified by the mechanism of action of M3814 that is aiming to decrease the repair of DSBs generated by RT, which might occur immediately after RT is administered (Kwok and Sutherland 1989; Schulz 2017).

Part FE

A total daily dose of 200 mg given as 100 mg BID M3814 tablet formulation has been selected as starting dose because 100 mg BID has already been declared safe and tolerable in combination with avelumab 800 mg Q2W in this study. CCI [redacted] Consequently, the room for an additional increase in absorption of tablet formulation due to a positive FE is expected to be low. CCI [redacted] Hence, a starting total daily dose of 200 mg M3814 administered as 100 mg BID tablet formulation is not expected to affect the safety profile of M3814.

Subsequent dose levels will be selected based on PK and safety data generated in both Part A and Part FE.

4.3.2 Radiotherapy

Radiotherapy is a successful, time-efficient, well-tolerated, and cost-effective intervention that is crucial for the appropriate delivery of palliative oncology care.

To achieve optimal patient care outcomes, one of the major goals of radiation therapy is the delivery of the desired dose distribution of IR to target tissue while limiting the radiation dose to the surrounding normal tissues to an acceptable level. Intensity-modulated radiation therapy, among other highly conformal techniques, represents an important advance in radiation therapy and, because of its ability to achieve a highly conformal dose distribution while sparing adjacent organs at risk, it has become widely used for a variety of clinical indications (Chandra 2005; Yom 2007; Nicolini 2012; Ettinger 2018).

It is currently widely agreed that palliative RT courses should be designed to minimize time and effort spent in travel and treatment for patients suffering from incurable diseases. Therefore, treatment courses of 8 to 30 Gy given in 1 to 10 fractions have been shown to be useful for a large range of advanced and metastatic solid tumors (Lutz 2014). Furthermore, it is increasingly recommended that the simultaneous multisite RT technique can be widely adopted with the new RT technologies such as IMRT in palliative setting in order to optimize cost-benefits in this patient population. (Wendt 2016).

Therefore, Part B of this study will enroll participants with advanced or metastatic solid tumors amenable to receive 30 Gy total RT dose given in 10 fractions (3 Gy/fraction, 5 fractions/week, 10 days total duration of treatment) to up to 3 primary and/or metastatic sites using the IMRT technique. CCI [redacted] other palliative RT dose and/or fractionation schedules may be included by amendment.

4.3.3 Avelumab

To date, avelumab has been administered at the clinically active tolerable dose of 10 mg/kg Q2W to more than 1800 patients across multiple indications. Furthermore, this 10 mg/kg every 2-week avelumab dosing regimen has been approved by the FDA as the first treatment for Merkel Cell Carcinoma and UC. Avelumab was originally dosed on a mg/kg basis in order to reduce inter participant variability in drug exposure. However, emerging data for monoclonal antibodies, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab, reveal that body weight based dosing regimens do not result in less variability in measures of exposure over fixed (i.e. body weight independent) dosing regimens (Wang 2009; Freshwater 2017; Zhao 2017). Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

The dose regimen of avelumab at 800 mg flat dose Q2W has been approved by the FDA. The flat dose regimen has been studied via modeling and simulation and is currently being investigated in a few clinical studies in combination with other agents. Avelumab was originally dosed on a mg/kg basis to reduce inter participant variability in drug exposure. However, the Pop PK model data, reveal that body weight-based dose regimens do not result in less variability in measures of exposure over fixed (i.e. body weight independent) dose regimens.

Simulation showed that exposures to avelumab across the available range of body weights are less variable with 800 mg Q2W compared with 10 mg/kg Q2W; exposures were similar near the

population median weight. Furthermore, the 800 mg Q2W dose regimen is expected to result in C_{trough} >1 mg/mL required to maintain avelumab serum concentrations at > 95% target occupancy throughout the entire Q2W dosing interval in all weight categories.

The advantages of flat dosing are minimizing drug wastage, facilitating preparation and administration, and reducing pharmacy errors (Wang 2009).

Therefore, in this clinical study, a fixed dosing regimen of 800 mg administered as 1-hour IV infusion Q2W will be utilized for avelumab.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the Safety Follow-up Visit as shown in Section 1.3 (Schedule of Activities).

The end of the study is defined as the date of 1 year after the last participant has received the last dose of study interventions or the last participant in this study dies, whichever comes first.

This end of study date will allow sufficient time to collect data on the efficacy endpoints (OS, confirmed BOR, duration of response, PFS time, and tumor size).

The Sponsor may terminate the study at any time once access to study intervention for participants still benefiting is provisioned via a rollover study, expanded access, marketed product or another mechanism of access as appropriate.

5 Study Population

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

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

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

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participants must have:

- **Part A and Part FE (M3814 + avelumab):** histologically or cytologically proven advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide clinical benefit for their condition.
- **Part B (M3814 + RT + avelumab):** histologically or cytologically proven advanced or metastatic solid tumors for which no standard therapy exists, standard therapy has failed, or participants are intolerant to or have rejected established therapy known to provide benefit for their condition and are amenable to receive RT.

  Lesions to be targeted with RT need to fulfill the following criteria:

  - Should be of malignant origin
  - Must not be arising from the brain or spinal canal
  - Must not be esophageal, gastric or small bowel lesion
  - Must not be primary liver cancer (hepatocellular carcinoma [HCC], intrahepatic cholangiocarcinoma [ICC], mixed HCC-ICC)
  - The lesion or composite lesion target maximum longest diameter (sum of maximum longest diameters for all tumor targets to be irradiated) must be at least 1 cm ($\geq$ 1 cm). For individual tumor where the longest diameter is $>$ 5 cm, a target volume could be created within the gross tumor volume to limit the treated tumor to 5 cm.

  Additional details related to radiation target selection are outlined in Appendix 8.

Part A, Part B, and Part FE

3. Measurable or evaluable disease according to RECIST v 1.1.

4. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 at study entry.

5. Adequate bone marrow function including: Absolute neutrophil count $\geq$ 1,500/mm^3 or $\geq$ 1.5 $\times$ 10^9/L; platelets $\geq$ 100,000/mm^3 or $\geq$ 100 $\times$ 10^9/L; hemoglobin $\geq$ 9 g/dL (may have been transfused). Participants with documented benign cyclical neutropenia are allowed if white blood cell count is $\geq$ 1.5 $\times$ 10^9/L with absolute neutrophil count $\geq$ 1.0 $\times$ 10^9/L.

6. **Only for Part A and Part B:** availability of formalin-fixed paraffin-embedded (FFPE) block containing tumor tissue or a minimum of 10 (preferably 25) unstained tumor slides from a recently obtained (within 6 months before D1) biopsy from a nonirradiated area.

7. Adequate hepatic function defined by a total bilirubin level $\leq$ 1.5 $\times$ the upper limit of normal range (ULN), an AST level $\leq$ 3 $\times$ ULN, and an ALT level $\leq$ 3 $\times$ ULN or, for

participants with documented metastatic disease to the liver, AST and ALT levels ≤ 5 × ULN. Participants with documented Gilbert disease are allowed if total bilirubin is less than 3 × ULN.

8. Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula or by 24-hour urine collection for creatinine clearance or according to local institutional standard method.

Sex

9. Are male or female

   a. Male participants:

Agree to the following during the intervention period and for at least 90 days (a spermatogenesis cycle) after the last dose of study intervention:

- Refrain from donating sperm

PLUS, either:

- Abstain from any activity that allows for exposure to ejaculate

OR

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

b. Female participants:

- Are **not** pregnant or breastfeeding, and at least one of the following conditions applies:
  - **Not** a WOCBP, as defined in Appendix 3

  OR

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

      OR

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

AND

- A barrier method, as described in Appendix 3.

- During the intervention period
- After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 90 days after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

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

- Have a negative serum pregnancy test, as required by local regulations, within 4 weeks before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.5.

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.

10. Estimated life expectancy of at least 3 months.

Informed Consent

11. Capable of giving signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1. Persisting toxicity related to prior therapy of NCI-CTCAE v 5.0 Grade > 1; however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 AEs not constituting a safety risk based on Investigator's judgment are acceptable.

2. Clinically significant (i.e. active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication or uncontrolled conduction abnormalities including a history of long QTc syndrome [QTcF > 480 ms] and/or pacemaker, or myocardial infarction (< 6 months prior to enrollment).

3. History of uncontrolled intercurrent illness including but not limited to:

a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)

b. Uncontrolled active infection

c. Uncontrolled diabetes (e.g. hemoglobin A1c ≥ 8%)

4. Previous malignant disease (other than the indication for this study) within the last 5 years (except adequately treated nonmelanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the participant was deemed to have been cured with no additional therapy required or anticipated to be required.

5. All participants with brain metastases, except those meeting the following criteria:

   a. Brain metastases that have been treated locally and are clinically stable for ≥ 4 weeks prior to randomization

   b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)

   c. Participants must be either off steroids or on a stable or decreasing dose of < 10 mg daily prednisone (or equivalent).

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

7. 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 impair participant well-being or preclude full participation in the study.

8. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for entry into this study.

9. In immunotherapy pretreated participants, any history of DLTs with prior immunotherapy agents, including Grade 3/4 irAEs; irreversible irAEs; Grade ≥ 3 irAEs that did not respond to steroid rescue; or neurologic irAE with significant clinical sequelae.

Note: Potential participants with irAE requiring hormone replacement therapy (e.g. thyroxine, insulin, or physiologic dose of corticosteroid replacement therapy for adrenal or pituitary insufficiency) are eligible as long as the endocrinopathy is well controlled and the participant is not otherwise symptomatic from hormone insufficiency. Physiologic corticosteroid dose is defined as ≤ 10 mg daily of prednisone or equivalent.

10. Significant acute or chronic infections, including, among others:

    a. Known history of human immunodeficiency virus or known acquired immunodeficiency syndrome.

    b. Hepatitis B virus or hepatitis C virus infection at Screening (positive hepatitis B virus surface antigen or hepatitis C virus RNA if anti-hepatitis C virus antibody Screening test positive). Participants with history of infection must have a polymerase chain reaction (PCR) documentation that infection is cleared.

11. Active or history of autoimmune disease that might deteriorate when receiving an immune-stimulatory agent. Participants with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

12. Any participant with possible area of ongoing necrosis (non-disease related), such as active ulcer, nonhealing wound, or intercurrent bone fracture that may be at risk of delayed healing due to protocol therapy.

13. Known prior severe hypersensitivity to any of the investigational products or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI-CTCAE 5.0 Grade ≥ 3).

Part B only:

14. If the participant has symptoms of ongoing esophagitis and the treating Investigator estimates that the radiation planning target volume (PTV) will include any portion of the esophagus, the participant is not eligible unless an esophageal endoscopy rules out the presence of esophagitis.

15. The participant will not be eligible if more than 10% of the total esophagus volume is estimated to receive more than 15 Gy (50% of the prescribed RT dose).

16. If hepatic metastatic lesion is selected to be irradiated:
    - The non-tumor liver volume < 700 mL
    - Child-Pugh score ≥ 8

17. If the participant has an acute or chronic interstitial pulmonary disease and the treating Investigator has selected a thoracic lesion to be irradiated, the participant is not eligible.

Prior/Concomitant Therapy

18. Received:

    a. Chemotherapy, hormonal anticancer therapy with the exception of luteinizing hormone-releasing hormone analogs, biologic therapy, or any other anticancer therapy within 28 days of the first dose of study intervention administration (6 weeks for nitrosoureas or mitomycin C). For participants with rapidly growing tumors where the treating physician cannot wait for 28 days or 6 weeks, inclusion may take place if the participant meets all the other eligibility criteria and if there is no residual toxicity related to previous treatment NCI-CTCAE Grade >1.

    b. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of the study intervention and/or if the participant has not fully recovered from the surgery within 4 weeks of the study intervention.

    c. Treatment with a live attenuated vaccine within 30 days of dosing.

19. Participants currently receiving (or unable to stop using prior to receiving the first dose of study intervention) medications or herbal supplements known to be strong inhibitors of CYP3A, CYP2C9, or CYP2C19 (must stop at least 1 week prior); strong inducers of CYP3A, CYP2C9, or CYP2C19 (must stop at least 3 weeks prior); or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior).

20. Participants receiving immunosuppressive agents (such as steroids) for any reason who cannot be tapered off these drugs before start of study intervention, with the following exceptions:

    a. Participants with adrenal insufficiency, may continue corticosteroids at physiologic replacement dose, equivalent to ≤ 10 mg prednisone daily.

    b. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) is permitted.

    c. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to ≤ 10 mg prednisone daily.

21. Prior organ transplantation, including allogeneic stem cell transplantation.

22. **Part B only:** prior RT to the same region as intended to be irradiated in this study within the past 12 months.

23. **Part B only:** extensive prior RT on ≥ 30% of bone marrow reserve as judged by the Investigator or prior bone marrow/stem cell transplantation within 5 years before study start.

Prior/Concurrent Clinical Study Experience

24. Participation in any clinical study within 1 month or 5 half-lives prior to Screening or during participation in this study.

Diagnostic Assessments

25. Oxygen saturation < 90% at rest, known pulmonary fibrosis, or active/history of interstitial lung disease or pneumonitis.

Other Exclusions

26. Pregnancy or lactation.

27. Legal incapacity or limited legal capacity.

28. Known alcohol or drug abuse as deemed by the Investigator.

29. Any other condition or circumstance that would, in the opinion of the Investigator, make the participant unsuitable for participation in the study.

5.3 Lifestyle Considerations

No specific lifestyle or dietary restrictions are required throughout the study.

5.3.1 Meals and Dietary Restrictions

Participants will be instructed to refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, (pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) from 7 days before the start of study intervention until after the final dose.

Food conditions during M3814 administration are presented in Section 6.6.5.1 (for Part A), Section 6.6.5.2 (for Part B) and Section 6.6.5.3 (for Part FE).

See also Section 6.8.

5.3.2 Caffeine, Alcohol, and Tobacco

No specific restrictions on caffeine, alcohol or tobacco use apply during the study.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened for hematology and chemistry parameters. Rescreened participants will be assigned a new participant number.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Table 11 Administration of Study Intervention(s)

Study Intervention Name:	M3814	Avelumab	Radiotherapy (Part B only)
Dose Formulation:	CCI [redacted]	Each single-use vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing mannitol, and polysorbate 20 (Tween 20). For administration, avelumab drug concentrate must be diluted with 0.9% saline solution (sodium chloride for injection) supplied in an infusion bag; alternatively, a 0.45% saline solution can be used if needed.	In the planning of RT, IMRT must be used. The dose planning can be CT or PET-CT according to institutional guidelines. The use of daily IGRT is recommended. Details on technical factors to consider including IMRT treatment planning will be provided in Appendix 8.
Unit Dose Strengths/Dosage Levels:	**Part A and Part FE:** A 50 mg tablet for oral administration is used during the treatment phase. The starting dose will be 100 mg BID. Subsequent doses and schedules will be determined: - In Part A: by the SMC. - In Part FE: by the Sponsor based on PK and safety data generated in previous cohorts of Part A and Part FE and will be within the range of doses determined as safe in Part A. **Part B:** A 50 mg tablet for oral administration is used during the treatment phase. The starting dose of M3814 in the first cohort of participants is expected to be 100 mg total QD. However, this starting dose might be adjusted by the SMC based on safety, PK, and Pd data generated during the first dose level in Part A and/or emerging data from the ongoing clinical studies involving M3814. M3814 will be given starting Day 1 for 5 days/week for 2 weeks. Subsequent doses and schedules will be determined by the SMC.	**Part A and Part FE:** Q2W as a fixed dose of 800 mg in all dose levels. **Part B:** Q2W as a fixed dose of 800 mg in all dose levels.	RT for single anatomic site: 3 Gy per fraction per day for 5 days a week to a total dose of 30 Gy, starting on Day 1 with M3814. Multisite RT (up to 3 anatomic sites): 3 Gy per fraction per day per site for 5 days a week to a total dose of 30 Gy, starting on Day 1 with M3814. All sites (up to 3) selected by the Investigator should be irradiated on the same day.

Study Intervention Name:	M3814	Avelumab	Radiotherapy (Part B only)
Route of Administration:	Oral	Intravenous infusion over 1 hour.	
Dosing Instructions:	See Section 6.6.5.		
Supplier/Manufacturer:	M3814 is supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.	Avelumab will be supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.	
[redacted]	CCI [redacted]	[redacted]	

BID=twice daily, CT=computed tomography, IGRT=image guided radiotherapy, IMP=investigational medicinal product, IMRT=intensity-modulated radiotherapy, Pd=pharmacodynamic, PET-CT=positron emission tomography-computed tomography, PK=pharmacokinetic, PVA=polyvinal alcohol, Q2W=once every 2 weeks, QD=once daily, RT=radiotherapy, SMC=safety monitoring committee.

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

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

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Study Reference Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study and prepared at the site.
    - The dose(s) each participant used during the study.
    - The disposition (including return, if applicable) of any unused study intervention(s).
    - Dates, quantities, batch numbers, container numbers CCI expiry dates, formulation, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Once available, an Interactive Voice Response System will be employed to assign study intervention to participants and facilitate resupply of study intervention at study sites.

6.3.2 Blinding

Not applicable.

6.4 Study Intervention Compliance

In this study, participants will receive avelumab and RT at the investigational site. M3814 will be taken at home by the participant in Part A and Part FE except for days with scheduled PK collection visits. M3814 will be taken at the investigational site in Part B. Well-trained medical staff will monitor and perform the study intervention administration. The information of each study intervention administration including the date, time, and dose of study intervention will be recorded on the electronic Case Report Form (eCRF). The Investigator will make sure that the information entered into the eCRF regarding study intervention administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing:

- More than 8 doses of M3814 during the DLT period in Part A, and the FE Assessment Period in Part FE
- Two doses of M3814 and RT during the DLT period in Part B,
- Four weeks of study intervention beyond the DLT period in either Part A or Part B, or beyond the FE Assessment Period in Part FE.

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e g. medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

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.

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

6.5.1 Rescue Medicine

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, iv antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions.

If hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Participants should be instructed to report any delayed reactions to the Investigator immediately. In addition, all hypersensitivity reactions are to be reported in a timely manner.

6.5.2 Permitted Medicines

The only permitted medications are the following:

- Any medications, therapies, or procedures (other than those excluded by the clinical study protocol) that are considered necessary for the participants' welfare and will not interfere with the study medication may be given at the Investigator's discretion.
- Other drugs to be used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Section 6.9.
- Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) and anti-infectious drugs are acceptable.
- Rescue medications may be administered due to anticipated adverse reactions or anticipated emergency situations.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

Prohibited medicines include those listed in the exclusion criteria (Section 5.2).

- As stated in Section 5.2, chemotherapy, hormonal anticancer therapy with the exception of luteinizing hormone-releasing hormone analogs, biologic therapy, or any other anticancer therapy within 28 days of the first dose of study intervention administration (6 weeks for nitrosoureas or mitomycin C). These therapies are also prohibited during the treatment period (**Part A, Part B, and Part FE**) and up to 30 days after the end of RT (**Part B**).
- During the treatment period (**Part A, Part B, and Part FE**) and up to 30 days after the end of RT (**Part B**), chemotherapy, extensive RT (involving ≥ 30% of bone marrow) or any other anticancer therapy (biologics or other targeted therapy or investigational agent) and antineoplastic steroid therapy are also prohibited.
- Use of any other investigational treatments, or participation in any other interventional studies, during the entire study duration (**Part A, Part B, and Part FE**) is not permitted.

Furthermore, the following treatments must not be administered during the study:

- Immunotherapy, immunosuppressive drugs (i.e. chemotherapy or systemic corticosteroids) except:
    - When required for the treatment of irAEs or infusion-related reactions/hypersensitivity
    - Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent
    - Systemic corticosteroids for management of participants with allergy to computed tomography (CT) IV radiographic contrast media.
- Administration of a live vaccine within 30 days of study intervention.
- Growth factors (e.g. granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Growth factors are allowed for treatment of study intervention-related myelosuppression and for prophylaxis of repeat myelosuppression after initial occurrence.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).
- Medications or herbal supplements known to be strong inhibitors or inducers of CYP3A, CYP2C9, or CYP2C19.
- Drugs mainly metabolized by CYP3A or CYP2C9 with a narrow therapeutic index as judged by the Investigator (and after optional consultation with the Sponsor; for details see Special Precautions below; Section 6.8).

The solubility of M3814 is pH dependent; therefore, antacid drugs, H2-blocker and proton pump inhibitors (PPI) might affect absorption. PPIs should be stopped 5 days prior to the first treatment and avoided during the entire treatment period with study intervention. Antacid drugs should not be taken 1 hour before study intervention administration until 2 hours after study intervention administration. H2 blockers may be allowed but should be taken at least 2 hours after M3814 dose and stopped at least 6 hours before the next dose of M3814.

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.

If the administration of a nonpermitted concomitant drug becomes necessary during the study, e.g. because of AEs, suspension of the participant from treatment should be performed. The requirement to discontinue the participant from treatment should be discussed with the Sponsor. In case of discontinuation and where possible, the End of Treatment Visit and Safety Follow-up Visit and phone call 30 and 90 days after end of treatment should be performed as per Schedule of Activities (Table 1, Table 2, Table 3, and Table 4). Furthermore, in participants who discontinue from study intervention prior to disease progression tumor assessments should continue according to the Schedule of Activities until confirmed disease progression or start of a new anticancer treatment.

6.5.4 Other Interventions

Surgery to any tumor lesion for symptom management or tumor control is permitted during the study intervention according to rules defined in Section 6.6.7. For any other surgical interventions planned during the study, study intervention should be delayed for up to a maximum of 4 weeks to allow participant's recovery.

Palliative short course, limited field (i.e. ≤ 10 fractions and ≤ 30% bone marrow involvement or per institutional standard) RT may be administered at any time after the end of the DLT period in **Part A and Part B,** and after the FE Assessment Period in **Part FE**. However, dosing of M3814 must be suspended ≥ 24 hours prior to start of RT and must not be resumed until ≥ 24 hours after the last RT dose. The assessment of PD will be made according to RECIST v 1.1 and not based on the necessity for palliative RT.

Radiotherapy (**Part A, Part B, and Part FE**) is not permitted, with the exception of palliative RT as described above.

6.5.5 Premedication for Avelumab

Premedicate participants with an antihistamine and with acetaminophen prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

6.6 Dose Selection and Modification

This Phase I open-label study consists of 3 parts:

- Part A and Part B with the primary objective to establish the MTD and/or RP2D of M3814 given respectively, by BID dosing in combination with avelumab and by QD dosing with avelumab and RT.
- Part FE with the primary objective of determining the FE on PK of M3814 given by BID dosing in combination with avelumab.

The 3 parts further investigate the safety, tolerability, PK/Pd and preliminary antitumor activity of M3814 in participants with advanced solid tumors (Part A and Part FE) and in participants with selected advanced solid tumors (Part B)

The criteria for dose escalation in Part A and Part B are based on the occurrence of AEs and/or DLTs during the DLT period in evaluable participants in each cohort. The definition of a DLT is presented in Section 6.6.3. Dose escalation rules are in Section 6.6.4. In Part FE, the dose escalation is based on PK and safety data generated in previous cohorts of Part A and Part FE and will be within the range of doses determined as safe in Part A.

6.6.1 Dose Selection (Part A and Part B)

Part A:

- The starting dose of M3814 will be 100 mg BID. Subsequent doses and schedules will be determined by the SMC (see Section 4.3.1 for dose rationale).
- Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels. Guidance on premedication is given in Section 6.5.5.

Part B:

- The starting dose of M3814 in the first cohort of participants will be 100 mg total daily dose (i.e. 2-fold lower than in Part A). However, this starting dose might be adjusted by the SMC based on safety, PK and Pd data generated during the first dose level in Part A and/or emerging data from the ongoing clinical studies involving M3814.
- Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels. Guidance on premedication is given in Section 6.5.5.
- Radiotherapy: 3 Gy per fraction per day for 5 days a week to a total dose of 30 Gy, starting on Day 1 with M3814.

The SMC will review the safety and any available PK/Pd data on a regular basis. During Part A and Part B, the SMC will decide on relevant DLTs (Section 6.6.3) based on protocol criteria. They will decide by consensus on dose escalation or de-escalation of M3814, or suspension of enrollment and/or declaration of the maximum safe dose (i.e. maximum administered dose/MTD) and the RP2D of M3814 in combination with avelumab (Part A) and with avelumab and RT (Part B).

For Part A only, in the event that an AE which meets the definition of DLTs as defined per the protocol occur in Part FE, after a higher dose level has been opened in Part A, the data will be reviewed by the Sponsor and the SMC to determine the best course of actions for currently enrolling participants at the highest dose level.

The DLT period is considered completed, and a participant evaluable for dose escalation decisions, when the minimum safety evaluations have been performed (hematology, chemistry, and clinical assessments), and the participant has received:

- **Part A:** at least 80% of the planned doses of M3814 (i.e. 34 of 42 doses with BID dosing regimen) and 100% of the planned avelumab doses (2 administrations) during the DLT assessment period of 3 weeks.
- **Part B:** at least 80% of the planed doses of M3814 (i.e. 8 of 10 doses with QD dosing regimen), and RT (8 of 10 fractions of 3 Gy each) and 100% of the planned avelumab doses (3 administrations) during the DLT assessment period of 4 weeks.

6.6.2 Dose Selection (Part FE)

The starting dose of M3814 would be 200 mg total daily dose given as 100 mg BID. Subsequent doses and schedules will be determined based on the PK and safety data generated in previous

cohorts of Part A and Part FE and should be within the dose ranges already declared safe and tolerable in Part A. Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels. Guidance on premedication is given in Section 6.5.5.

The FE Assessment Period is considered completed and a participant evaluable for subsequent dose level decisions, when the PK and minimum safety evaluations have been performed (hematology, chemistry, and clinical assessments), and the participant has received:

- at least 80% of the planned doses of M3814 (i.e., 34 of 42 doses with BID dosing regimen) and 100% of the planned avelumab doses (2 administrations) during the FE Assessment Period of 3 weeks.

The results from Part FE will be reviewed and evaluated by the Sponsor and if deemed necessary by the SMC to determine a potential impact on the study dosing recommendations for M3814 and/or safety profile of M3814 when given in combination with avelumab.

Cohorts of at least 3 participants each will be treated at the same dose level of M3814 (starting dose: 100 mg tablet formulation, BID) in combination with avelumab. On the day of avelumab administration, M3814 can be given prior to the start or just after the end of avelumab infusion. A preselected set of acceptable doses as described in Table 12, will be considered once declared as safe and tolerable in Part A, however, doses which are not part of the prespecified set may be chosen as well, as long as they are within the prespecified dose ranges based on considerations of PK and safety data generated in previous cohorts. If the sample size in Part FE has to be increased to accommodate additional dose levels, a protocol amendment with rationale will be submitted prior to implementation. The Sponsor and/or the SMC may decide to continue or stop the assessment of FE in subsequent dose level (s). This decision will be based on PK and safety data generated in the previous cohorts in Part A and/or Part FE and/or emerging data from the clinical studies which are currently evaluating the human pharmacology, safety, and tolerability of M3814. It is anticipated that 6 to 12 participants (3 to 6 participants at each dose level) may be needed.

Table 12 Example of Possible Dose Levels of M3814 in Combination with Avelumab in Part FE

Dose Level	M3814 Schedule (mg; BID)	Total Daily M3814 Dose (mg)	Avelumab Schedule[a]	Avelumab Dose (mg)
-1[b]	50	100	Q2W	800
1[c]	100	200	Q2W	800
2	200	400	Q2W	800

BID=twice daily, PK= pharmacokinetics, Q2W=once every 2 weeks

Dose escalation will be based on the food effect data on PK in the previous cohort. Available safety data on the presence/absence of study intervention-related clinically relevant adverse events will also be taken into consideration.

a Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels.

b Dose Level -1 can be evaluated upon consideration of pharmacokinetic and safety data.

c Dose Level 1 is the starting dose.

6.6.3 Definition of Dose-Limiting Toxicity

Part A and Part B:

A DLT is defined as any Grade ≥ 3 nonhematologic AE or any Grade ≥ 4 hematologic AE according to the NCI-CTCAE v 5.0, occurring during the DLT period (up to 3 weeks for Part A and up to 4 weeks for Part B) that is related to any of the study interventions.

A DLT must be confirmed by the SMC.

In addition, a DLT is considered:

- Grade 3 thrombocytopenia with medically concerning bleeding
- Any febrile neutropenia
- A study intervention-related TEAE that in the opinion of the SMC is of potential clinical significance such that further dose escalation would expose participants to unacceptable risk
- Any toxicity related to study intervention that causes the participant to receive less than 80% of M3814 during DLT period (4 days treatment in Part A and 2 days treatment in Part B)
- Evidence of study treatment-related hepatocellular injury for more than 3 days, such as > 5-fold elevations above the ULN of ALT or AST (CTCAE Grade 3 or 4) 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

The following treatment-related AEs are exceptions to the above mentioned DLT definition and are **not** considered to be DLTs:

Part A and B:

- Neutropenia of Grade 4 lasting for ≤ 5 days and not associated with fever
- Isolated Grade 4 lymphocytopenia without clinical correlate
- Any laboratory value of Grade ≥ 3 out of the normal range that have no clinical significance, and that resolve to Grade 2 or less with adequate management within 6 days
- Grade 3 autoimmune thyroid-related toxicity that clinically resolves to ≤ Grade 2 within 6 days of initiating therapy
- Grade 3 diarrhea persisting ≤ 3 days after medical management
- Grade 3 nausea and vomiting persisting ≤ 3 days with adequate and optimal therapy
- Grade 3 nonrecurrent skin toxicity that resolves to Grade ≤ 1 in less than 14 days after medical management (e.g. immunosuppressant treatment) has been initiated
- Transient (≤ 3 days) Grade 3 fatigue, local reactions excluding skin reactions, flu-like symptoms, fever, headache, nausea, emesis that resolves to Grade ≤ 1 with adequate treatment
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 2 within 6 days

For Part B only:

- Mucositis (mucosal inflammation), including oral mucositis (stomatitis) or esophagitis of Grade ≥ 3 lasting for ≤ 4 weeks after completion of the study treatments
- Stomatitis associated toxicities (e.g., swallowing dysfunction [odynophagia, dysphagia], decreased appetite, or weight loss due to difficulty or painful swallowing) of Grade ≥ 3 lasting for ≤ 4 weeks after completion of the study treatments
- Radiation dermatitis and associated toxicities of Grade ≥ 3 lasting for ≤ 4 weeks after completion of the study treatments
- For participants suffering from squamous cell carcinoma of head and neck and who receive RT in the head and neck region: the duration of feeding tube (FT) use (nasogastric tube, percutaneous endoscopic gastrostomy) should not define the severity of the toxicity (e.g., severe swallowing dysfunction, nausea, vomiting). A careful evaluation of the participant's symptoms by the Investigator at each visit is required in order to identify participants who are FT dependent (e.g., participants who refuse/avoid swallowing, etc).

At any time during the study, the SMC may identify as a DLT any adverse drug reactions (ADR) in participants treated with M3814 in combination with avelumab (Part A) and with avelumab and RT including in-field late radiation toxicities (Part B).

6.6.4 Dose Escalation Rules

The criteria for dose escalation are based on the occurrence of AEs and/or DLTs during the DLT period in evaluable participants in each cohort. The DLT assessment period of 3 weeks (Part A) or 4 weeks (Part B) after the start of M3814 treatment allows an evaluation of acute toxicity. M3814 dose escalation will not proceed to the next dose level until the SMC has decided to escalate. Moreover, RT and the combination of RT and M3814 and avelumab can also give rise to later toxicities, especially radiation toxicities. A 30-day and 90-day Safety Follow-up will be performed in all participants in both Parts (A and B) of the study. Once available, these data, alongside with emerging safety, PK, and Pd data from the ongoing clinical projects involving M3814, will also guide subsequent dose escalation and the establishment of the RP2D. Furthermore, RT Safety Follow-up Visits will be performed in all participants in Part B 1 month (Short-Term RT Safety Follow-up), 3 months (Mid-Term RT Safety Follow-up), and 12 months (Long-Term RT Safety Follow-up, by telephone) after the last RT treatment, to assess any late RT toxicity. These data will be considered in determining the safety profile of the treatment combination.

Dose Escalation Part A (M3814 + avelumab 800 mg Q2W)

A Bayesian two-parameter logistic regression model with overdose control will be used to assist the SMC with dose selection during the Part A dose escalation. Cohorts of at least 3 participants each will be treated at the same dose level of M3814 (starting dose: 100 mg tablet formulation, BID) in combination with avelumab. On the day of avelumab administration, M3814 can be given prior to the start or just after the end of avelumab infusion. The model incorporates available CCI clinical data and observed data from each completed cohort (and data from all previous cohorts) to provide a recommended dose for the next cohort. A preselected set of

acceptable doses are considered by the model as described in Table 13; however, doses which are not part of the prespecified set may be chosen as well, as long as they are within the prespecified dose ranges based on considerations of safety, PK, and Pd data generated in previous cohorts, and the model. Yet, if the sample size in Part A has to be increased to accommodate additional dose levels, a protocol amendment with rationale will be submitted prior to implementation. Moreover, the SMC or the Sponsor may decide to stop the ascending dose process as soon as the first dose level is declared safe and tolerable. This decision will be based on safety, PK and/or Pd data available during the first cohort and/or emerging data from the clinical studies which are currently evaluating the human pharmacology, safety and tolerability of M3814. It is anticipated that 6 to 30 participants (3 to 6 participants at each dose level) may be needed.

Table 13 Example of Possible Dose Levels of M3814 in Combination with Avelumab (Part A)

Dose Level	M3814 Schedule (mg; BID)	Total Daily M3814 Dose (mg)	Avelumab Schedule[a]	Avelumab Dose (mg)
-1[b]	50	100	Q2W	800
1[c]	100	200	Q2W	800
2	200	400	Q2W	800
3	400	800	Q2W	800
4	800	1600	Q2W	800

BID=twice daily, DLT=dose-limiting toxicity, IV=intravenous, Pd= pharmacodynamic, PK=pharmacokinetic, Q2W=once every 2 weeks, SMC=Safety Monitoring Committee.

Dose escalation will be based on the presence/absence of DLTs and study intervention-related clinically relevant adverse events during the DLT period. Available PK and Pd data will also be taken into consideration.

a Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels.

b Dose Level -1 can be evaluated upon decision of the SMC.

c Dose Level 1 is the starting dose.

Dose Escalation Part B (M3814 + radiotherapy + avelumab 800 mg Q2W)

Similar to Part A, a separate Bayesian two-parameter logistic regression model with overdose control will be used in Part B to assist the SMC. Following completion of the first cohort (Dose level 1) in Part A, participants with selected advanced or metastatic will be enrolled in the first cohort and will receive M3814 tablet formulation, QD, to be given 1.5 hours (± 30 minutes) prior to the start of RT. On the day of avelumab administration, M3814 can be given at any time after the end of the avelumab infusion. Assuming that the first starting dose level in Part A is declared safe and tolerable, the starting dose of M3814 in the first cohort of participants will be 100 mg total daily dose (i.e. 2-fold lower than in Part A). However, this starting dose might be adjusted by the SMC, based on safety, PK, and Pd data generated during the first dose level in Part A and/or emerging data from the ongoing clinical studies involving M3814 and RT that may justify another starting dose.

Based on the occurrence of AEs and/or DLTs, the SMC will decide if the dose can be escalated or de-escalated to the next dose level. The model will incorporate CCI [redacted] clinical data and observed data from each completed cohort to provide a recommended dose for the next cohort.

A preselected set of acceptable doses are considered by the model (Table 14), however, doses which are not part of the prespecified set may be chosen as well, as long as they are within the prespecified dose ranges based on considerations of safety, PK, and Pd data generated in previous cohorts, and the model. Yet, if the sample size in Part B has to be increased to accommodate additional dose levels, a protocol amendment with rationale will be submitted prior to implementation. It is anticipated that 6 to 24 participants (3 to 6 participants at each dose level) may be needed.

Table 14 Example of Possible Dose Levels of M3814 in Combination with Radiotherapy and Avelumab (Part B)

Dose Level	M3814 Schedule[a] (mg; QD)	Total Daily M3814 Dose (mg)	Radiotherapy Schedule[b]	Avelumab Schedule[c]	Avelumab Dose (mg)
-1[d]	50	50	30 Gy as 3 Gy × 10 (5 F/W)	Q2W	800
1[e]	100	100	30 Gy as 3 Gy × 10 (5 F/W)	Q2W	800
2	200	200	30 Gy as 3 Gy × 10 (5 F/W)	Q2W	800
3	300	300	30 Gy as 3 Gy × 10 (5 F/W)	Q2W	800

DLT=dose-limiting toxicity, F/W=fractions/week, IV=intravenous, Pd= pharmacodynamic, PK=pharmacokinetic, Q2W=once every 2 weeks, QD=once daily, RT=radiotherapy, SMC=Safety Monitoring Committee.

Dose escalation will be based on the presence/absence of DLTs and study intervention-related clinically relevant adverse events during the DLT period. Available relevant safety data which occur during the RT Safety Follow-up at 1, 3, and 12 months. Available PK and Pd data will also be taken into consideration.

a M3814 will be administered once a day for 5 days followed by 2 days off for 10 days in total (i.e. to the same schedule as RT).

b Radiotherapy, 30 Gy is delivered as 3 Gy per fraction per day for 5 days followed by 2 days off for 10 days in total (i.e. to the same schedule as M3814).

c Avelumab will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels.

d Dose Level -1 can be evaluated upon decision of the SMC.

e Dose Level 1 is the starting dose.

6.6.5 Dosing Instructions

6.6.5.1 Part A (M3814 + Avelumab)

M3814: A 50 mg tablet for oral administration is used during the treatment phase. The starting dose will be 100 mg BID. Subsequent doses and schedules will be determined by the SMC.

For M3814 administrations, participants will be instructed as follows:

- For all treatment days, fast at least 1 hour prior to M3814 dose and continue fasting for at least 1 hour postdose for both morning and evening M3814 dose.
- Take the prescribed dose of M3814 at approximately the same time each day.

On days with scheduled PK collection visits, the morning dose should not be taken until the participant is admitted to the clinic/hospital and the morning (predose) PK collection has been completed.

If a participant misses taking a scheduled dose of M3814, it is acceptable to take the missed dose within a window of 5 hours. If more than 5 hours has passed after the scheduled dose time, the missed dose should not be taken, and the participant should be instructed to take the next dose at the next scheduled time. Any change from dosing schedule, dose interruptions, and dose reductions should be recorded in the eCRF.

On the day of avelumab administration, M3814 can be administered at any time before or after the end of avelumab infusion at home or clinic except on the days of M3814 PK collection where M3814 should be only taken in clinic after predose PK sample has been collected.

Avelumab: will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels. Guidance on premedication is given in Section 6.5.5.

6.6.5.2 Part B (M3814 + Radiotherapy + Avelumab)

M3814: 50 mg tablets for oral administration is used during the treatment phase. The starting dose of M3814 in the first cohort of participants is expected to be 100 mg total daily dose, given QD (i.e. 2-fold lower than in Part A). However, this starting dose might be adjusted by the SMC based on safety, PK, and Pd data generated during the first dose level in Part A and/or emerging data from the ongoing clinical studies involving M3814. M3814 will be given starting Day 1 for 5 days/week for 2 weeks.

For M3814 administrations, participants will be instructed as follows:

- For all treatment days, fast at least 1 hour prior to M3814 dose and continue fasting for at least 1 hour postdose.
- Take the prescribed tablets of M3814 1.5 hours (± 30 minutes) before each RT fraction is started.
- On the day of avelumab treatment (Day 1), M3814 can be taken at any time after the end of avelumab infusion as long as the above conditions are met.
- On days with serial PK collection (Day 1 and Day 12), the morning dose should not be taken until the participant is admitted to the clinic/hospital and the morning (predose) PK collection has been completed.
- On the day of avelumab treatment (Day 1), M3814 can be taken at any time after the end of avelumab infusion as long as the above conditions are met.

Avelumab: to be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels. Guidance on premedication is given in Section 6.5.5.

Radiotherapy: 3 Gy per fraction per day for 5 days a week for 2 weeks to a total dose of 30 Gy, starting Day 1 with M3814.

Multisite simultaneous RT is allowed:

- Up to 3 primary and/or metastatic lesions could be irradiated
- If more than one lesion is selected to be irradiated, symptomatic or clinically relevant primary tumors and/or metastases should be prioritized.
- All selected lesions should be irradiated the same day.

6.6.5.3 Part FE

M3814: A 50 mg tablet for oral administration is used during the treatment phase. The starting dose will be 100 mg BID. Subsequent doses and schedules will be determined based on PK and safety data.

For M3814 administrations, participants will be instructed as follows:

On Day 1 and Day 22, participants will be instructed to fast overnight for at least 8 hours followed by the meal provided at the site. M3814 should be administered within 30 minutes after the meal. The drug should be taken with approximately 240 mL (8 fluid ounces) of water. Additional water is allowed ad libitum except for 1 hour before and 1 hour after M3814 administration.

On Day 15, participants will be instructed to fast overnight for at least 8 hours followed by the M3814 administration at the site. The drug should be taken with approximately 240 mL (8 fluid ounces) of water. Additional water is allowed ad libitum except for 1 hour before and 1 hour after M3814 administration. Participants should not consume any food for at least 4 hours after the M3814 dose.

Composition of a high-fat diet: 800 to 1000 calories (protein [150 calories], carbohydrates [250 calories], fat [500 to 600 calories]). Example of high-fat diet: Two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, eight ounces of whole milk.

On days with scheduled PK collection visits, the morning dose should not be taken until the participant is admitted to the clinic/hospital and the morning (predose) PK collection has been completed.

If a participant misses taking a scheduled dose of M3814, it is acceptable to take the missed dose within a window of 5 hours. If more than 5 hours has passed after the scheduled dose time, the missed dose should not be taken, and the participant should be instructed to take the next dose at the next scheduled time. Any change from dosing schedule, dose interruptions, and dose reductions should be recorded in the eCRF.

On the day of avelumab administration, M3814 can be administered at any time before or after the end of avelumab infusion.

Avelumab: will be administered Q2W as an IV infusion over 1 hour, starting on Day 1, at a fixed dose of 800 mg in all dose levels. Guidance on premedication is given in Section 6.5.5.

6.6.5.4 Part A, Part B and Part FE

For **M3814** administrations, participants will be instructed as follows:

- Take the assigned tablets of M3814 with a full glass of water (approximately 240 mL/8 fluid ounces).
- Swallow the tablets whole and not bite into the tablets, break them, or attempt to dissolve the contents in water prior to taking their assigned dose.
- If the participant vomits within 1 hour of M3814 dose, no further PK sampling should be performed. The participant should be given an antiemetic, but no further dose will be given that day. Prophylactic antiemetics should then be given prior to subsequent doses of M3814. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

Each participant will stay on the avelumab assigned dose until the criteria for discontinuation are met (Section 7.1). Dosing modifications (changes in infusion rate and dose delays) as a result of AEs are described in Section 6.9.2.1. There will be no intraparticipant dose reductions for toxicity reasons.

6.6.6 Treatment Beyond Progression

6.6.6.1 Treatment Beyond Initial Progression

Participants will receive avelumab with or without M3814 in Part A and Part FE and avelumab in Part B as outlined in the Schedule of Activities (Section 1.3) until PD. Avelumab with or without M3814 in Part A and Part FE, and avelumab in Part B may continue past the initial determination of PD according to RECIST v 1.1 as long as the following criteria are met:

- Treatment with avelumab is ongoing,
- No new unacceptable treatment or disease-related toxicity,
- Tolerance of study interventions,
- Stable ECOG PS,
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with avelumab with or without M3814 in Part A and Part FE, and avelumab in Part B.

6.6.6.2 Treatment Beyond Confirmed Progression

Participants who experience PD may continue treatment with study interventions if the Investigator believes the participant will experience clinical benefit from the treatment and there

is no unacceptable toxicity resulting from the treatment. The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

If the participant continues with treatment after confirmed PD, they should remain on the study and continue to receive monitoring according to the Schedule of Activities (Section 1.3). Participants who continue beyond progression will be evaluated for further tumor response as per the protocol schedule.

Treatment should be discontinued permanently upon documentation of further, unequivocal, PD unless there are no alternative therapeutic options and the benefit-risk assessment is favorable in consultation between the Investigator and the Medical Monitor. In case of continuation of treatment beyond PD, treatment will be discontinued once any other criteria for withdrawal are met (see Section 7.1).

6.6.7 Continuation of Study Intervention After Local Treatment of Disease Progression

If PD is due to brain metastasis, participants may continue study interventions after the local treatment of the brain lesions with respect to the criteria defined in Section 6.5.4 and provided that the above criteria are met in addition to the following:

- Tumor assessment showing PD has been performed and was documented according to RECIST v 1.1. prior to the procedure.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to reinitiation of study interventions.
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of $\leq$ 10 mg daily prednisone (or equivalent).
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

In addition, if PD is mainly due to a metastatic lesion which in the opinion of the Investigator may be surgically removed, participants may continue study interventions after the local treatment of such a lesion provided that:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v 1.1. prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

6.7 Study Intervention After the End of the Study

After a participant 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 participant's individual medical needs. The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for participants with advanced malignancies.

6.8 Special Precautions

Avelumab

As a routine precaution, participants enrolled in this study must be observed for 1-hour post infusion for the first 4 infusions, in an area with resuscitation equipment and emergency agents. At all times during avelumab treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible hypersensitivity reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

The treatment recommendations for infusion-related reactions are outlined in Section 6.9.2.1.

Investigators should also monitor participants closely for potential irAEs, which may become manifest at any time during treatment. Such events include but are not limited to pneumonitis, hepatitis, colitis, endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, and type 1 diabetes mellitus), myocarditis, myositis, and rash. See Section 6.9.2.2 for details on the management of irAEs.

Investigators should also monitor participants closely for potential irAEs, which may become manifest earliest after weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. The spectrum of hypothetical irAEs also includes formation of auto antibodies like antinuclear antibodies or antineutrophil cytoplasmic antibodies. See Section 6.9.2.2 for details on the management of irAEs.

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Participants should be instructed to report any delayed reactions to the Investigator immediately.

M3814

In vitro studies suggest that CYP3A, CYP2C9, and CYP2C19 are involved in the metabolism of M3814. Using physiologically based PK modeling and simulation, potent inhibitors and inducers of CYP3A, CYP2C9, and CYP2C19 are predicted to have an influence on the PK of M3814. Therefore, foods (e.g. grapefruit and Seville oranges) or concomitant medications that are potent inducers or inhibitors of these enzymes should be used with caution. Participants will be instructed to avoid any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days before the first administration of the study intervention and during the study intervention administration.

The effect of M3814 on CYP3A-metabolized substrates is complex due to the time dependent inhibition and induction. It cannot be excluded that at high concentrations, M3814 affects the PK

of sensitive CYP3A substrates; therefore, sensitive CYP3A substrates with a narrow therapeutic index should also be used with caution and avoided if possible, during treatment with M3814. Drugs mainly metabolized by CYP2C9 with a narrow therapeutic index are to be used with caution and if possible, avoided during treatment with M3814.

The solubility of M3814 is pH dependent; therefore, antacid drugs and proton pump inhibitors might affect absorption (Section 6.5).

Drugs which are substrates of P-glycoprotein (P-gp) (e.g. dabigatran etexilate, digoxin), breast cancer resistance protein (BCRP) (e.g. rosuvastatin, sulfasalazine), or organic cation transporter 1 (OCT1) (e.g. metformin) with a narrow therapeutic index are to be used with caution. The Investigator may decide not to include a participant in the study, if the participant cannot be withdrawn from the drugs that have a narrow therapeutic index and that are known to be substrates of P-gp, BCRP, or OCT1; if the Investigator decides to enroll a participant who is treated with a drug that is known to be substrate of P-gp, BCRP, or OCT1 and has a narrow therapeutic range, close safety monitoring is advised.

The study will be performed in a study unit with direct access to a Hospital Emergency Unit. Equipment and medications, such as epinephrine and prednisolone equivalents, will be available at the study site for the treatment of emergencies.

Radiotherapy

Refer to Appendix 8 for details of RT.

6.9 Management of Adverse Events of Interest

6.9.1 Adverse Drug Reactions Requiring M3814 Treatment Discontinuation or Modifications

Part A and Part FE (M3814 + Avelumab)

There is no dose reduction allowed for M3814 or avelumab during the DLT period or the FE Assessment Period. The study intervention can only be discontinued due to toxicity. Details on criteria for discontinuation of study interventions are in Section 7.1.

After the DLT and the FE Assessment Period, if not tolerated, treatment with M3814 may be interrupted, modified or stopped at the Investigator's discretion.

Where a SAE (Grade ≥ 3) is believed to be due to M3814, M3814 will be withheld until the SAE has resolved to Grade ≤ 2. On subsequent cases of the same SAE, permanent dose reductions in 50 mg steps must be done.

In case of a nonserious AE Grade 3, assessed by Investigators as related to M3814, a dose reduction should be considered.

In the case of participants vomits within 1 hour of M3814 dose, please see Section 6.6.5.4.

If M3814 50 mg BID is not tolerated, M3814 will be stopped. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

If avelumab treatment is discontinued while M3814 treatment is ongoing, M3814 treatment could be continued if the Investigator believes the participant is experiencing clinical benefit from M3814 treatment.

Part B (M3814 + Radiotherapy + Avelumab)

The formal criteria for M3814 and RT dose modification are presented in Table 15.

Early and late toxicities related to RT and/or M3814 will be managed according to the local institute's guidelines.

Table 15 Dose Modifications for M3814 and Radiotherapy During Part B of the Study

Toxicity	Dose Modifications[a]	
	M3814[b]	Radiotherapy[c]
Toxicities in Radiation Field Grade ≥ 3 • Mucositis • Radiation dermatitis	Temporarily interrupt treatment. Resume treatment once severity resolves to Grade ≤ 2	Temporarily interrupt treatment. Resume treatment once severity resolves to Grade ≤ 2
Systemic Toxicities • Hematologic Toxicities: - Any Grade ≥ 4 toxicity, excluding: o Grade 4 neutropenia lasting for ≤ 5 days and not associated with fever o Isolated Grade 4 lymphocytopenia without clinical correlate • Febrile neutropenia • Grade 3 thrombocytopenia with medically concerning bleeding	Temporarily interrupt treatment. Resume treatment (at the same dose) once severity resolves to Grade ≤ 1 or Baseline. In case of a second recurrence, permanently discontinue study intervention.	No action to be taken.
Systemic Toxicities • 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 outside 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. In case of a second recurrence, permanently discontinue study intervention. In case of Grade ≥ 3 liver enzyme values, the participant must be monitored at least every 4 days until recovery to Grade ≤ 2.	No action to be taken.

Toxicity	Dose Modifications[a]	
	M3814[b]	Radiotherapy[c]
• Treatment-related hepatocellular injury for more than 3 days, such as Grade ≥ 3 ALT or AST with or without elevation of serum total bilirubin to > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) or other apparent clinical causality.		

AE=adverse event, ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events, RT=radiotherapy, ULN=upper limit of normal.

Severity of AEs will be graded using the CTCAE (v 5.0) toxicity grades.

a Upon the Investigator decision and once discussed with the Sponsor.

b As all treatments with M3814 will be given in combination with RT, an interruption in the administration of RT would lead to an interruption in treatment with M3814.

c A maximum RT delay of up to and including 7 days in total is allowed within the complete treatment period. If RT and M3814 treatment have to be delayed by more than 7 days, the participant must be discontinued from M3814 (unless the participant derives a clinical benefit from the study intervention).

Within Part B of this study, a maximum delay of M3814 and/or RT up to and including 7 days in total is allowed within the complete treatment period. If RT and M3814 treatment have to be delayed by more than 7 days, the participant must be discontinued from study intervention unless the Investigator feels that the participant continues to achieve clinical benefit by continuing avelumab according to the study schedule, in this case the participant should be replaced for DLT assessment but could remain on the study and continue to receive monitoring according to the Schedule of Activities (Section 1.3).

If 50 mg QD is not tolerated, M3814 will be stopped. Any change from dosing schedule, dose interruptions, or dose reductions should be recorded in the eCRF.

6.9.2 Adverse Drug Reactions Requiring Avelumab Treatment Discontinuation or Modifications

Treatment with avelumab should be permanently discontinued, if any of the following ADRs occurs:

- Any Grade 4 ADRs:
  - Permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlate.
- Any Grade 3 ADRs:
  - Withhold avelumab except for laboratory values out of normal range that do not have any clinical correlate.
  - Permanently discontinue avelumab if toxicity does not resolve to Grade ≤ 1 or Baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the Medical Monitor before permanently discontinuing the treatment).

If dosing is delayed more than 4 weeks, treatment may be resumed after consultation with the study Medical Monitor. Any delay in dosing in excess of 12 weeks is not permitted.

Infusion-related reactions and irAEs should be handled according to guidelines in Section 6.9.2.1.

6.9.2.1 Management of Infusion-Related Reactions

To mitigate infusion-related reactions associated with avelumab, participants have to be premedicated with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and the presence/severity of prior infusion reactions.

Management of symptoms should follow the guidelines shown in Table 16.

Table 16 Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the participant. • Participants have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

IV=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

6.9.2.2 Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of irAEs should follow guidelines as shown in Table 17.

Table 17 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate participant to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5 to 7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy. Symptomatic therapy (for example, antihistamines, topical steroids)	If Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.

Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life-threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

Pulmonary irAEs

Grade of Pneumonitis	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Reassess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Reassess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).

Hepatic irAEs

Grade of Liver Test Elevation	Initial Management	Follow-up Management
Grade 1 Grade 1 AST or ALT > ULN to 3.0 × ULN and/or Total bilirubin > ULN to 1.5 × ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.

Grade 2 AST or ALT > 3.0 to ≤ 5 × ULN and/or total bilirubin > 1.5 to ≤ 3 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 × ULN and/or total bilirubin > 3 × ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increase 1.5 × baseline or creatinine increased > ULN to 1.5 × ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 × baseline and ≤ 6 x ULN or creatinine increased > 1.5 and ≤ 6 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 × ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and/or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult. [a] Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, restart avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.[a] 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

[a] Local guidelines, or e.g. ESC or AHA guidelines
PPD
AHA guidelines website:
PPD

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), antithyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule out secondary endocrinopathies (i.e. hypopituitarism/hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), antithyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule out secondary endocrinopathies (i.e. hypopituitarism/hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone) • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month. • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Other irAEs (not described above)		
Grade of other irAEs	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider restarting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

ADL=activities of daily living, AHA=American Heart Association, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BNP=B-type natriuretic peptide, CK-MB=creatine kinase MB, CT= computed tomography, ESC=European Society of Cardiology, FSH=follicle-stimulating hormone, GH=growth hormone, IGF-1=insulin-like growth factor 1, irAE=immune-related adverse event, IV=intravenous, LH=luteinizing hormone, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, PRL=prolactin, T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

6.9.3 Radiotherapy

6.9.3.1 Management of Adverse Drug Reactions for Radiotherapy

Toxicities related to RT will be managed according to the local institute's guidelines. More details on the treatment of most frequent radiation AEs are outlined in Appendix 8.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

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

- Participants meeting the definition of confirmed PD while on treatment based on RECIST v 1.1. (**Note:** participants who experience confirmed PD may continue treatment with study drugs in the conditions described in Section 6.6.7). Such participants will be withdrawn from the treatment if any other criteria for withdrawal are met or if alternative treatment options are available and indicated.
- Occurrence of an exclusion criterion which is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent additional therapeutic intervention (if applicable, see allowable local treatment in Section 6.5).
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- Occurrence of AEs that require discontinuation of study intervention as judged by the Investigator and/or the participant (if applicable).
- Occurrence of any clinically significant and study-intervention-related Grade ≥ 3 nonhematologic or Grade ≥ 4 hematologic ADRs or as described in Section 6.6.3.
- Use of a nonpermitted concomitant drug, as defined in Section 6.5.3, where the predefined consequence is withdrawal from the study intervention(s).
- New approved therapy that is considered more suitable according to the Principal Investigator.
- Noncompliance as defined in Section 6.4 only if the benefit-risk assessment for continuation of study interventions is negative in the individual case as per Investigator judgment.
- Request of the participant to discontinue study intervention. Participants will be followed on the study according to schedule except in case of withdrawal of consent.
- If the benefit-risk assessment for continuation of treatment is negative according to Investigator assessment.
- Adverse drug reactions that cause RT delays of > 7 days or discontinuation of RT **(for Part B only)**.
- Pregnancy.

Participants who come off treatment must be followed on study including completion of all study assessments, most importantly tumor assessments until confirmed disease progression, and resolution of toxicity or discontinuation of the study.

Participants may be withdrawn from one of the study interventions, e.g. in case of intolerance or toxicity clearly attributable to a specific study intervention. Participants who are partially withdrawn from one of the study interventions and continue to achieve clinical benefit may continue with the other study interventions according to schedule until the protocol-defined criteria for discontinuation from treatment are met.

If avelumab treatment is discontinued while M3814 treatment is ongoing, M3814 treatment could be continued if the Investigator believes the participant is experiencing clinical benefit from M3814 treatment.

The Schedule of Activities specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Rechallenge

Rechallenge with study intervention after discontinuation due to AEs is allowed as defined in Section 6.9.

If participants discontinue the study intervention for a confirmed CR, one reinitiation of study intervention is permitted. If a participant does reinitiate, study intervention should resume using the same treatment regimen the participant was receiving prior to discontinuation, unless the Investigator decides to reinitiate avelumab only.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to discontinue the study at any time without giving their reasons.

Part A, Part B, and Part FE:

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

In Part B only, participants must be withdrawn prior to initiation of study intervention in the event of either of the following:

- A participant with confirmed esophagitis for whom the radiation PTV includes any portion of the esophagus.

- A participant for whom more than 10% of the total esophagus volume receives more than 15 Gy (50% of the prescribed RT dose), based on the radiation PTV.

If a participant has failed to attend scheduled study activities, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the study, the investigations scheduled for the End of Treatment Visit should be performed, with focus on the most relevant assessments. In any case, the appropriate eCRF section must be completed.

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

Participants who are not DLT evaluable will not formally be replaced.

7.3 Lost to Follow Up

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

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

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

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Activities.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for Screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments and Procedures

No primary efficacy endpoints have been planned for this study. The following secondary efficacy endpoints will be assessed: BOR, duration of response, PFS, and OS.

8.1.1 Clinical Assessments

8.1.1.1 Tumor Response Assessment

Computed tomography (CT)/magnetic resonance imaging (MRI) scans will be performed and collected until confirmed disease progression is assessed by the Investigators according to RECIST v 1.1 or the start of new cancer therapy.

Radiographic images and physical findings (physical assessments) will be used by the Investigators for the local determination of disease progression and participant's treatment decisions.

For each participant, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual participant. 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. Tumor assessments will be performed at Screening (up to 28 days before start of study intervention treatment for Part A and Part FE and up to 35 days before start of study intervention treatment for Part B), and then Q8W for 6 months. After 6 months, tumor assessments will be Q12W until PD or the end of the study.

For each participant, the Investigator will designate one or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the study period will be considered. The most appropriate measures to evaluate the tumor status of a participant should be used. The measure(s) to be chosen for

sequential evaluation during the study must correspond to the measures used to document the progressive tumor status that qualifies the participant for enrollment. The tumor response assessment will be assessed and listed according to the Schedule of Activities (Table 1, Table 2, Table 3, and Table 4).

Treatment decisions will be made by the Investigator based on the Investigator's assessment of disease status. Investigator's assessment of objective tumor response to treatment will be performed according to RECIST v 1.1 (all measurements should be recorded in metric notation, as described in RECIST v 1.1).

At Baseline, tumor lesions will be categorized in target and nontarget lesions as described in RECIST v 1.1.

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any CR or PR or PD should be confirmed, preferably at the next subsequent scheduled imaging interval, but no sooner than 4 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR.

The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if the Investigator suspects PD. Participants who withdraw from the study intervention for clinical or symptomatic deterioration before objective documentation of PD or who discontinue from study intervention for reasons other than objective disease progression will be requested to continue appropriate imaging according to the study schedule until determination of confirmed PD or discontinuation of the study, whichever occurs earlier. Every effort should be made to confirm a clinical diagnosis of PD by imaging.

8.1.1.2 Survival Follow-up

Participants without PD according to RECIST v 1.1 at the End of Treatment Visit will be followed up for disease progression (CT/MRI scans Q8W calculated from Day 1, and after 6 months Q12W, using the same procedures and review as while on treatment) until PD. In the case of PD with discontinuation of treatment, any subsequent local tumor assessments should be documented. Any subsequent anticancer therapies and the date of any response and subsequent progression should be captured in the eCRF.

At EoT/long-term FU, tumor assessment is not required if participant has progressed or has started a new treatment.

Participants will be followed every 12 weeks (± 1 week) for survival (including assessment of any further antitumor therapy). The survival follow-up will continue until 1 year after the last participant receives the last dose of study intervention, or the last participant dies, whichever occurs first.

8.2 Safety Assessments and Procedures

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

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting AE and SAE Information). Due to the combined administration of treatments in this study, it is important that the Investigator carefully review and attempt to differentiate causality of AEs (for avelumab or M3814 in Part A and Part FE, and for avelumab or M3814 or RT in Part B) to ensure appropriate toxicity treatment recommendations.

Blood samples for the tests listed in Appendix 6 will be taken from nonfasted participants during the Screening period (Day -28 to Day -1) for Part A/Part FE and (Day -35 to Day -1) for Part B, the Treatment period, the EoT Visit, and at the 30-day Safety Follow-up at the time points specified in the Schedule of Activities for each part of the study (Table 1, Table 2, Table 3, and Table 4).

8.2.1 Physical Examinations

A complete physical examination will be conducted as indicated in the Schedule of Activities (Section 1.3). At other visits, either a complete physical examination or symptom-oriented physical examination if deemed necessary by the Investigator will be conducted as indicated in the Schedule of Activities (Section 1.3) and documented in the eCRF. Abnormal findings are to be reassessed at subsequent visits.

- A complete physical examination will include, at a minimum, assessments of the head/neck, extremities, eyes, ears, nose, throat, cognitive status, general appearance, dermatological, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, neurologic and musculoskeletal systems. Height (at Screen) and weight will also be measured and recorded.
- A brief physical examination (i.e. a symptom-oriented physical examination) will include, at a minimum, assessments of those systems that are tailored to the participant's symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

In addition, after the Baseline visit **in Part B only**:

- The physical exam will report findings in the irradiated area during all RT FU periods.

8.2.2 Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, respiratory rate, and pulse oximetry. Three readings of blood pressure and pulse will be taken. The first reading should be rejected.

The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

8.2.3 Electrocardiograms

12-lead ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and Fridericia's Correction Formula (QTcF) intervals. Refer to Section 7 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary. 12-lead ECGs will be in triplicate in Part A and Part FE but not Part B.

For Part A and Part FE, at each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Electrocardiograms will be recorded after the participant has been in a supine position breathing quietly for at least 5 minutes.

In Part A and Part FE: Assessments should be performed predose and 1, 2, and 6 hours postdose before blood collection for PK, Pd, and pharmacogenomic sampling, with a triplicate 12-lead ECG being performed first, followed by vital signs after the morning dose only. The schedule times may be modified based on emergent PK data.

8.2.4 Esophageal Endoscopy

In Part B only: If the radiation fields involve the esophagus, an esophageal endoscopy must be performed at Screening in case of active esophagitis or clinical signs of esophagitis.

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6, at the time points listed in the Schedule of Activities. All samples should be clearly identified. Further details will be provided in the Laboratory Manual.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

The tests will be performed by the local laboratory.

The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor.

The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The most recent results for complete hematology and core chemistry must be available and reviewed prior to avelumab dose administration.

In case of liver function test elevations (AST, ALT, and/or total bilirubin) requiring additional laboratory draws (according to guidelines set forth in Table 17), an unscheduled laboratory draw should be sent to the central laboratory for analysis.

Blood samples will be drawn, processed, and stored in accordance with directions provided in the Study Manual and as per timing shown in the Schedules of Assessments (Table 1, Table 2, Table 3, and Table 4).

The report of the results must be retained as a part of the participant's medical record or source documents. Blood samples for the full safety tests listed in Appendix 6 will be taken from nonfasted participants as detailed in the Schedules of Assessments (Table 1, Table 2, Table 3, and Table 4). The free T4, TSH, and urinalysis will only be assessed at the time points defined in Table 1, Table 2, Table 3, and Table 4. If confirmation of a participant's postmenopausal status is necessary, a follicle-stimulating hormone (FSH) level will also be performed at Screening.

For women of childbearing potential, pregnancy testing (serum β-HCG) will be performed during the Screening period and pregnancy testing (urine β-HCG) at the visits specified in the Schedule of Activities (Section 1.3). Participants after menopause (age-related amenorrhea ≥ 12 consecutive months and a high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient) or participants who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing.

If a participant has a clinically significant abnormal laboratory test value that is not present at Baseline, the test will be repeated weekly and the participant will be followed until the test value has returned to the normal range or the Investigator has determined that the abnormality is chronic or stable.

8.2.6 Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at Screening to assess eligibility (Section 5), and then reassessed according to the Schedule of Activities (Table 1, Table 2, Table 3, and Table 4).

8.2.7 Safety Monitoring Committee

An SMC will regularly review the safety data of participants enrolled in Part A and Part B of this study. It will decide on relevant DLTs based on criteria defined in the protocol and will provide recommendation by consensus on dose escalation, dose de-escalation, or suspension of enrollment and/or declaration of the MTD and/or the RP2D. Further details on the SMC can be found in Appendix 2. Definitions of DLTs are provided in Section 6.6.3, dose escalations rules are presented in Section 6.6.4, and analysis of DLTs is described in Section 9.4.2.

In addition, SMC will review the entire PK and safety data generated in Part FE once the last planned dose/last cohort is completed.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE are in Appendix 4, as is the definition of an Adverse Event of Special Interest (AESI).

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the last Long-term Follow-up Visit.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

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

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and all nonserious AEs of special interest must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and SAE Information) and are assessed for their outcome at the last Long-term Follow-up Visit. All SAEs ongoing at the last Long-term Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4 (AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

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

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

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g. resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting AE and SAE Information) must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting SAEs and AEs of Special Interest and Dose-Limiting Toxicities.

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

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains

an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

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

8.4 Treatment of Overdose

For this study, any dose of avelumab greater than 10% above the dose for that particular administration, and/or any dose of M3814 greater than that specified in this clinical study protocol, will be considered an overdose.

There are no known symptoms of avelumab or M3814 overdose to date. The Investigator should use his or her clinical judgment when treating an overdose of the study intervention. Even if it not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting SAEs and AEs of Special Interest and Dose-Limiting Toxicities.

8.5 Pharmacokinetics

The following PK parameters will be calculated, when appropriate, for M3814 and avelumab, where data permit:

Symbol	Definition
AUC_{0-t}	AUC from time of dosing to the time of the last observation
$AUC_{0-\infty}$	AUC from time of dosing to infinity
C_{max}	Maximum serum (avelumab) / plasma (M3814) concentration observed postdose
C_{min}	Minimum serum (avelumab) / plasma (M3814) concentration observed postdose
C_{avg}	Average serum (avelumab) / plasma (M3814) concentration observed postdose
t_{max}	Time to maximum concentration observed postdose
$t_{1/2}$	Apparent elimination half-life
λ_z	Terminal rate constant
CL/f	Oral clearance
Vz/f	Apparent volume of distribution during terminal phase
$R_{acc}[AUC]$	Accumulation ratio for AUC
$R_{acc}[C_{max}]$	Accumulation ratio for C_{max}
Fluctuation index	Fluctuation between maximum and minimum concentrations
$F_{rel,\ Fed/Fasted}$	Relative bioavailability of M3814 after a breakfast versus after an overnight fast (only for Part FE)

- Whole blood samples of approximately 2.0 mL will be collected for measurement of plasma concentrations of M3814, as specified in the Schedule of Activities (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.
- The quantification of M3814 in plasma will be performed using a validated liquid chromatography/mass spectrometry assay. Concentrations will be used to evaluate the PK of M3814.
- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of avelumab, as specified in the Schedule of Activities (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.
- The quantification of avelumab in serum will be performed using a validated immunoassay. Concentrations will be used to evaluate the PK of avelumab.
- Remaining samples collected for analysis of avelumab serum concentration may also be used to evaluate immunogenicity and safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and shipment of these samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- These samples may also be used for evaluations of metabolites of M3814, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic

pathways used by or affected by. In addition, PK samples may be stored for future analyses of protein binding, other protein related analyses, biochemistry, biomarker, and metabolite profiling.

- The PK sampling schedule may be modified upon agreement of the clinical pharmacologist and Investigators to optimize the sampling time for M3814 disposition (Table 5, Table 6, and Table 7).
- All efforts will be made to obtain the PK samples within acceptable window of exact nominal time relative to dosing (see Table 18 and Table 19). Actual time of dosing and PK sample collection times must be documented by the site. Details of the sampling and processing procedures, storage, and transportation will be provided in a separate Laboratory Manual.
- The PK and antidrug antibody (ADA) samples collected for avelumab at the same predose time points may be used interchangeably if the dedicated sample has insufficient quantity as the participants will have consented to all collections and tests.

Table 18 Acceptable Pharmacokinetic Windows for Avelumab

Sampling Time	Time From Scheduled Sampling Allowed
Before BOI	Within 120 minutes prior to dose
EOI	Within 15 minutes before EOI

BOI=beginning of infusion, EOI=end of infusion.

Table 19 Acceptable Pharmacokinetic Windows for M3814

Sampling Time	Time From Scheduled Sampling Allowed
Predose	within 60 minutes prior to dose administration
0.5 to 2 hours postdose	± 20 minutes
> 2 hours postdose	± 30 minutes

CCI [redacted]

[redacted]

CCI

CCI

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Whole blood samples of approximately 3.5 mL will be collected for detection of antibodies against avelumab in serum, as specified in the Schedule of Activities (Section 1.3). Samples will be collected prior to any avelumab administration on the same study day.

The detection of antibodies to avelumab will be performed using a validated immunoassay method. Confirmed positive antibodies may be further characterized.

CCI [redacted]

Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

9 Statistical Considerations

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

CCI [redacted]

[redacted]

[redacted]

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Analysis Population	Description
Enrolled	All participants who sign informed consent
Dose Escalation Analysis Set	**Part A**: All participants who have received at least 34 of 42 daily doses of M3814 and 2 administrations of avelumab and complete the DLT period. The Dose Escalation Analysis Set will also include participants treated in dose escalation cohorts who experience a DLT during the DLT period, regardless of the amount of each study intervention received/completion of the DLT period. **Part B**: All participants who have received at least 8 of 10 daily doses of M3814 and 3 administrations of avelumab and 8 fractions (24 Gy) of RT and complete the DLT period. The Dose Escalation Analysis Set will also include participants treated in dose escalation cohorts who experience a DLT during the DLT period, regardless of the amount of each study intervention received/completion of the DLT period.
Full Analysis Set /Safety Analysis Set	**Part A, Part B, and Part FE:** All participants who receive at least one dose of study intervention.
Pharmacokinetic	**Part A and Part FE**: All participants who complete 1 administration of M3814 and avelumab starting on Day 1 and who provide at least 1 postdose sample with measurable concentrations of M3814. **Part B**: All participants who have received at least the first dose of M3814 and provided PK samples as per protocol for at least 6 hours following first dosing on Fraction Day 1.
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Immunogenicity (ADA) Population	**Part A, Part B, and Part FE**: All participants who complete at least 1 administration of M3814 and avelumab, and who have at least one valid ADA result.

ADA=antidrug antibody, ADME=absorption, distribution, metabolism, and excretion, CCI [redacted] DLT=dose-limiting toxicity, ctDNA=circulating tumor DNA, CCI [redacted] PK=pharmacokinetic, RT=radiotherapy.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Confirmed BOR rate, defined as the proportion of participants having achieved confirmed CR or PR as BOR, according to RECIST v 1.1 assessed by Investigator (from the first dose of study intervention until disease progression, death from any cause, or last tumor assessment). PFS time, defined as the time (in months) from first treatment day to the date of the first documentation of objective PD according to RECIST v 1.1 assessed by Investigator, or death due to any cause, whichever occurs first. OS time, defined as the time from first treatment day to the date of death due to any cause. For time-to-event analyses, the Kaplan-Meier estimates will be provided. The confidence interval for the median will be calculated according to Brookmeyer and Crowley 1982. All analyses for secondary endpoints will be performed on the Full Analysis Set unless otherwise specified.

BOR=best overall response, CR=complete response, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PR=partial response, RECIST=Response Evaluation Criteria In Solid Tumors.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population.

Endpoint	Statistical Analysis Methods
Primary	Occurrence of DLTs (descriptive tabulation) – Dose Escalation Analysis Set
Secondary	Occurrence of TEAEs and treatment-related AEs, treatment-related Grade ≥ 3 AEs, irAEs, and RT-induced toxicity according to NCI-CTCAE v 5.0, occurrence of abnormalities (Grade ≥ 3) in laboratory test values, serious adverse events. (descriptive tabulation) – Safety Analysis Set
Tertiary/Exploratory	Not applicable.

AE=adverse event, DLT=dose-limiting toxicity, irAEs=immune-related adverse events, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, TEAE=treatment-emergent adverse event.

Analysis of Primary Endpoint (Part A and Part B)

For the dose escalation part, the analysis will focus on the number of participants experiencing a DLT. The SMC will receive results of a Bayesian two-parameter logistic model with overdose control updated with the observed DLT data.

The recommended dose level from the Bayesian model for the next cohort is the dose with the lowest loss function:

1 × P(under dosing (0% to 20%) + 0 × P(target dosing (> 20% to 33%)) + 1 × P(over dosing (> 33% to 60%) + 2 × P(excessive dosing (>60%))

In addition, only doses that have a corresponding probability of less than 25% that the true DLT rate is more than 33% (overdose control) are recommended by the model. This Bayesian escalation approach will be used to assist the SMC to select the next dose from a predicted set of acceptable doses (Section 2.1). The SMC may choose a different dose or dosing regimen than suggested by the Bayesian escalation approach.

If the SMC decides to change the dosing regimen, a separate model will be set up or the model extended to a partial order Continual Reassessment Method.

Only participants included in the Dose Escalation Analysis Set will be considered in the Bayesian model. Participants who are not DLT evaluable will not formally be replaced. The SMC can still meet, and the Bayesian model will be updated with the data from the evaluable participants. In exceptional cases the SMC may decide (based on available data) upon enrolment and dose for the next dosing cohort before all participants in a cohort have completed the DLT period. The full data of such delayed participants will be considered at the next SMC. For each SMC review at least 2 DLT evaluable participants should be available.

The relationship between dose and toxicity rate in the two-parameter logistic regression model is defined by:

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

where d_j is the dose at level i, d_{ref} the reference dose and (α, β) are bivariate normally distributed.

The model for Part A will be specified in the SMC charter before first patient in (FPI) and for Part B after the starting dose for the second part of this study is determined (but also before FPI in the second part).

Posterior distribution and the recommended next dose level will be calculated using R Version 3.1.2 or higher with library package bcrm (Bayesian Continual Reassessment Method) or package CRMpack or EAST Version 6.4 or higher.

At interim analysis, after the end of dose escalation, and main analysis, the number and proportion of participants experiencing DLTs will be reported by dose level, based on observations during the DLT period. Posterior probabilities (2.5%, 25%, 50%, 75%, and 97.5% quintiles) for DLT probabilities at selected doses will be estimated from the model.

The Dose Escalation Analysis Set will be used for this analysis.

Part FE: Not applicable.

Adverse Events

All safety analyses will be performed on the Safety Analysis population.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0 or higher. The severity of AEs will be graded using NCI-CTCAE v 5.0 toxicity grades. Adverse events related to study intervention will be defined as any AE considered related to any study intervention. In addition, missing classifications concerning study intervention relationships will be considered related to the study intervention(s).

Adverse events observed from the first dose until 30 days after last study intervention administration (i.e. TEAEs) will be summarized according to MedDRA system organ classes and preferred terms. The incidence and type of the following will be analyzed:

- TEAEs and SAEs
- TEAEs and SAEs related to study intervention
- TEAEs with NCI-CTCAE Grades ≥ 3
- TEAEs related to study intervention with NCI-CTCAE Grades ≥ 3
- AEs leading to withdrawal, dose modifications, or permanent study intervention discontinuation
- Deaths.

Participants who terminate treatment will be displayed in a by-participant listing and summarized by primary withdrawal reason.

All reported deaths after first dose of study intervention as well as reasons for death will be tabulated (for all participants enrolled). Deaths within 30 days from last dose administration and deaths beyond this period up to 90 days follow-up and reasons for them will also be tabulated.

Laboratory Variables

Laboratory results will be classified by grade according to NCI-CTCAE v 5.0. The worst on-study grades after the first study intervention will be summarized.

Shifts in toxicity grades from first treatment to highest grade will be displayed. Results for variables that are not part of NCI-CTCAE will be presented as below, within, or above normal limits. Only participants with postbaseline laboratory values will be included in these analyses.

Physical Examination

Physical examination, including vital signs (body temperature, respiratory rate, heart rate, and blood pressure), and 12-lead ECG, recorded at Baseline and after administration of study intervention will be presented.

Further details will be provided in the Integrated Analysis Plan.

9.4.3 Other Analyses

General Considerations

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

- Continuous variables: number of nonmissing observations, mean, standard deviation, median, minimum, and maximum, 95% confidence intervals for the mean, as appropriate.
- Categorical variables: frequencies and percentages.
- The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the study Integrated Analysis Plan.
- Participants will be summarized by dose level for Part A, Part B, and Part FE.

Baseline

In general, the last nonmissing measurement prior to the first study intervention will serve as the Baseline measurement.

Estimation of Individual PK Parameters:

- PK, immunogenicity, pharmacodynamic, and biomarker exploratory analyses will be specified in the Integrated Analysis Plan finalized before database lock. Integrated analyses across studies, such as the population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).
- Noncompartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® Version 6.3, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows Version 9.1 or higher) may be used to produce tables, listings and figures and in the calculation of PK Parameters if appropriate.

PK concentrations of avelumab, M3814, and/or metabolites will be summarized descriptively and may be pooled with data from other studies to conduct population PK analysis.

Full PK, pharmacodynamic, and biomarker exploratory analyses will be specified in the Integrated Analysis Plan finalized before database lock. The population PK analysis, if conducted, and pharmacodynamic analyses will be presented separately from the main CSR.

ADA/Immunogenicity

Individual participants will be categorized across all valid ADA results as ever-positive versus never-positive. ADA ever-positive participants will be further categorized as pre-existing, including treatment-boosted, versus treatment-emergent. ADA treatment-emergent participants will be further subdivided into transient positive and persistent positive.

9.4.4 Sequence of Analyses

Interim and Additional Planned Analyses

This is an exploratory study. Available data will be evaluated during the study by the SMC.

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

The cut off for an exploratory main analysis of the safety and preliminary antitumor activity data from the complete dose escalation will be triggered when all participants in Part A and Part B reaches the first on-treatment tumor assessment or experiences death or premature withdrawal for any reason, whichever comes first.

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11 Appendices

Appendix 1 Abbreviations

ADA	Antidrug Antibody
ADR	Adverse Drug Reactions
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistance Protein
BED	Biologically Effective Dose
BID	Twice Daily
BOR	Best overall response
CR	Complete Response
CRO	Contract Research Organization
CRT	Chemoradiotherapy
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated Protein 4
DDR	DNA damage repair
DLT	Dose-Limiting Toxicity
DSB	Double-strand Break
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FE	Food Effect
FFPE	Formalin-fixed Paraffin-embedded
FIH	First In Human
FPI	First patient in
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
CCI	[redacted]
HR	Homologous recombination
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMRT	Intensity-Modulated Radiation Therapy

IR	Ionizing Radiation
irAE	Immune-related adverse event
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
OCT1	Organic Cation Transporter 1
OS	Overall Survival
PE	Physical examination
CCI	[redacted]
PD	Progressive Disease
PD-L1	Programmed death-ligand 1
PFS	Progression-free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPI	Proton pump inhibitor
PR	Partial Response
PVT	Planning Target Volume
Q2W	Once every 2 weeks
QD	Once Daily
QTcF	Fridericia's Correction Formula
RECIST v 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RILT	Radiation-Induced Lung Toxicities
RP2D	Recommended Phase II Dose
RT	Radiotherapy
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
TEAE	Treatment-emergent Adverse Events
ULN	Upper limit of normal
WOCBP	Woman of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally authorized representative (an individual or judicial or other body authorized to consent on behalf of a prospective participant under applicable law to the participant's participation in the procedure(s) involved in the research) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; International Council for Harmonisation (ICH) guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be reconsented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- CCI [redacted]
- A participant who is rescreened is not required to sign another ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

Approximately 5 study sites in the USA will take part in this study. Sites in the EU may also be opened.

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

The study will appear in the following clinical studies registries: ClinicalTrials.gov.

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

Safety Monitoring Committee

The Safety Monitoring Committee (SMC) consists of core (voting) members from the Sponsor (Global Patient Safety Product Leader [Chair], Medical Responsible, Clinical Pharmacologist and Biostatistician), the Coordinating Investigator, and (if applicable) the Medical Monitor of the Contract Research Organization (CRO). Ad hoc members may be invited as needed (if deemed necessary).

The SMC will regularly review the safety data of participants enrolled in any part of this study. It will decide on relevant Dose-Limiting Toxicities (DLTs) based on criteria defined in the protocol and will provide recommendation by consensus on dose escalation, dose de-escalation, or suspension of enrollment and/or declaration of the Maximum Tolerated Dose (MTD) and/or the RP2D.

CCI [redacted]

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
    - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations

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

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard process established for Investigators.

  When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator.

Publication

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

Dissemination of Clinical Study Data

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

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

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

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

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or

electronically signing the electronic Case Report Form (eCRF). Details for managing eCRFs are in the Operations Manual.

- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
    - Participant's full name, date of birth, sex, height, and weight
    - Medical history and concomitant diseases
    - Prior and concomitant therapies (including changes during the study)
    - Study identifier (i.e. the Sponsor's study number) and participant's study number
    - Dates of entry into the study (i.e. signature date on the informed consent) and each visit to the site
    - Any medical examinations and clinical findings predefined in the protocol
    - All AEs
    - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

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

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the first site is opened and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound

Appendix 3 Contraception

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

A WOCBP is **not**:

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

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

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

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a 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.

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

Periodic abstinence (calendar, symptothermal, 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 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

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

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

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

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), Version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

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

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

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

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

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will

not be recorded as separate event. Only, if no cause of death can be reported (e.g. sudden death, unexplained death), the death per se might then be reported as an SAE.

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

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

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

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

Serious Adverse Events

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

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

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

Events that Do Not Meet the Definition of an SAE

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

Events Not to Be Considered as AEs/SAEs

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

AE/SAEs Observed in Association with Disease Progression

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

Adverse Events of Special Interest

Avelumab

Immune-related adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies [thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders]), immune-related nephritis and renal dysfunction and other immune-related AEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis, pancreatitis, and myasthenia gravis/myasthenic syndrome) have been identified as Adverse Event of Special Interest (AESI) for avelumab.

Any AE that is suspected to be a potential immune-related adverse reaction will be considered an AESI. These AESI do not require expedited reporting unless they are serious. Should the AESI be serious, a SAE form should be filled and the reporting process for SAEs should be followed.

M3814

No AESI have been defined for M3814 to date.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE

onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT this is documented accordingly.

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

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 of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (e.g. medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g. laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

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

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

Adverse Events of Special Interest

AESI do not require expedited reporting unless they are serious. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

Dose-Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.6.3, must be recorded in the eCRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments

During treatment with avelumab immune-related hepatitis may occur. See Section 6.9 for details on management of hepatic irAEs. Minor liver toxicity findings only have been reported for M3814.

Appendix 6 Clinical Laboratory Tests

Table 20 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: • MCV • MCH • MCH concentration %Reticulocytes	WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils Basophils	
Clinical Chemistry	Blood urea nitrogen	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Nonfasting Glucose	Calcium	Alkaline phosphatase	Gamma glutamyltransferase
	Magnesium	Creatine phosphokinase	Albumin	Lactate dehydrogenase
	Phosphorous	Uric acid		
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 (Discontinuation of Study Intervention) and Appendix 5.				
Routine Urinalysis	Full Urinalysis should be performed only at Screening and at EoT. • Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal).			

Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential **only**)
	• Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
	• Infection Screen:
	  • Hepatitis B
	  • Hepatitis C
	  • Human immunodeficiency virus (according to local practice and local regulatory guidance)			

	• TSH • Free T4			
ALT = alanine aminotransferase; AST = aspartate aminotransferase; hCG = human chorionic gonadotropin; EoT = End of treatment; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SGPT = Serum Glutamic-Pyruvic Transaminase; free T4 = free thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.				

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Appendix 8 Radiation Therapy

Radiation Target Selection

For participants in Part B, the radiation tumor target may include between 1 and 3 sites of disease excluding sites arising from the brain or spinal canal, esophagus, gastric, small bowel and must not be primary liver cancer (hepatocellular carcinoma [HCC], intrahepatic cholangiocarcinoma [ICC], mixed HCC-ICC).

In addition, the radiation tumor target per anatomical site may include a single parenchymal tumor OR a composite target including involved lymph nodes with or without an associated parenchymal tumor. Inclusion of involved lymph nodes in addition to an involved parenchymal lesion is at the discretion of the treating radiation oncologist.

The lesion or composite lesions target maximum longest diameter (inclusive of all target tumors to be irradiated) must be at least 1 cm. A maximum composite tumor target diameter is not defined; however, proposed radiation treatment plan must meet the dose constraints (at least acceptable variation) outlined in Table 22.

In the event that in the same anatomical site, multiple potential parenchymal tumor target lesions exist, in general the largest lesion should be selected unless it is necessary to select a smaller target for symptom palliation. In such cases where palliative radiation is necessary, smaller lesions likely to benefit from palliative radiation may be selected instead of the largest lesion as long as the maximum tumor diameter additive for all included tumor targets is at least 1 cm. However, for individual tumor where the longest diameter is > 5 cm, a target volume could be created within the gross tumor volume to limit the treated tumor to 5 cm. Any questions about target selection may be reviewed on a case by case basis with the Radiation Oncology Principal Investigator.

Simultaneous multisite RT is allowed. However, owing to limitations of IMRT planning, not all primary or metastatic lesions should be targeted. Three sites maximum could be selected to be irradiated provided that all selected sites could be irradiated on the same day. When selecting metastases to be irradiated, symptomatic or clinically relevant metastases could be prioritized.

Radiation Dose Specification

The total dose per selected site of 30 Gy will be given in 10 daily fractions of 3 Gy prescribed to the PTV with at least 95% of the PTV receiving 30 Gy. An acceptable variation is at least 90% of the PTV receiving 30 Gy. The maximum dose for any contiguous volume of no more than 0.03 cc inside the PTV must not exceed 120% of the prescribed dose. An acceptable deviation is a maximum dose inside the PTV of up to 125% of the prescribed dose. The minimum dose (0.03 cc) to the PTV volume should be no less than 27 Gy. All radiation doses will be calculated with inhomogeneity corrections.

Radiation Treatment Schedule

Localization, Simulation, and Immobilization for radiation treatment planning, as outlined in "Localization, Simulation, and Immobilization", will be performed no more than 35 days and no

less than 1 day before the first day of radiation treatment. The participant can initiate treatment any day of the week. Treatment will be delivered daily for 10 working days (generally Monday to Friday, with 2 days off [Saturday and Sunday]). Disruptions to the planned radiation treatment schedule should be avoided if at all possible. Any unexpected treatment break lasting > 2 days should be reported to the Investigator.

Table 21 Radiation Treatment Schedule

RT Planning Simulation	RT Treatment Day 1-5	RT Treatment Day 8-12	No. Fractions and Total Dose
Between Day -35 and Day -1	Week 1	Week 2	3 Gy per fraction per irradiated site for all participants To a total dose of 30 Gy in 10 fractions for each site Uniform dose prescription in all participants and uniform dose to all PTVs throughout the RT course

PTV=planning target volume, RT=radiotherapy.

Dose Calculations

All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences **within the irradiated volume**.

Technical Factors

Beam Energy

Six- to 18-MV photons are recommended for non-superficial tumor targets; however, beam energy and type will be left to the discretion of the treating radiation oncologist in order to obtain the best dose distribution for the site being treated.

Beam Shaping

Multileaf collimation (MLC) or individually shaped custom blocks should be used to protect normal tissues outside of the target volume.

Localization, Simulation, and Immobilization

A volumetric treatment planning CT study will be required for treatment planning. A four-dimensional CT to account for respiratory motion may be beneficial and can be utilized to limit the overall size of the PVT. Evaluation and/or fusion (according to each institution's standard practice) of a diagnostic PET-CT or CT with IV contrast may assist with target delineation. Each participant will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices with a no more than 3-mm thickness will be obtained through the regions harboring target disease and the entirety of all organs in the treatment field.

Treatment Planning/Target Volumes

The definitions of volumes will be in accordance with the 1993 ICRU Reports #62:

Definition of GTV: Gross tumor volume (GTV) will include the planned radiation target tumor(s) as determined by imaging studies and physical examination and selected according to " Radiation Target Selection".

Definition of CTV: The clinical target volume (CTV) will be defined as the contoured GTV plus 0 to 1 cm expansion volume accounting for anatomic boundaries. CTVs will be labeled to correspond to the appropriate GTV.

Definition of PTV: The planning target volume (PTV) is the CTV plus a margin to account for treatment set up uncertainty and organ motion. The most appropriate PTV margin is to be determined by the treating radiation oncologist and could range from 0.3 to 1.5 cm depending on the use of respiratory motion management and image guided radiation therapy techniques.

Utilization of advanced planning techniques, IMRT to minimize dose to normal tissues is mandatory in this clinical study.

Respiratory Motion Assessment and Management: Utilization of advanced planning techniques to account for respiratory motion can limit the volume of normal tissue. By utilizing respiratory motion management, the PTV margin that accounts for organ motion can be made smaller. 4D-CT based planning to account for any residual tumor motion as well as hilar-mediastinal motion is one form of respiratory motion management. Alternative options to account for respiratory motion include but are not limited to fiducial marker placement, gating and breath hold approaches.

Internal Target Volume (ITV) Approach: If a 4D-CT was collected at the time of simulation for respiratory motion management, then an ITV approach can be utilized to account for internal motion. Utilization of an ITV approach allows for limiting PTV expansion as outlined above.

IMRT Treatment Planning: Institutions are intended to use IMRT planning and delivery for any participant entered on this study.

Table 22 Example of Key Components of an Intensity-modulated Radiation Therapy System

Component	Description
Written treatment directive	Clear communication from physician to dosimetrist/physicist regarding treatment planning goals including target doses and normal tissue limits
Treatment planning system (TPS)	Software used to create the representation of the participant, define volumes for treatment and avoidance, position and shape beams for planning, optimize the intensities (weights) of small beamlets, and calculate dose. IMRT treatment planning is typically an iterative process that requires interaction between physicians, dosimetrists, and physicists. The TPS may use a fluence-based approach by creating larger segments from the small beamlets to achieve more efficient dose delivery
Conversion of desired fluence into a field consisting of segments	For fluence-based systems, the fluence is converted into a series of segments or sequences as a function of time (and monitor units) which can be delivered by the treatment machine. The number of MLC segments may range from 5 to greater than 100 for a given field. Approximations in the TPS modeling may result in differences between the optimized and actual delivered fluence.
Plan transfer to the treatment management system (TMS)	The treatment data are transferred from the TPS to the TMS for delivery. Verifying the correctness and integrity of all data, as well as confirming the deliverability of the leaf sequences to be used, are among the most critical steps to be confirmed in the IMRT QA process.
Participant-specific pretreatment quality assurance	Equipment for IMRT typically includes multiple complementary detectors and phantoms verify the accuracy of the data transfer and dose calculations. Some centers may also have monitor unit check software of treatment field calculations, and this capability is often used in combination with measurements.
Analysis of software	Many systems utilize the gamma analysis technique to compare calculations and measurements. Users typically specify the number of points that are expected to satisfy the criteria for dose (in Gy or in %) and distance (in mm) for agreements when they establish their program.
Linear accelerator for treatment delivery	The linear accelerator needs to be capable of accurately delivering intensity-modulated treatments. For Gantry-based systems using an arc delivery technique (e.g. VMAT), additional information regarding to accuracy of the gantry information at multiple delivery points need to be validated as well. For these systems, derivation of the delivery information as described for leaf sequencing above would also include verification that the gantry sequences, leaf positions, dose delivery, and time information are correct and registered (in time and MU) correctly.

Moran et al. 2011.

Gy=Grays, IMRT=Intensity-modulated Radiation Therapy, MLC=multileaf collimator, QA=quality assurance, TMS=treatment management system, TPS=treatment planning system, VMAT=volumetric modulated arc therapy.

Target Volume and Critical Structure Constraints with Compliance Criteria

Table 23 Target Volume and Critical Structure Constraints with Compliance Criteria

Structure	Dose Constraint	Acceptable Variation	Unacceptable Deviation
PTV	30 Gy ≥ 95%	30 Gy ≥ 90%	30 Gy < 90%
	Min (0.03 cc) ≥ 27 Gy	Min (0.03 cc) ≥ 25.5 Gy	Min (0.03 cc) < 25.5 Gy
	Max (0.03 cc) ≤ 36 Gy	Max (0.03 cc) ≤ 37.5 Gy	Max (0.03 cc) > 37.5 Gy
Total Parotid Glands	Mean < 17 Gy	Mean < 25 Gy	Mean > 25 Gy
Pharyngeal Constrictors	Mean < 20 Gy	Mean < 25Gy	Mean > 25 Gy
Larynx	D2cc < 30Gy	D2cc < 33Gy	D2cc > 33 Gy
	Mean < 20Gy	Mean < 25 Gy	Mean > 25 Gy
Oral mucosa	Mean < 20Gy	Mean < 25Gy	Mean > 25 Gy
Lungs	V20 Gy ≤ 20%	V20 Gy ≤ 35%	V20 Gy > 35%
	Mean ≤ 15 Gy	Mean ≤ 20 Gy	MLD > 20 Gy
Liver	> 700 cc ≤ 10 Gy	> 700 cc ≤ 18 Gy	< 700 cc ≤ 18 Gy
Spinal canal	Max (0.03 cc) ≤ 33 Gy	NA	
Heart	Max (0.03 cc) ≤ 33 Gy	Max (0.03 cc) > 36 Gy	NA
	V30 Gy ≤ 30%	V30 Gy > 30%	Min (0.03 cc) > 30 Gy
Esophagus/Stomach/Small bowel	Max (0.03 cc) ≤ 33 Gy	NA	
	V15 Gy < 10cc		
	V15 Gy < 10%	NA	V15 Gy > 10%
Brachial Plexus/Sacral Plexus/	Max (0.03 cc) < 33 Gy	Max (0.03 cc) < 36 Gy	Max > 36 Gy
Bladder	Max (0.03 cc) < 33 Gy	Max (0.03 cc) < 36 Gy	Max > 36 Gy
Total Kidney	V18 Gy < 33%	V18 Gy < 50%	V18 Gy > 50%
NonPTV	Max (1 cc) < 36 Gy	NA	

Min = minimum, Max = maximum, NA=not applicable (the dose constraint must be met, otherwise the participant should be withdrawn), PTV=planning target volume, RT=radiotherapy.

Note: All required structures must be labeled as listed in the table below for digital RT data submission.

Documentation Requirements

As IMRT is used in this study, portal images will not be obtained, but participant-specific QA will be performed prior to the first fraction.

Cone beam CT, kV imaging, or other in-room imaging for set up is allowed.

Isodose plans for IMRT planning with dose-volume histograms of GTV, CTV, PTV, and critical structures are required.

Acceptable variations are allowed only when the geometrical arrangement of the target and critical structures is challenging. Unacceptable deviations should be avoided whenever possible and plan modifications should be attempted to improve results. The details of each radiation treatment plan

are to be collected by the study Sponsor and all acceptable variations and unacceptable deviations will be appropriately documented in the study record.

Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Principal Investigator, or designee, will review all radiation treatment plans within 3 months after the study has reached the target accrual or as soon as complete data for all cases enrolled have been received. In addition, a digital record of the radiation treatment plan can be collected on a case by case basis whenever deemed necessary to be reviewed by the Sponsor and the Radiation Oncology Principal Investigator.

Radiation Therapy Adverse Events

Side effects of RT will vary depending on the location of disease, volume of normal and radiosensitive tissues in or near the radiation planning target volume. Even though, IMRT, the RT technique used in this study, may facilitate a better normal tissue sparing, all attempts should be made to minimize toxicity to surrounding healthy tissues by limiting the normal tissue radiation dose as much as possible and adhering to dose volume constraints for the main organs at risks as provided in Table 23.

Short-term or acute adverse effects occur during therapy or within 3 months after RT while long-term or late adverse effects are observed thereafter. Acute toxicities (for example mucositis) generally heal within weeks to months; late toxicities, such as fibrosis, are generally considered irreversible and progressive over time.

Potential Radiotherapy Adverse Events

Radiotherapy is associated with a wide variety of acute and late effects in different organs. In this study, the NCI-CTCAE v5.0 grading scale will be used to standardize definitions of adverse events including RT-induced toxicities.

Most patients experience mild to moderate fatigue, skin toxicity and mucosal injury, which causes mucositis and diarrhea during treatment. The majority of patients recover well from acute effects.

The acute and late adverse effects of RT are strongly dependent on the tissue targeted and can include skin toxicities, gastrointestinal damage, lung injury, cardiac toxicity, cognitive impairment, reproductive disorders, deformity and impairments to bone growth, hematological disorders, hair loss and secondary malignancy.

Management of Radiotherapy Adverse Events

Follow-up

Follow-up is an essential component of RT management. All participants diagnosed with RT toxicity should be followed-up with a tailored schedule defined by the treating Investigator. Acute adverse effects should be treated until resolution. If late, chronic adverse effects are diagnosed, any underlying conditions should be treated as this may improve the symptoms of participants.

In this study, in addition to the Safety Follow-up relating to the combination of study interventions planned after the last dose of avelumab, further Safety Follow-ups should be scheduled at 1, 3 and 12 months after the end of RT in order to identify, assess and manage potential acute and late toxicities related to RT in combination with M3814 and avelumab.

Symptomatic Management

The management of acute and late radiation toxicity is merely symptomatic. As inflammation has a role in many radiation adverse effects, anti-inflammatory drugs are frequently prescribed. Fibrosis may occur later, causing organ dysfunction, and is mostly, but not always, irreversible. However, the consequences of organ dysfunction due to RT may be mitigated by specific measures that interfere with the physiology of the affected organ (e.g., inhaled).

β-mimetics may treat bronchial hyper-reactivity, and angiotensin-converting enzyme inhibitors may be used in heart failure. Unfortunately, most interventions are based largely on expert opinion.

Given the breadth of RT toxicities, a few key examples of management strategies are provided. **In this study, participants experiencing an adverse event, should be evaluated and treated as appropriate according to institutional guidelines. All attempts should be made to limit the symptoms and the overall impact of acute and late effects of radiation.**

Skin Toxicities

Radiation dermatitis is a common adverse effect of RT, particularly in the context of skin, breast and head and neck malignancies, among others (Bolderston 2006) The clinical presentation escalates from early erythema, dry desquamation and moist desquamation to late adverse effects including pigmentation changes, telangiectasias, alopecia, fibrosis, atrophy, and ulceration. The management of radiation dermatitis are largely symptomatic. Emollients with topical steroids and dexpanthenol are often prescribed for radiation dermatitis, although there is insufficient evidence to firmly support or refute this recommendation (Bolderston 2006).

Upper Gastrointestinal Tract Mucositis

Mucositis describes a clinical condition characterized by oral erythema, ulceration and pain and is a common complication of RT, particularly of the head and neck and gastrointestinal luminal structures (Blijlevens 2000).

General behavioral measures are often helpful in reducing or mitigating mucositis. Participants should be strongly advised against smoking, drinking alcohol and consuming acidic or spicy foods during RT (Blijlevens 2000; Blanchard 2014). Pain related to mucositis should be treated in a step-wise manner, first using topical anesthetics, and then for severe pain escalating to using gabapentin and opioid analgesics (Blanchard 2014).

Esophagitis

Radiation-induced esophagitis (RIE) and painful swallowing odynophagia are common treatment toxicities for patients undergoing RT particularly for lung, breast, or head and neck cancers.

Therefore, to minimize the risk of radiation esophagitis which could increase with the study intervention, the following measures have been adopted:

- If the participant has symptoms of ongoing esophagitis and the treating Investigator estimates that the radiation planning target volume will include any portion of the esophagus, the participant is not eligible unless an esophageal endoscopy rules out the presence of esophagitis.
- The participant will not be eligible if >10% of the total esophagus volume is estimated to receive more than 15 Gy (50% of the prescribed RT dose).

In general, acute RIE occurs typically 2 weeks after treatment begins and lasts until 4 weeks after treatment concludes, with progressively worsening odynophagia, nausea, dysphagia, and, if ineffectively managed, anorexia (Murro 2015; Baker 2016). Late RIE occurs more than 3 months after RT ends, with an average time from treatment to symptom onset of 6 months.

Radiation-induced esophagitis does not constitute a reason to interrupt or delay RT or the study interventions provided oral intake is sufficient to maintain hydration.

Radiation-induced esophagitis is treated symptomatically. Mild to moderate odynophagia is managed with topical analgesics such as oral viscous lidocaine (Berkey 2010; Sasso 2001). Treatment with nonsteroidal anti-inflammatory agents has been proposed. Reflux frequently associated with RIE can be treated with proton pump inhibitors or H2 receptor blocker and dietary modifications. Prophylactic antifungal agents are recommended due to a high incidence of thrush and candida esophagitis.

Participants should also be strongly advised to avoid alcoholic, acidic, or spicy foods or beverages during RT.

Radiation-Induced Lung Toxicity (RILT)

Common radiation lung toxicity includes radiation pneumonitis and fibrosis and pleural effusion.

Traditionally, RILT, which includes clinical radiation pneumonitis and clinical fibrosis should only be diagnosed after exclusion of infection, tumor progression, and other etiology for the clinical symptoms.

Several studies have evaluated the use of various drug therapies to mitigate radiation pneumonitis, but there are none outside of steroid therapy that are in routine use (Abratt 2002). Minimizing the volume of irradiated lung is particularly important as several studies have correlated dose and/or volume effects of RT with the risk of pneumonitis (De Ruysscher 2019).

Supportive care may include antitussive therapy to suppress coughing, supplemental oxygen and treatment of comorbid diseases, such as chronic obstructive pulmonary disease or heart failure, which may contribute to symptoms. Moderate to high-dose steroid therapy is a common and effective therapeutic strategy that is generally given for a period of several weeks with a gradual taper as the symptoms settle (De Ruysscher 2019). However, steroids are minimally effective in the late consolidative phase of pneumonitis, when pulmonary fibrosis is well established (Abratt 2002).

Appendix 9 Protocol Amendment History

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

Protocol Version 2.0 (26 June 2019)

Overall Rationale for the Amendment

The major purpose of this global protocol amendment is to include the assessment of the food effect (FE) on pharmacokinetics (PK) of M3814 following administration of M3814 in combination with avelumab under fasted and fed conditions. The dose-limit toxicity (DLT) definition was also revised as well as the eligibility criteria of the study population, mostly in Part B of the study. The key changes are listed below.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated the Coordinating Investigator and the US Medical Monitor name and contact information	To be consistent with current information
Title Page, 1.1 Synopsis, 1.2 Schema, 1.3 Schedule of Activities, 2.1 Study Rationale, 3.3 Part FE, 6.6 Dose Selection and Modification, 6.6.5.3 Part FE and throughout document, as applicable	Included a third cohort (Part FE)	To assess the FE on PK of M3814 following administration of M3814 in combination with avelumab
1.3 Schedule of Activities	Changed the End of Treatment (EoT) period from "-1 to 7" to "within 7 days of decision to discontinue" and added a clarification note	For clarity and readability
1.3 Schedule of Activities, and throughout document, as applicable	Increased the screening window in Part B from 28 days to 35 days	To allow the assessment of the eligibility criteria related to radiotherapy (RT) which requires a multi-disciplinary team
1.3 Schedule of Activities, and throughout document, as applicable	• Corrected the approximate volume blood for soluble factors and immune phenotyping • Added the information "approximately" for blood volume	To add clarity and to be consistent with current information
1.3 Schedule of Activities 8.5 Pharmacokinetics	Updated the acceptable PK window for avelumab and M3814	To facilitate PK sampling schedule

Section # and Name	Description of Change	Brief Rationale
2.3.1 Summary of M3814 Data and Potential Benefits and Risks 2.3.1.1 Summary of M3814 Tablet Formulation and Potential Benefits and Risks	Revised according to the most updated information from the Investigator's Brochure	To be consistent with the current Investigator's Brochure of M3814
2.3.3 Summary of Potential Benefits and Risks of Radiotherapy 4.3.2 Radiotherapy and throughout document, as applicable	Updated information about the RT including the role of palliative RT in several solid tumors beyond thoracic tumors and justification of multisite RT for treating metastatic disease	To provide rationale supporting the revised eligibility criteria for participants and RT schedule
5.1 Inclusion Criteria, 5.2 Exclusion Criteria and throughout document, as applicable	Revised the eligibility criteria of the study population in Part B of the study	To reflect both Part B targeted population (selected solid tumors) and multisite RT. These changes will allow to assess safety of RT when delivered to different selected solid tumors to either one or multiple sites (up to 3 sites) in combination with M3814 and avelumab
5.1 Inclusion Criteria, Appendix 3	Revised criteria for contraception	For consistency with current Sponsor standards and consistency across the development program
5.2 Exclusion Criteria	• Revised exclusion criteria #2 • Revised exclusion criteria #10b	• To excluded participants with history of long QTcF as requested by FDA • To clarify the requirements of inclusion of participants with history of infections
5.3.1 Meals and Dietary Restrictions	Updated the information for meal and dietary restrictions	For consistency with current Sponsor standards regarding clinical trials
6.5.3 Prohibited Medicines	Added a clarification note about the use of H2 blocker	To provide precautions considering the use of H2
6.6.3 Definition of Dose-Limiting Toxicity	Updated the DLT definition	To consider the known toxicities associated with RT, so that the adverse events (AEs) related to M3814 will be more accurately detected, thereby enabling a better understanding of the safety profile of M3814 when coadministered with avelumab and RT
6.9.1 Adverse Drug Reactions Requiring M3814 Treatment Discontinuation or Modifications	Revised the dose modification for M3814 and RT in Part B	To be consistent with the new definitions of DLTs in Part B of the study
Appendix 8	Section was updated to assist Investigators in delivering appropriate radiation oncology care to the study participants as required per the protocol	The updated document provides: ▪ Guidance on treatment planning and delivery of IMRT to decrease the dose of radiation to normal tissues in the intent to prevent the AEs of RT. ▪ Broad overview of most common RT related toxicities, as well the symptomatic treatment of certain RT toxicities arising in different regions of the body.

Section # and Name	Description of Change	Brief Rationale
		Yet, the ultimate judgement regarding RT procedure or course of action must be made by the Investigator in light of all the circumstances presented. The sole purpose of this document is assisting Investigators and study team to deliver effective and safe medical care to participants to this study
Throughout	Minor editorial and document formatting revisions	Minor text revisions are made for clarity, readability, consistency of language across the development program, and compliance with current Sponsor guidelines

Appendix 10 Sponsor Signature Page

Study Title:	A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors
Regulatory Agency Identifying Numbers:	CCI [redacted]
Clinical Study Protocol Version:	PPD /Version 3.0

I approve the design of the clinical study:

Signature Date of Signature

PPD [redacted]

Appendix 11 Coordinating Investigator Signature Page

Study Title: A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors

Regulatory Agency Identifying Numbers: CCI [redacted]

Clinical Study Protocol Version: PPD /Version 3.0

Site Number:

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

_____ _____

Signature Date of Signature

PPD [redacted]

Coordinating Investigator Signature Page

Study Title: A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors

Regulatory Agency Identifying Numbers: CCI

Clinical Study Protocol Version: PPD /Version 3.0

Site Number:

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

Signature

Date of Signature

PPD

Appendix 12 Principal Investigator Signature Page

Study Title: A Multicenter, Open-Label, Dose Escalation Phase I Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect on Pharmacokinetics of the DNA-PK Inhibitor M3814 in Combination with Avelumab with and without Palliative Radiotherapy in Participants with Selected Advanced Solid Tumors

Regulatory Agency Identifying Numbers: CCI [redacted]

Clinical Study Protocol Version: PPD /Version 3.0

Site Number:

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

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

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: