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Title Page

Protocol Title:

An open-label, multicenter, Phase 1/2 study of radium-223 dichloride in combination with pembrolizumab in participants with stage IV non-small cell lung cancer

Protocol Number: 19781

Global Amendment 2

Compound Number: BAY 88-8223 / radium-223 dichloride / Xofigo®
Study Phase: Phase 1/ 2

Short Title:

Phase 1/2 study of radium-223 dichloride in combination with pembrolizumab in non-small cell lung cancer

Sponsor Name: Bayer Consumer Care AG

Legal Registered Address:

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Regulatory Agency Identifier Number(s)

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Medical Monitor Name and Contact Information will be provided separately.

This is an electronically generated document that does not bear any sponsor signatures. The signature of the Sponsor's medically responsible person is filed in the TMF and available on request.

Protocol amendment summary of changes table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	18 SEP 2020
Amendment 1	29 OCT 2019
Original Protocol	28 FEB 2019

Amendment 2 (18 Sep 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

This protocol amendment was mainly prepared to address the following points: clarification on eligibility criteria, adoption only of RECIST 1.1 criteria as primary/secondary endpoints, clarification on statistical assumptions and planned analyses, provision of additional guidance to the participating sites as well as additional background information on study rationale.

Section # and name	Description of change	Brief rationale
Title Page Sponsor Signatory	The signature of the Sponsor's medically responsible person was removed from the clinical study protocol.	Administrative change of Bayer process.
1.1 Synopsis 3. Objectives and Endpoints 9.4.1 Efficacy analyses 9.4.1.2. Phase 2 Efficacy Variables	Tumor assessment per iRECIST moved from secondary to exploratory endpoints. Listed efficacy endpoints for Phase 1. Correction of typos in the subsection title.	To use iRECIST criteria as exploratory efficacy endpoints only. Additions for completeness.
1.1 Synopsis 3. Objectives and Endpoints	PFS and OS added as exploratory endpoints to Phase 1.	To explore additional indicators of efficacy of the combination of radium-223 dichloride and pembrolizumab in Phase 1.
1.1 Synopsis 4.1.2.1 Phase 1 Part	Specified the number of evaluable participants at the RP2D in Phase 1 to be at least 10 instead of approximately 10.	To ensure enough data are available before moving into Phase 2.

Section # and name	Description of change	Brief rationale
1.1 Synopsis 4.1.3.1 Active follow-up	Clarification on withdrawal criteria for study intervention discontinuation and follow-up.	To align the study drug discontinuation and follow-up withdrawal criteria across the protocol.
1.3. Schedule of Activities	Addition of the option of additional contacts to collect survival data.	To allow survival sweeps for collection of up to date data for overall survival analysis.
1.3. Schedule of Activities 4.1.2.3 End of Treatment 8.2.4 Clinical Safety Laboratory Assessments 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Addition of description for EoT visit to be performed 14 days after decision of permanent discontinuation of treatment in case of dose delay/interruption.	To provide instructions on the EoT visit completion when the definitive decision of study drug discontinuation is made following a study intervention delay/interruption.
1.3. Schedule of Activities 7.2. Participant Discontinuation/Withdrawal from the Study 8.2.7 Pregnancy Test 10.2 Appendix 2: Clinical Laboratory Tests	Added serum from C1 onwards as an acceptable sample for pregnancy testing.	Clarification to allow sites to indifferently use blood (serum) or urine testing according to local clinical practice.
1.3. Schedule of Activities 5.1 Inclusion Criteria	Addition of requirement for availability of BRAF testing results at baseline. Clarification on tumor tissue requirements for driver mutation testing.	To align with international guidelines on driver mutation testing in NSCLC patients. To ensure comparable testing results.
2.1 Study Rationale 2.2 Background 2.3. Benefit/Risk Assessment	Addition of more detailed preclinical and clinical information on synergy of radiotherapy and immunotherapy. Addition of more details on available safety data of radium-223 in combination therapy and expected toxicity in combination with pembrolizumab.	To ensure more comprehensive background information is available to the reader.
1.1 Synopsis 3. Objectives and Endpoints 8.2.6 Patient Reported Outcome 9.4.1.2 Phase 2 Efficacy Variables 9.4.1.4 Statistical Methods for Phase 2 Efficacy Analyses	Specification of the endpoints and analyses for assessment of PRO.	To add clarity on the planned PRO endpoints and analyses.

Section # and name	Description of change	Brief rationale
5.1 Inclusion Criteria	Clarification on prior chemotherapy and immune checkpoint inhibitor treatment in IO refractory participants	To ensure participants are not deprived of any platinum-based chemotherapy as of local standard of care and have progressed within 12 weeks from the last dose of a prior immunotherapy
5.1 Inclusion Criteria	Addition of requirement for male participants with a pregnant partner to use condom during sexual intercourse. Addition that male participants should be advised on the conservation of sperm.	Additional precautionary measure for contraception. Instruction because of potential effects on spermatogenesis associated with radiation.
6.1 Study Interventions Administered	Clarification on administration of radium-223 and pembrolizumab.	To provide guidance in case of dose delays for any study intervention administration.
6.5.1 Prohibited Concomitant Therapy	Addition of guidance on administration of live vaccines after the last dose of study intervention.	To better define the duration of avoidance.
6.6.1 Toxicity Management and Dose Modifications Recommendations for Radium-223	Changing of the requirement of participants non-hematological toxicities to be resolved to Grade ≤2 instead of Grade ≤1.	To align with dose modification guidelines across radium-223 trials and consistency with the requirements at inclusion.
7.2. Participant Discontinuation/Withdrawal from the Study 8.1 Efficacy Assessments	Changing the participant's withdrawal from intervention period and requirements for signing an additional informed consent from RECIST to iRECIST.	To align with the iRECIST criteria which allow treatment beyond progression (in case of iUPD).
8.4 Treatment of Overdose 8.5 Pharmacokinetics 8.8.2 Immunogenicity Assessments	Correction of the sample for analysis to be serum instead of plasma.	To align with laboratory requirements.
9.1 Statistical Hypotheses 9.1.2 Phase 2 Efficacy	Revision of the language to support the statistical hypotheses and correction of typos.	Clarification and correction.
9.3 Populations for Analyses 9.3.1 Phase 1 9.3.2 Phase 2 9.4.1.3 Statistical Methods for Phase 1 Efficacy Analyses 9.4.1.4. Statistical Methods for Phase 2 Efficacy Analyses	Clarification on analyses sets.	To properly define each analysis set across study phases and cohorts. To clarify the handling where the assigned treatment is not followed.

Section # and name	Description of change	Brief rationale
9.4.2 Safety analyses	Addition of reference to time to bone fracture analysis.	To align with past Radium-223 AESI analyses.
9.5 Interim Analyses 9.5.1 Data Monitoring Committee	Delayed interim analysis for unconfirmed response.	To clarify interim for completeness.
10.1.3 Informed Consent Process	For Germany, participants who are not capable of providing informed consent will not be included in this study.	To meet Health Authority requirements.

In addition to the modifications described above, protocol text was revised to address changes of editorial nature including clarification to ensure consistency throughout the protocol.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: An open-label, multicenter, Phase 1/2 study of radium-223 dichloride in combination with pembrolizumab in participants with stage IV non-small cell lung cancer

Short Title: Phase 1/2 study of radium-223 dichloride in combination with pembrolizumab in non-small cell lung cancer

Rationale:

For the past two decades, platinum-based combination chemotherapy has been the standard of-care first-line treatment for patients with advanced non-small cell lung cancer (NSCLC). Over the last years, new treatment options including immunotherapy have led to improvement in overall survival (OS) in first and later lines of treatment in these patients.

Radiation has been shown to induce increased antigen expression, to release pro-inflammatory cytokines, to recruit immune cells, and ultimately to induce immunogenic cell death. While most data have been generated with gamma radiation, effects of radium-223 are expected to not be impacted by hypoxia (which is a known resistance mechanism against gamma radiation). In addition, radium-223 is targeting osteoclasts which exhibit immunosuppressive properties in bone metastases. In vitro, radium-223 increases antigen expression and stress response and induces immunogenic cell death markers in prostate, breast and lung cancer cell lines (Malamas et al. 2016).

Based on complementary modes of action between radium-223 dichloride and immune checkpoint inhibitors, and their potentially synergistic effects on the cancer-immunity pathway, the addition of radium-223 dichloride to pembrolizumab therapy might provide a greater clinical benefit to NSCLC patients.

The safety profile of both, radium-223 dichloride and pembrolizumab, are well characterized. Overlapping side effects such as gastrointestinal (GI) toxicities are possible, but further overlapping toxicities are not expected to be observed.

Altogether, available data support the evaluation of radium-223 dichloride in combination with pembrolizumab in NSCLC.

The purpose of the study is to determine the safety and assess the efficacy of the combination of radium-223 dichloride and pembrolizumab in participants with stage IV NSCLC with bone metastases who are either treatment naïve or have progressed on prior anti programmed cell death protein (ligand) 1 (PD-L1/PD-1) therapy.

Objectives and Endpoints:

Phase 1

Objectives	Endpoints
Primary	
• To assess the safety of the combination of radium-223 dichloride and pembrolizumab and to determine the recommended Phase 2 dose (RP2D)	• Adverse events (AE) assessments using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (v.5.0) and Incidence of dose limiting toxicities (DLTs)

Objectives	Endpoints
Secondary	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab	• Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Duration of response (DoR) per RECIST v1.1 • Disease control rate (DCR) per RECIST v1.1
Tertiary/Exploratory	
• To evaluate predictive, prognostic and pharmacodynamic biomarkers • To assess the pharmacokinetics (PK) and immunogenicity of pembrolizumab in combination with radium-223 dichloride (if applicable) • To explore additional indicators of efficacy of the combination of radium-223 dichloride and pembrolizumab	• PD-L1, tumor mutational burden (TMB), bone markers, immune cell analysis and circulating protein markers • Trough PK Concentrations and Titers for anti-drug antibodies (ADAs) and neutralizing antibodies (nABs) for pembrolizumab (if applicable) • ORR per iRECIST • DoR per iRECIST • DCR per iRECIST • Progression free survival (PFS) per v1.1 RECIST and iRECIST • Overall survival (OS)

Phase 2 (Cohort 1 and 2)

Objectives	Endpoints
Primary	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone)	• ORR per RECIST v1.1
Secondary	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone) • To evaluate the safety of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone)	• DoR per RECIST v1.1 • DCR per RECIST v1.1 • Progression free survival (PFS) per RECIST v1.1 • OS • AE assessments using NCI CTCAE (v.5.0)
Tertiary/Exploratory	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone) • To evaluate predictive prognostic and pharmacodynamics biomarkers • To assess patient reported outcome (PRO) (only applicable to Cohort 1)	• Symptomatic skeletal event-free survival (SSE-FS) • ORR per iRECIST • DoR per iRECIST • DCR per iRECIST • PFS per iRECIST • PD-L1, TMB, bone markers, immune cell analysis and circulating protein markers • Time to deterioration in global health status • Time to deterioration in dyspnea • Change from baseline on European

Objectives	Endpoints
	Organization for Research of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 quality of life scale score and item scores • Change from baseline in EORTC QLQ-LC13 scale scores and item scores
• To assess the PK and immunogenicity of pembrolizumab in combination with radium-223 dichloride (if applicable)	• PK trough concentrations and titers for ADAs and nABs for pembrolizumab (if applicable)

Overall Design:

This is an open-label, multicenter, Phase 1/2 study which includes a safety run-in as well as two distinct cohorts to assess the efficacy of the combination of radium-223 dichloride and pembrolizumab in participants with NSCLC.

Phase 1

The Phase 1 part of the study will include participants with stage IV NSCLC either treatment naïve (PD-L1 tumor protein score [TPS] ≥ 50%) or after progression on prior therapy with immune checkpoint inhibitors (irrespective of PD-L1 TPS). It is designed to determine the tolerable dose of radium-223 dichloride in combination with standard dose of pembrolizumab (200 mg pembrolizumab every 3 weeks for a maximum of 35 cycles). Participants enrolled in the Phase 1 part of the study will receive the starting dose of 55 kilo Becquerel (kBq)/kg body weight of radium-223 dichloride which is the approved monotherapy dose for metastatic Castration Resistant Prostate Cancer (mCRPC). Radium-223 dichloride will be administered every 6 weeks for up to 6 administrations. All participants will be evaluated for occurrence of DLTs during the DLT observation window (6 weeks after first dose of pembrolizumab). In case of DLTs, the radium-223 dichloride dose may be reduced by one dose level to 33 kBq/kg body weight (see Section 4.1.2.1).

Phase 2

The main purpose of the Phase 2 part of the study is to evaluate the efficacy of the combination of radium-223 dichloride and pembrolizumab. The Phase 2 includes 2 distinct cohorts. In Cohort 1 participants with treatment naïve stage IV NSCLC (PD-L1 TPS ≥ 50%) will be randomized 1:1 to receive either radium-223 dichloride plus pembrolizumab or pembrolizumab monotherapy. In Cohort 2 (single arm) participants with stage IV NSCLC who have progressed on prior therapy with immune checkpoint inhibitors (irrespective of PD-L1 TPS) will receive radium-223 dichloride plus pembrolizumab. Radium-223 dichloride will be administered every 6 weeks at the RP2D as determined in the Phase 1 part (for a total of up to 6 administrations). Pembrolizumab 200 mg will be administered every 3 weeks for a maximum of 35 cycles.

Disclosure Statement:

This is an open-label study consisting of a Phase 1 part to determine the RP2D of radium-223 dichloride in combination with pembrolizumab and a Phase 2 part to evaluate the efficacy and safety of radium-223 dichloride in combination with pembrolizumab.

Number of Participants:

In Phase 1, approximately 10 – 20 participants will be treated for a total of at least 10 evaluable participants at the RP2D

In Phase 2, Cohort 1, approximately 104 participants will be randomized to study intervention. All randomized participants will be considered part of the Full Analysis Set (FAS).
In Phase 2, Cohort 2, approximately 40 participants will be treated. A participant that has started treatment is considered evaluable.

Intervention Groups and Duration:

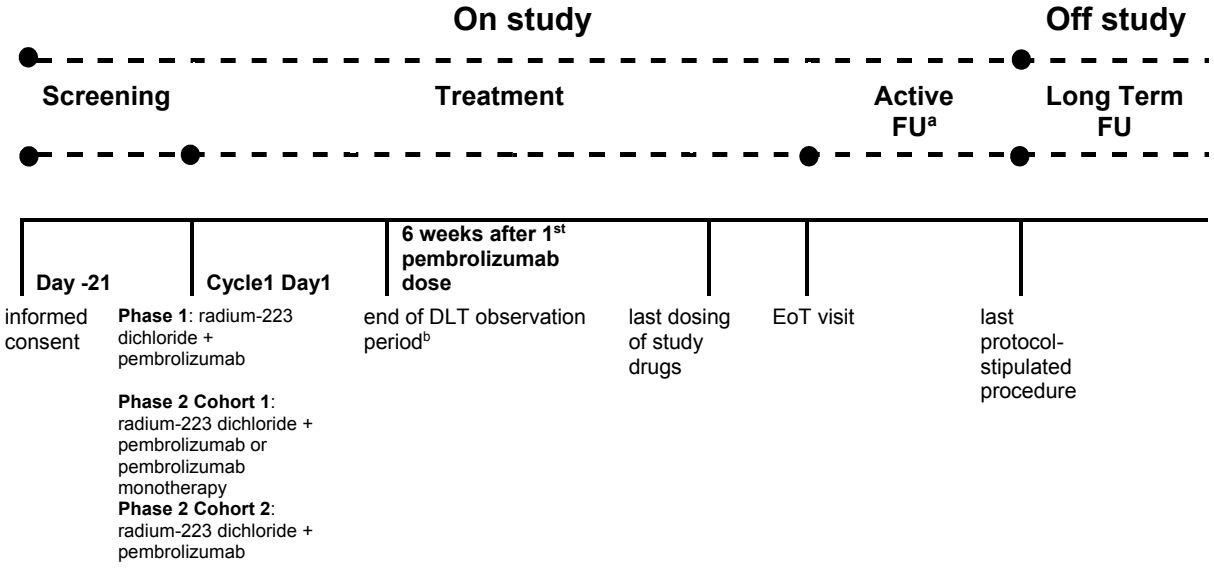
Pembrolizumab will be administered every 3 weeks for up to 35 cycles or until progressive disease (PD), death, unacceptable toxicity, withdrawal of consent or other withdrawal criteria are met (whichever occurs first). Radium-223 dichloride will be administered every other cycle of pembrolizumab (every 6 weeks) for a total of up to 6 administrations or until PD, death, unacceptable toxicity, withdrawal of consent or other withdrawal criteria are met (whichever occurs first).

Regular safety calls with participation of the sponsor and the investigators:
Yes (Phase 1)

Data Monitoring Committee:
Yes (Phase 2)

1.2 Schema

Table 1-1: Study Periods



DLT = dose-limiting toxicity; EoT = end of treatment ; FU = follow-up
a: Active FU visits, if applicable
b: DLT observation period applicable to phase 1 only

1.3 Schedule of Activities

Table 1-2: Schedule of Assessments

Procedure	Screening	Intervention Period[a]					EoT Visit[h]	Active FU[b]	Long-Term FU[b]	Notes and Indices
		C1		C2		≥ C3 - C35				
	Within 21 days	D1	D15*	D1	D15*	D1	30 days after last dose of study inter-vention	Every 3 months until PD, death or, withdrawal of consent	Every 6 months until death, withdrawal of consent	*D15 applies to phase 1 only
Time window			±3 days[c]	±3 days[c]	±3 days[c]	±3 days[c]	+7 days	±14 days	±28 days	
Signing of informed consent	X									
General										
Check of inclusion / exclusion criteria	X									
Demographic data	X									
Documentation of primary diagnosis	X									including classification of cancer under study, previous systemic anti-cancer treatment and radiotherapy
Smoking history	X									
Medical history	X									including prior fractures, bone-associated events (e.g., osteoporosis)
Height	X									
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	in active FU and long-term FU only BHAs need to be reported
First new anticancer therapy							X	X	X	
Safety										
ECOG PS assessment	X	X	X	X	X	X	X			
Physical examination	X	X	X	X	X	X	X			including neurological examination
AE/SAE assessment	X	X	X	X	X	X	X	X	X	including fractures, and any bone-associated events (e.g., osteoporosis) regardless of the investigator's causality assessment. Please refer to 4.1.3 for collection of AEs/SAEs in active and long-term FU
12-lead ECG	X	X		X		X	X			
Hematology	X	X	X	X	X	X	X			not required on Day 1 of Cycle 1, if done ≤ 5 days prior to start of treatment.
Blood chemistry	X	X	X	X	X	X	X			ALT, AST, ALP, creatinine, urea/BUN, total bilirubin, total protein, albumin, sodium, potassium, chloride, calcium, magnesium, phosphorus, glucose (non-fasting); not required on Day 1 of Cycle 1, if done ≤5 days prior to start of treatment

Table 1-2: Schedule of Assessments

Procedure	Screening	Intervention Period[a]					EoT Visit[h]	Active FU[b]	Long-Term FU[b]	Notes and Indices
		C1		C2		≥ C3 - C35				
	Within 21 days	D1	D15*	D1	D15*	D1	30 days after last dose of study inter-vention	Every 3 months until PD, death or, withdrawal of consent	Every 6 months until death, withdrawal of consent	*D15 applies to phase 1 only
Time window			±3 days[c]	±3 days[c]	±3 days[c]	±3 days[c]	+7 days	±14 days	±28 days	
Coagulation	X	X	X	X	X	X	X			aPTT, PT/INR; not required on Day 1 of Cycle 1, if done ≤5 days prior to start of treatment
Vital signs: blood pressure, heart rate, body temperature	X	X	X	X	X	X	X			
Calculation of eGFR	X	X		X		X				by Cockcroft Gault, only if Creatinine > 1.5 X ULN; not required on Day 1 of Cycle 1, if done ≤5 days prior to start of treatment
Weight	X	X		X		X				
Thyroid function	X	X				X	X			TSH, T3 free and T4 free every 2nd cycle; not required on Day 1 of Cycle 1, if done ≤5 days prior to start of treatment
Pregnancy test	X	X		X		X	X			serum at screening and urine or serum after C1; Female participants of child-bearing potential only
DLT assessment (Phase1 only)		X	X	X	X	X				DLT window: 6 weeks after 1st dose of pembrolizumab
Efficacy										
Imaging/tumor assessment (Chest, abdominal and pelvic MRI or CT scan)	X	X Following Cycle1 Day 1 every 6 weeks (±7 days) up to week 36, thereafter every 9 weeks (±7 days) up to 2 years, after 2 years every 3 months (±14 days).								Assessments acc. to RECIST 1.1 and iRECIST by local investigator/radiologist. Bone metastases detected by bone scan should be confirmed by MRI (preferable) or CT. At screening tumor scans are acceptable if taken within 4 weeks of randomization/confirmation of eligibility
Technetium-99m bone scan	X									Bone metastases detected by bone scan should be confirmed by MRI (preferable) or CT. At screening bone scan is acceptable if taken within 4 weeks of randomization/confirmation of eligibility. If in the opinion of the investigator, the bone scan is not considered appropriate, whole-body FDG-PET or FDG-PET/CT scan is acceptable.
Symptomatic Skeletal Events (SSEs) (Phase 2 only)[g]	X	X		X		X	X	X		SSEs need to be reported as either AEs or SAEs regardless of the investigator's causality assessment

Table 1-2: Schedule of Assessments

Procedure	Screening	Intervention Period[a]					EoT Visit[h]	Active FU[b]	Long-Term FU[b]	Notes and Indices
		C1		C2		≥ C3 - C35				
	Within 21 days	D1	D15*	D1	D15*	D1	30 days after last dose of study inter-vention	Every 3 months until PD, death or, withdrawal of consent	Every 6 months until death, withdrawal of consent	*D15 applies to phase 1 only
Time window			±3 days[c]	±3 days[c]	±3 days[c]	±3 days[c]	+7 days	±14 days	±28 days	
PRO (Phase 2 cohort 1)[e]	X			X		X				D1, every 2nd cycle
PRO (Phase 2 cohort 2)	X									
Study intervention administration										
Randomization (Phase 2 cohort 1 only)		X								
Radium-223 dichloride administration[d]		X				X				every 2nd cycle of pembrolizumab for a total of 6 administrations or until progression, death or withdrawal of consent (whatever comes first) First administration should occur not later than 14 days after C1D1 of pembrolizumab. Thereafter the radium-223 administration should occur not later than 7 days after pembrolizumab infusion in the respective cycle
Pembrolizumab administration		X		X		X				for up to 35 cycles or until progression, death or withdrawal of consent (whatever comes first)
Survival status									X	Participants may be contacted at additional times throughout the course of the study in order to collect survival data
Research sample collection/analyses[f]										
PK sampling[f]		X		X		C4, C6, C8, C12 + every 4th cycle thereafter	X			pembrolizumab PK blood samples in all participants. The PK blood samples will be stored, and analysis will be performed only if required. If ongoing PK sampling is deemed to be unnecessary by the sponsor, it may be reduced or discontinued.
Immunogenicity (ADA/NABs) sampling[f]		X		X		C4, C6, C8, C12 + every 4th cycle thereafter	X			immunogenicity samples in all participants. The samples will be stored, and analysis will be performed only if required. If ongoing immunogenicity sampling is deemed to be unnecessary by the sponsor, it may be reduced or discontinued.
Biomarker fresh or archival	X									PD-L1, TMB, exploratory biomarkers

Table 1-2: Schedule of Assessments

Procedure	Screening	Intervention Period[a]					EoT Visit[h]	Active FU[b]	Long-Term FU[b]	Notes and Indices
		C1		C2		≥ C3 - C35				
	Within 21 days	D1	D15*	D1	D15*	D1	30 days after last dose of study inter-vention	Every 3 months until PD, death or, withdrawal of consent	Every 6 months until death, withdrawal of consent	*D15 applies to phase 1 only
Time window			±3 days[c]	±3 days[c]	±3 days[c]	±3 days[c]	+7 days	±14 days	±28 days	
tumor tissue										
Biomarker blood[f]		X	X	X		X	X			FACS
Biomarker serum[f]		X	X	X		X	X			bone markers (PINP, bCTX, ICTP, bone specific alkaline phosphatase, osteocalcin)
Biomarker urine[f]		X	X	X		X	X			bone markers (N-telopeptide, creatinine, calculation urine n-telopeptide/creatinine)
Biomarker plasma[f]		X	X	X		X	X			ctDNA/proteins
PD-L1 testing/results (mandatory for participants eligible for first line treatment only)	X									
EGFR/ALK/ROS/BRAF testing results	X									Testing must be performed on tumor tissue

Abbreviations: acc. = accordingly; ADA = anti-drug antibodies; AE = adverse event; ALK = anaplastic lymphoma kinase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; bCTX = B-carboxyl-terminal cross-linking telopeptide of type I collagen; BHA = bone health agent; BRAF = v-Raf murine sarcoma viral oncogene homolog B; BUN = blood urea nitrogen; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; DLT = dose limiting toxicity; EBRT = external beam radiation therapy; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate; EGFR = epidermal growth factor receptor; EoT = end of treatment; FACS = fluorescence activated cell sorting; FDG = 2-deoxy-[^{18}F]fluoro-D-glucose; FU = follow-up; ICTP = C-terminal cross-linking telopeptide of type I collagen; INR = international normalized ratio; MRI = magnetic resonance imaging; NAB =neutralizing antibodies; PD = progressive disease; PD-L1 = programmed cell death protein ligand 1; PET = positron emission tomography; PINP = procollagen-type-I-N-terminal propeptide; PK = pharmacokinetics; PRO = patient reported outcome; PT = prothrombin time; RECIST = response evaluation criteria in solid tumors; ROS =reactive oxygen species; SAE = serious adverse event; SSE = symptomatic skeletal event; TMB = tumor mutational burden; TSH = thyroid stimulating hormone; T3= triiodothyronine; T4 = thyroxine; ULN = upper limit of normal

a: a cycle is defined as 3-week interval
b: via phone call or on site visit
c: indicated **time-windows refer to cycles/pembrolizumab infusion only**
d: not applicable to participants randomized to pembrolizumab monotherapy in Phase 2 Cohort 1
e: completion of PRO questionnaires as the first activity before any other assessment, procedure, measurement or treatment
f: Biomarker, PK, and immunogenicity **(ADA/NABs)** samples should be taken on the day of pembrolizumab administration
g: Symptomatic Skeletal Events:
- use of EBRT to relieve skeletal symptoms
- new symptomatic pathological bone fractures (vertebral and nonvertebral)
- tumor-related orthopedic surgical intervention
- spinal cord compression

h: If the treatment was permanently discontinued after dose interruption/delay per protocol and the decision to withdraw the participant occurred more than 30 days after last dose of study treatment, the EoT visit should be performed within 14 days of the permanent discontinuation

2. Introduction

2.1 Study Rationale

For the past 2 decades, platinum-based combination chemotherapy has been the standard-of-care first-line treatment for patients with advanced NSCLC. Over the last years, new treatment options including immunotherapy have led to improvement of OS in first and later lines of treatment in these patients.

However, although additional treatments have become available for NSCLC over the last years, not all patients will respond and will eventually progress. New treatment options are needed to induce longer lasting responses in more patients and improve their outcome.

Radiation has been shown to induce increased antigen expression, to release pro-inflammatory cytokines, to recruit immune cells, and ultimately to induce immunogenic cell death (Soukup and Wang 2015). While most data have been generated with gamma radiation, effects of radium-223 are expected to not be impacted by hypoxia (which is a known resistance mechanism against gamma radiation) (Kassis and Adelstein 2005). In addition, radium-223 is targeting osteoclasts which exhibit immunosuppressive properties in bone metastases. In vitro, radium-223 increases antigen expression and stress response and induces immunogenic cell death markers in prostate, breast and lung cancer cell lines (Malamas et al. 2016). There is a robust, growing body of preclinical data describing mechanistic synergy between external beam radiation and immunotherapy (Rodriguez-Ruiz et al. 2019).

Clinical studies (Antonia et al. 2017, Antonia et al. 2018, Shaverdian et al. 2017, Theelen et al. 2019) that combined radiotherapy with immune checkpoint inhibitors have demonstrated synergistic antitumor responses in NSCLC. The data have been generated in both early lines as well as later lines of therapy.

In the randomized, Phase 3 PACIFIC trial, patients with NSCLC who received at least 2 cycles of platinum-based chemotherapy with radiation and did not develop disease progression were randomly assigned in a 2:1 manner to receive durvalumab, anti–programmed death ligand 1 (PD-L1) antibody, at 10 mg/kg every 2 weeks up to 12 months or placebo (Antonia et al. 2017, Antonia et al. 2018). With a median follow-up of 25.2 months, the overall survival in the intent-to-treat analysis was significantly increased among patients who received durvalumab compared with placebo, with a hazard ratio of 0.68 (p=0.0025). The median overall survival was not reached in the durvalumab arm and was 28.7 months in the placebo arm. Progression-free survival was significantly improved with durvalumab (17.2 months vs 5.6 months). The secondary endpoints also favored durvalumab, and safety was similar in both the durvalumab and placebo groups.

The safety and efficacy of combined pembrolizumab and stereotactic body radiotherapy (SBRT) in NSCLC patients (regardless of PD-L1 status) has been studied in a Phase 2 study (PEMBRO-RT) (Theelen et al. 2019). Of the 92 patients enrolled, 76 were randomized to receive pembrolizumab (200 mg every 3 weeks) either alone (control arm) or after radiotherapy (3 doses of 8 Gy) (experimental arm) to a single tumor site. Doubling of ORR in the experimental arm was observed (36% vs. 18%), although the results did not meet the study's pre-specified endpoint criteria for meaningful clinical benefit. Progression-free survival (PFS) (6.6 vs 1.9 months, HR 0.74 (95% CI 0.42 - 1.18); p = 0.19) and OS (15.9 vs 7.6 months, HR 0.66 (95% CI 0.37 - 1.18); p = 0.16) were improved in the experimental arm. Subgroup analyses showed the largest benefit from the addition of radiotherapy in patients with PD-L1–negative tumors. No increase in treatment-related toxic effects was observed in the experimental arm.

The primary objective of the Phase 1 KEYNOTE-001 study was to determine the tolerability and safety profile as well as the anti-tumor activity of pembrolizumab in patients with advanced NSCLC (Shaverdian et al. 2017). Patients received pembrolizumab at a dose of either 2 mg/kg or 10 mg/kg of bodyweight every 3 weeks, or 10 mg/kg every 2 weeks. Forty-two (43%) of 97 patients had previously received any radiotherapy for the treatment of NSCLC before the first cycle of pembrolizumab. For secondary analysis, patients were divided into subgroups to compare patients who previously received radiotherapy with patients who had not. Study results showed that previous treatment with radiotherapy in patients with advanced NSCLC resulted in longer PFS (4.4 vs 2.1 months, HR 0.56 (95% CI 0.34 – 0.91); p = 0.019) and OS (10.7 vs 5.3 months, HR 0.58 (95% CI 0.36 – 0.94);p = 0.026) with pembrolizumab treatment than that seen in patients who did not have previous radiotherapy, with an acceptable safety profile.

Based on available preclinical as well as clinical data as outlined above and based on complementary modes of action between radium-223 dichloride and immune checkpoint inhibitors, and their potentially synergistic effects on the cancer-immunity pathway, the addition of radium-223 dichloride to pembrolizumab therapy might provide a greater clinical benefit to NSCLC patients.

The purpose of the study is to determine the safety and assess the efficacy of the combination of radium-223 dichloride and pembrolizumab in participants with stage IV NSCLC with bone metastases who are either treatment naïve or have progressed on prior anti programmed cell death protein (ligand) 1 (PD-1/PD-L1) therapy.

2.2 Background

NSCLC remains the most common cancer worldwide in terms of new cases (1.8 million in 2012) (Ferlay et al. 2015) as well as death cases. Common sites of metastases are bone, lung, brain, liver, and adrenal glands. Bone metastases are detected with an incidence of 20% to 40% during the clinical course of the disease (Kuchuk et al. 2013). The presence of bone metastases is not only known to represent a negative prognostic factor for patients with NSCLC (O'Connell et al. 1986), but it also significantly affects the quality of life of patients.

Radium-223 dichloride solution for injection is a targeted alpha particle-emitting radiopharmaceutical that exhibits a dual targeting mechanism of action: it destroys tumor cells and inhibits tumor-induced pathological bone reaction. The bone-targeting property of radium-223 is similar to that of other alkaline earth elements, like calcium or strontium-89. However, the radiation characteristics of an alpha particle-emitting radionuclide appear to be more advantageous than that of a beta-emitting radionuclide. Radium-223, with a physical half-life ($t_{½}$) of 11.4 days, emits high linear energy transfer (LET) alpha radiation, with a range limited to less than 100 micrometers. The high LET of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an antitumor effect on bone metastases.

Radium-223 is an isotope which decays and is not metabolized by any enzyme. No impact on radium-223 is, therefore, expected by polymorphic enzymes. Radium-223 dichloride is administered intravenously (IV); therefore, absorption related differences are not applicable for this compound. Given these properties of radium-223 dichloride, it is unlikely that PK interaction may occur.

Radium-223 dichloride was first approved in the EU in 2013 to treat men with mCRPC and symptomatic bone metastases based on data from the ALSYMPCA study. In this study radium-223 dichloride increased OS (hazard ratio [HR] 0·70, p<0·001), reduced the risk of

symptomatic skeletal events (SSEs) (HR 0·66, p<0·001), and improved quality of life (odds ratio 1·82, p=0·004) compared with placebo when added to best standard of care in patients with mCRPC and bone metastases who previously had either received docetaxel or were not candidates for docetaxel treatment (Nilsson et al. 2016, Parker et al. 2013, Parker et al. 2017). There were fewer treatment-emergent AEs with radium-223 dichloride than with placebo (Parker et al. 2013) in ALSYMPCA, confirmed with data from long-term FU (Parker et al. 2017).

In ERA-223 – a Phase 3, double-blind, randomized controlled trial, concurrent treatment of abiraterone acetate plus prednisone/prednisolone (AAP) plus radium-223 dichloride resulted in an increased fracture risk compared to AAP alone in patients with mCRPC. At the primary analysis, treatment-emergent fractures occurred in 103 (26%) of 392 patients in AAP plus radium-223 dichloride group and 38 (10%) of 394 patients in the AAP plus placebo group. Most fractures were outside of sites of bone metastases in both treatment groups. Osteoporotic fractures accounted for most of the observed differences in fracture incidence between the study groups. Bone health agent (BHA) use at baseline was lower in patients who experienced a fracture than in those who had not. Concurrent treatment with AAP plus radium-223 dichloride did not improve symptomatic skeletal event-free survival (SSE-FS) compared to treatment with AAP plus placebo. There was no statistically significant difference in OS between the groups.

While ERA-223 demonstrates that radium-223 dichloride should not be administered in combination with AAP, radium-223 dichloride remains a life-prolonging treatment option for patients with bone-dominant mCRPC and disease progression, based on robust clinical and post-marketing data.

As summarized in the Investigator's Brochure (IB), radium-223 dichloride has also been studied in combination with other anticancer treatments (beyond antiandrogens), namely paclitaxel (tumors with bone metastases, study #17110), docetaxel (prostate cancer, study #15469), exemestane/everolimus (breast cancer, study #17096), standard of care hormonal treatment (breast cancer, study # 16298) as well as bortezomib/dexamethasone (multiple myeloma, study #18987).
In addition, in a clinical trial in prostate cancer evaluating the combination of standard doses of atezolizumab plus radium-223 dichloride (NCT02814669), no dose-limiting toxicities, safety signals, or changes in serum biomarkers were observed beyond the known safety profiles of either drug (Morris et al. 2020).

No safety signal has been identified in these studies and none of these studies has been stopped for safety.

A detailed description of the chemistry, pharmacology, efficacy, and safety of radium-223 dichloride is provided in the investigator's brochure (IB).

Pembrolizumab (Keytruda®) is a potent humanized immunoglobulin G4 monoclonal antibody with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and PD ligand 2 (PD-L2). Based on the preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.
Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous immunotherapy for advanced malignancies. Pembrolizumab is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

In the first-line setting, pembrolizumab is approved for the treatment of NSCLC, both as a single agent (for PD-L1 tumor protein score [TPS] ≥50%) and in combination with cisplatin or carboplatin+pemetrexed (non-squamous only, regardless of PD-L1 TPS) as well as in combination with carboplatin-nab-paclitaxel or carboplatin-paclitaxel (squamous NSCLC, regardless of PD-L1 TPS). In the second line setting after failure of platinum-based chemotherapy, single agent pembrolizumab is indicated for treatment of NSCLC with a PD-L1 TPS ≥1%. There are no comprehensive data regarding the efficacy of pembrolizumab in patients treated after progression on an immune checkpoint inhibitor.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

2.3 Benefit/Risk Assessment

Radium-223 dichloride has a favorable safety profile. The anticipated risks attributed to radium-223 dichloride include the following AEs: GI (constipation, transient but treatable diarrhea, nausea, and vomiting); hematological (transient reduction in neutrophil count, mild to moderate myelosuppression, low grade thrombocytopenia). Due to its radioactive nature, radium-223 dichloride has the potential of inducing long-term toxicities such as other primary cancers.

There is extensive clinical experience available with pembrolizumab in monotherapy and in combination with various agents. Pembrolizumab 200mg every 3 weeks has been shown to be active and tolerable in NSCLC in different treatment settings. Overall, the safety profile is well-characterized as immune-mediated, and considered manageable and acceptable. The immune-related AEs may be fatal and may occur after discontinuation of pembrolizumab.

Overlapping side effects of pembrolizumab and radium-223 dichloride such as GI toxicities are possible and specific guidance for patient monitoring and dose modifications has been included in Section 6.6.1. GI toxicity in the form of diarrhea could be a very common and potentially serious event caused by radium-223 dichloride and pembrolizumab combination therapy. Diarrhea could be either the only presenting symptom of GI toxicity, potentially self-limiting, or part of immune-checkpoint inhibitor-induced colitis that could require hospitalization and intensive treatment. As such, it is important to distinguish among different types of diarrhea and exclude alternative etiology (e.g., disease progression, other medications, infections). Special attention should be given to participants who have undergone prior pelvic radiation therapy, as cases of pelvic radiation disease (characterized by symptoms such as diarrhea, tenesmus, incontinence and rectal bleeding) have been reported.

In addition, a potential increase (severity and/or incidence) in reproductive toxicity for the combination of radium-223 dichloride and pembrolizumab should be taken into consideration. Precautions will be strictly applied to prevent pregnancy.

While no overlapping bone toxicity is expected for the combination of pembrolizumab and radium-223 dichloride, precautionary safety measures have been implemented. All patients must be on a BHA treatment (such as bisphosphonates or denosumab) unless such treatment is contraindicated or not recommended per investigator's judgement (in line with available local guidelines). Patients with history of osteoporotic fracture will be excluded from the study.

Based on the potential effect of radium-223 dichloride on the cancer immunity pathway and the known activity of pembrolizumab in NSCLC, the combination of radium-223 dichloride and pembrolizumab might provide additional clinical benefit to participants.

A positive benefit/risk for the combination treatment of radium-223 dichloride and pembrolizumab is expected since potential antitumor activity is anticipated with a manageable AE profile while the unmet medical need remains high in patients with NSCLC.

3. Objectives and Endpoints

Objectives and Endpoints:

Phase 1

Objectives	Endpoints
Primary	
• To assess the safety of the combination of radium-223 dichloride and pembrolizumab and to determine the recommended Phase 2 dose (RP2D)	• AE assessments using NCI CTCAE v.5.0 and Incidence of DLTs
Secondary	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab	• ORR per RECIST v1.1 • DoR per RECIST v1.1 • DCR per RECIST v1.1
Tertiary/Exploratory	
• To evaluate predictive, prognostic and pharmacodynamic biomarkers • To assess the pharmacokinetics (PK) and immunogenicity of pembrolizumab in combination with radium-223 dichloride (if applicable) • To explore additional indicators of efficacy of the combination of radium-223 dichloride and pembrolizumab	• PD-L1, TMB, bone markers, immune cell analysis and circulating protein markers • Trough PK Concentrations and Titers for ADAs and nABs for pembrolizumab (if applicable) • ORR per iRECIST • DoR per iRECIST • DCR per iRECIST • PFS per v1.1 RECIST and iRECIST • OS

Phase 2 (Cohort 1 and 2)

Objectives	Endpoints
Primary	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone)	• ORR per RECIST v1.1
Secondary	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone) • To evaluate the safety of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab alone)	• DoR per RECIST v1.1 • DCR per RECIST v1.1 • PFS per RECIST v1.1 • OS • AE assessments using NCI CTCAE (v.5.0)
Tertiary/Exploratory	
• To assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (for Cohort 1: compared to pembrolizumab	• SSE-FS • ORR per iRECIST • DoR per iRECIST

Objectives	Endpoints
alone) • To evaluate predictive prognostic and pharmacodynamics biomarkers • To assess patient reported outcome (PRO) (only applicable to Cohort 1) • To assess the PK and immunogenicity of pembrolizumab in combination with radium-223 dichloride (if applicable)	• DCR per iRECIST • PFS per iRECIST • PD-L1, TMB, bone markers, immune cell analysis and circulating protein markers • Time to deterioration in global health status • Time to deterioration in dyspnea • Change from baseline in EORTC QLQ-C30 quality of life scale score and item scores • Change from baseline inEORTC QLQ-LC13 scale scores and item scores • PK trough concentrations and titers for ADAs and nABs for pembrolizumab (if applicable)

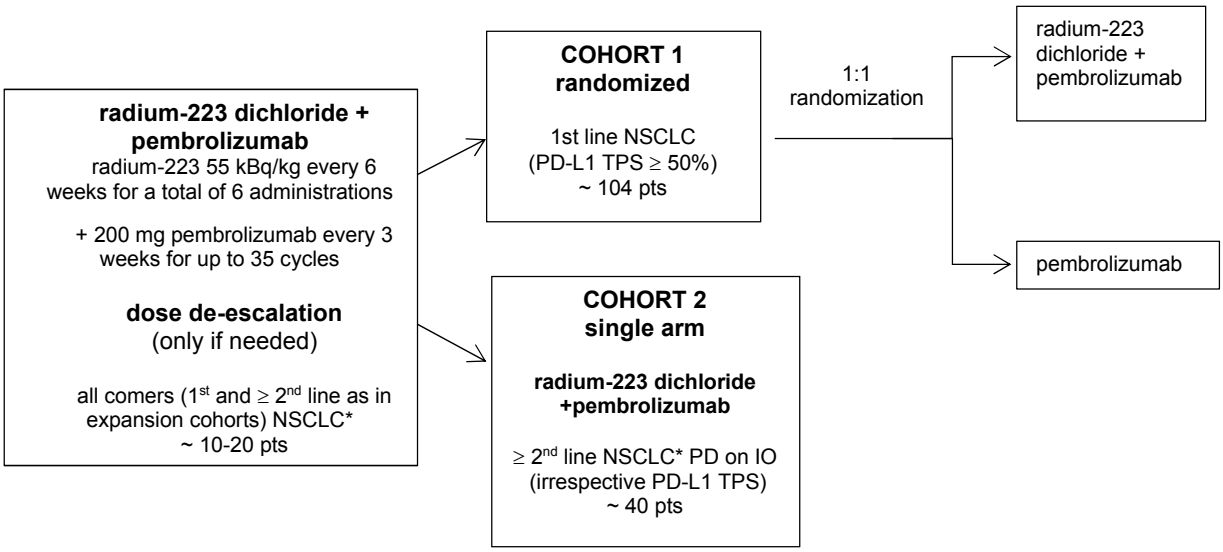
4. Study Design

4.1 Overall Design

This is an open-label, multicenter, Phase 1/2 study which includes a safety run-in as well as two distinct cohorts to assess the efficacy of the combination of radium-223 dichloride and pembrolizumab.

The study schema is provided in Section 1.2, and the Schedule of Activities (SoA) is provided in Section 1.3. For details of treatments given during the study, see Section 6.1. For details on study assessments, see Section 8.

Figure 4-1: Overall Study Design: Phase 1/ 2



Abbreviations: IO = immune oncology; kBq = kilo Becquerel; NSCLC = non-small cell lung cancer; PD = progressive disease; PD-L1 = programmed cell death protein ligand 1; TPS = tumor protein score
* For ≥ 2nd line pretreated with appropriate tyrosine kinase inhibitor (TKI)) in case of EGFR/ALK/ROS1/BRAF genomic tumor aberrations

4.1.1 Screening Phase

Screening examinations will only be performed after the participant has signed the informed consent form (ICF). Participants with NSCLC will be screened for eligibility for up to 21 days prior confirmation of eligibility (Phase1, Phase 2 Cohort2) or randomization (Phase 2 Cohort 1). During this period, the inclusion and exclusion criteria will be evaluated and all screening procedures will be performed. Results of all screening evaluations must be reviewed by the investigator or his/her designee prior to enrollment of each participant into the study to ensure that all inclusion and exclusion criteria have been satisfied (Section 5).

After eligibility has been confirmed and documented (Phase1, Phase 2 Cohort2) or randomization has been performed (Phase 2 Cohort 1), an additional period of up to 21 days may take place before the administration of the first treatment dose, to account for all logistical needs related to radium-223 dichloride dose preparation and transportation. All efforts will be made to shorten this period as much as possible.

4.1.2 Treatment Phase

4.1.2.1 Phase 1 Part

The purpose of the Phase 1 part of the study is to determine the Recommended Phase 2 Dose (RP2D) of radium-223 dichloride in combination with the standard dose of pembrolizumab (200 mg pembrolizumab every 3 weeks [Q3W]) and establish the safety of the combination.

The starting dose of radium-223 dichloride will be the monotherapy dose approved for castration resistant prostate cancer (55 kBq/kg body weight). Radium-223 dichloride will be administered every 6 weeks (every 2nd cycle of pembrolizumab) for a total of 6 administrations. All participants must be evaluated for the occurrence of DLTs during the DLT observation window, which is defined as 6 weeks from the first dose of pembrolizumab. Participants not evaluable for DLT due to early discontinuation (i.e., who have not completed 1 dose of radium-223 dichloride and 2 cycles of pembrolizumab) for reasons other than DLT will be replaced until the RP2D has been determined, additional participants may be recruited until at least 10

evaluable participants have been treated with the RP2D. In case of toxicities, the radium-223 dichloride dose may be reduced to 33 kBq/kg body weight every 6 weeks. The dose de-escalation will follow a 3+3 design.

Decisions on whether to step down to the lower dose level of 33 kBq/kg body weight for radium-223 dichloride will follow the rules described below:

- If 0 out of 3 participants experience a DLT: the dose level will then enroll to a total of up to 10 evaluable participants
- If 1 out of 3 participants experience a DLT: 3 more participants will be enrolled at this dose level
- If 1 out of the 6 participants experience a DLT: the dose level will then enroll a total of up to 10 evaluable participants
- If 2 or more out of 6 participants experience a DLT: step-down to the lower dose level will be implemented.

If during enrollment of the 10 participants, 3 participants experience a DLT, this dose level will be considered not tolerable and a step down from 55 kBq/kg to 33 kBq/kg will be implemented. If no more than 2 out of 10 participants experience a DLT, 55 kBq/kg radium-223 dichloride will then be recommended for the Phase 2 part of the study.

In case of dose de-escalation, the rules as outlined above will be followed with the exception that further dose de-escalation will not be allowed. If 2 or more out of 6 participants or 3 out of 10 participants experience a DLT at the lower dose level of 33 kBq/kg, the study will be terminated. If no more than 2 out of 10 participants experience a DLT, 33 kBq/kg radium-223 dichloride will then be recommended for the Phase 2 part of the study.

Phase 1 should include a minimum of three participants meeting Cohort 2 eligibility criteria at each dose level, if applicable. As participants who already failed prior therapy with an immune checkpoint inhibitor may behave differently in terms of safety than participants receiving first line treatment, the determination of the RP2D might be done separately for the two patient populations, if needed.

Regular safety calls will be implemented with participation of the investigators and sponsor. The decision on potential dose de-escalation and the recommended Phase 2 dose will be made by the sponsor in consultation with the investigators during the dose decision meetings and will be made based on the incidence of DLTs, clinical assessment and all available safety data. The dose decision meeting will be held after 3, 6 and/or 10 evaluable participants have completed the DLT observation period (at each dose level, if applicable). Details of the dose decision meeting will be described in a separate document.

Additional participants may be treated at the RP2D in Phase 1.

All Phase 1 participants will stay in the study and continue receiving study drug at the assigned dose level until withdrawal criteria are met. No intra participant dose escalation or de-escalation is allowed.

4.1.2.2 Phase 2 Part

In Cohort 1 participants with treatment naïve stage IV NSCLC will be randomized 1:1 to receive either radium-223 dichloride plus pembrolizumab or pembrolizumab monotherapy. In Cohort 2 (single arm) participants with stage IV NSCLC who have progressed on prior therapy with immune checkpoint inhibitors will receive radium-223 dichloride plus pembrolizumab. Participants in both cohorts will be treated every 6 weeks with the RP2D of radium-223

dichloride as determined in the Phase 1 part of the study plus 200 mg pembrolizumab every 3 weeks.

4.1.2.3 End of Treatment

Participants will be followed up to 30 days (+ 7 days) after the last treatment. If the treatment was permanently discontinued after dose interruption/delay per protocol and the decision to withdraw the participant occurred more than 30 days after last dose of study treatment, the EoT visit should be performed within 14 days of the permanent discontinuation. During the end of treatment (EoT) visit, procedures to monitor participant' health, to identify potential toxicities, to assess efficacy and to evaluate biomarkers will be performed.

4.1.3 Follow-up

4.1.3.1 Active Follow-up

Participants, who discontinue study treatment due to any reason other than locally confirmed radiological or clinical PD, will be monitored every 3 months (±14 days) for general safety and for efficacy according to the schedule defined in Section 8.1, until any withdrawal criterion for active FU is met.

During active FU participants will be followed for:

- Response according to the protocol defined tumor assessment schedule (see Section 8.1).
- SSEs (Phase 2 only):
  - use of external beam radiotherapy (EBRT) to relieve skeletal symptoms
  - new symptomatic pathological bone fractures (vertebral and nonvertebral)
  - tumor-related orthopedic surgical intervention
  - spinal cord compression
- Treatment related AEs/serious AEs (SAEs).
- SAEs regardless of the investigator's causality assessment, per pembrolizumab requirements with an onset up to 90 days after cessation of study intervention or up to EoT visit (30 [+ 7] days following cessation of study intervention) if the participant initiates new anticancer therapy, whichever is earlier, need to be documented
- New primary malignancy (including acute myeloid leukemia [AML]) or hematological conditions (e.g., myelodysplastic syndrome [MDS], aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment.
- Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage.
- Bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Any anti-cancer treatment and BHA.

4.1.3.2 Long-Term FU

All participants who completed the active FU, will be contacted every 6 months (±28 days) up to at least 2 years after the last dose of radium-223 dichloride to determine survival and long-term safety. This visit may be done by telephone call or on site. Note: participants with confirmed PD during the treatment period enter long-term FU immediately after the EoT visit. During long-term FU participants will be followed for

- Survival status.
- Treatment related AEs/SAEs.
- SAEs regardless of the investigator's causality assessment, per pembrolizumab requirements with an onset up to 90 days after cessation of study intervention or up to EoT visit (30 [+ 7] days following cessation of study intervention) if the participant initiates new anticancer therapy, whichever is earlier, need to be documented.
- New primary malignancy (including AML) or hematological conditions (e.g., MDS, aplastic anemia, myelofibrosis) must be reported as SAEs at any time and regardless of the investigator's causality assessment.
- Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage.
- Bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Any anti-cancer treatment and BHA.

Participants may transition into a separate FU study to complete this long-term FU.

4.2 Scientific Rationale for Study Design

Numerous novel combinations with immunotherapy as backbone are being investigated in clinical trials for metastatic NSCLC. Although checkpoint blockade overcomes many immune-suppressive mechanisms in the tumor microenvironment, most patients do not benefit from this strategy or progress after an initial response. Based on a different and potentially synergistic mechanism of action, combining radium-223 dichloride with pembrolizumab in bone-metastatic NSCLC participants might enhance and consolidate the antitumor response in the first-line clinical setting, leading to durable responses and prolonged survival, and overcome immune suppression and resistance in participants progressing on or after an immune checkpoint therapy.

The study is a combined Phase1/2 study investigating radium-223 dichloride in combination with pembrolizumab which is approved in the treatment of patients with NSCLC. Based on the approval of pembrolizumab, PD-L1 expression ≥ 50% has been chosen as an inclusion criterion for the first line setting whereas participants who have progressed on prior immune checkpoint therapy can be enrolled regardless of PD-L1 expression of their tumor.

The participants are not expected to be exposed to undue risk as major overlapping toxicities are not expected to be observed. Overlapping side effects such as (GI) toxicities are possible.

The sample size and the design of the safety run in Phase 1 part is a standard approach intended to investigate the safety profile and tolerability of new combinations of drugs. Regular safety

calls with participation of the sponsor and the investigators will be held to evaluate and discuss the safety of the participants.

Once the dose of radium-223 dichloride has been determined, the Phase 2 part of the study will start to enable further exploration of tumor responses in participants with NSCLC. This Phase 2 part consists of 2 independent cohorts. Both cohorts will include interim analyses to ensure a minimum benefit is observed before exposing more participants to the new drug combination. An open label approach is considered justified for this signal generating Phase 2 due to the complex handling of the study drug radium-223 dichloride.

4.3 Justification for Dose

Radium-223 dichloride and pembrolizumab are both marketed products. The starting dose of radium-223 dichloride chosen for the study is the monotherapy dose approved for CRPC (55 kBq/kg body weight).

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a Physiologically Based Pharmacokinetic Modeling (PBPK) analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.4 End of Study Definition

The end of the study is defined as the date when the last participant has been followed for at least 2 years after the last dose of radium-223 dichloride or died or withdrew consent.

In the event participants roll over to a separate study for long-term FU, the present study will end when all participants have transitioned into the rollover-study or discontinued from this study for another reason (e.g., consent withdrawn, lost to FU, death). Until the transition to the rollover-study, participants will continue to follow all the procedures and visits required in the current version of the protocol.

The sponsor has the right to close this study or individual sections of this study (e.g., treatment arms; dose cohorts; centers) at any time.

Reasons for closure may include:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g., SAEs)
    - Results of parallel clinical studies or emerging data from literature
    - Results of parallel animal studies (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; dropout rate; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- For strategic reasons (e.g., the clinical development of the treatment combination is stopped)

If the trial is stopped but benefits are observed for ongoing participants, options for treatment continuation will be discussed and agreed between the investigator, sponsor and the participants.

Primary completion will be reached for each cohort respectively, when all participants in each cohort have been followed up for 36 weeks tumor assessment, prematurely discontinued the study for any reasons or have progressed before 36 weeks.

5. Study Population

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

5.1 Inclusion Criteria

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

Age

1. Participant must be ≥ 18 years of age (or age of legal maturity) at the time of signing the informed consent.

Disease Characteristics

2. Histologically or cytologically confirmed diagnosis of stage IV NSCLC.
   Phase 1 includes participants meeting either Cohort 1 or Cohort 2 inclusion criteria as outlined below.
   a. Phase 2 Cohort 1:
      - No Epidermal Growth Factor Receptor (EGFR)/v-Raf murine sarcoma viral oncogene homolog B (BRAF) mutation or anaplastic lymphoma kinase (ALK)/ROS1 rearrangement. Testing is required for all participants with a tumor of non-squamous or not otherwise specified (NOS) histology and for participants with squamous cell carcinoma (SCC) if testing is clinically recommended. Additional genomic tumor aberrations may be assessed per local standard of care
      - Treatment naïve (no prior systemic therapy) for their metastatic NSCLC. Completion of treatment with chemotherapy as part of neoadjuvant/adjuvant therapy is allowed as long as the therapy was completed at least 6 months prior to the diagnosis of metastatic disease
      - PD-L1 TPS ≥ 50% as per local assessment
   b. Phase 2 Cohort 2:
      - Progression on prior treatment with an immune checkpoint inhibitor to be documented within 12 weeks from the last dose (see Section 10.10). Only one prior treatment line with an immune checkpoint inhibitor is permitted unless it is part of an adjuvant or consolidation therapy and the participant did progress more than 9 months after completion of therapy.
      - Prior treatment with platinum-based chemotherapy in combination or in sequence in line with local standard of care
      - BRAF/EGFR sensitization (activating) mutation or ALK/ROS1 rearrangement
        Testing is required for all participants with a tumor of non-squamous or not otherwise specified (NOS) histology and for participants with squamous cell carcinoma (SCC) if testing is clinically recommended.
        - If no EGFR/BRAF mutation or ALK/ROS1 rearrangement: One or 2 prior lines of therapies for metastatic NSCLC
        - If EGFR/BRAF mutation or ALK/ROS 1 rearrangement: Prior treatment with an appropriate tyrosine kinase inhibitor and at

least one and not more than 3 prior lines of therapy for metastatic NSCLC. Participants with more than 3 prior lines of therapy for metastatic NSCLC, may be enrolled after prior discussion with the Sponsor. Additional genomic tumor aberrations may be assessed per local standard of care.

- Availability of tumor specimen for determination of PD-L1 status.

3. Measurable disease per RECIST v1.1 as assessed by the local site investigator/radiologist. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
4. At least 2 skeletal metastases identified at baseline confirmed by magnetic resonance imaging (MRI) (preferable) or computed tomography (CT).
5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.
6. Adequate bone marrow and organ function as assessed by the following laboratory tests:
    a. Hemoglobin ≥ 9 g/dL without transfusion or erythropoietin within the last 4 weeks
    b. Absolute neutrophil count (ANC) ≥ 1500/mm^3
    c. Platelet count ≥ 100000/mm^3 without platelet transfusion within the last 4 weeks
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal (≤ 5 X ULN in case of liver metastases)
    e. Total bilirubin ≤ 1.5 X ULN
    f. Creatinine ≤ 1.5 X ULN or estimated creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation
    g. Prothrombin International normalized ratio or prothrombin time and activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless participant is receiving anticoagulant therapy (as long as PT or aPTT is within therapeutic range of intended use of anticoagulants)
        - Participants being treated with anticoagulant will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. For anticoagulants that require monitoring, standards should be considered and controlled by the investigator. For new oral anticoagulants, an individual risk benefit in accordance with the applicable labels and/or local guidelines should be carefully assessed.

Contraception

7. Female participants of child-bearing potential must have a negative serum pregnancy test within 7 days before the start of study drug administration. Post-menopausal females and surgically sterilized females (please refer to 10.4) are exempt from a pregnancy test.
8. Females of childbearing potential and males must agree to use highly effective methods of birth control (i.e., failure rate <1% per year) from signing of the ICF until at least 120 days after the last administration of pembrolizumab or 6 months after last administration of radium-223 dichloride, whatever comes later, when sexually active (plus an additional 30 days [a menstruation cycle] for female participants and plus an additional 75 days [a spermatogenesis cycle] for male participants who must refrain

from donating sperm during this period).
Highly effective methods of contraception for female participants include: (i) combined hormonal contraception associated with inhibition of ovulation; (ii) progestogen-only hormonal contraception associated with inhibition of ovulation; (iii) intra-uterine device (IUD); intra-uterine hormone-releasing system (IUS); bilateral tubal occlusion; sexual abstinence. Abstinence is only considered an effective method if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment and when this is the preferred and usual lifestyle of the participant. Male participants are required to use condoms unless they have had vasectomy, bilateral orchiectomy and continuous androgen deprivation therapy (total serum testosterone should be less than 50 ng/mL or 1.7 nmol/L). The male participants' partner should use an adequate contraception as described above. Male participants with partners who are pregnant must use a condom during sexual intercourse. Male participants should be advised on the conservation of sperm as there is a potential risk that radiation from radium-223 dichloride could cause adverse effects on fertility.

The investigator or a designated associate is requested to advise the participants how achieve highly effective birth control.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for participants in clinical studies.

Informed Consent

9. Capable of giving informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol before performing any screening assessment.

Other Criteria

10. Participants must be on a BHA treatment, such as bisphosphonates or denosumab treatment unless such treatment is contraindicated or not recommended per investigator's judgement and inclusion is agreed to by the medical monitor.

5.2 Exclusion Criteria

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

Medical Conditions

1. Previous or concurrent cancer within 3 years prior to enrollment except for curatively treated carcinoma in situ (e.g., breast carcinoma, cervical cancer, prostate carcinoma, non-melanoma skin cancer, and superficial bladder tumors).
2. Condition by Cohort and Phase:
    a. Phase 2 Cohort 1 (and participants eligible for 1st line treatment in Phase 1): Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte antigen 4 [CTLA-4], OX40, cluster of differentiation [CD]137).
    b. Phase 2 Cohort 2 (and participants eligible for ≥ 2nd line treatment in Phase 1): Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor

(e.g., CTLA-4, OX40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE.

3. Known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (i.e., without evidence of progression for at least 4 weeks by repeat imaging) (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
4. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
5. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
6. Major surgical procedure or significant traumatic injury within the last 28 days. Note: If participants received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. Central line surgery is not considered major surgery.
7. Non-healing wound, non-healing ulcer, or non-healing bone fracture.
8. Evidence or history of any bleeding diathesis, irrespective of severity.
9. Known history or presence of osteonecrosis of jaw.
10. Known hypersensitivity to the active substance or to any of the excipients of radium-223 dichloride or pembrolizumab
11. Seizure disorder requiring medication.
12. Ongoing infection >Grade 2 NCI-CTCAE v.5.0 requiring systemic therapy
13. Significant acute GI disorders with diarrhea as a major symptom e.g., Crohn's disease, malabsorption, or ≥ NCI-CTCAE v.5.0 Grade 2 diarrhea of any etiology.
14. Pregnant or breast-feeding participants.
15. Congestive heart failure ≥ New York Heart Association (NYHA) class 2. See Section 10.8.
16. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months).
17. Myocardial infarction in the last 6 months
18. Uncontrolled cardiac arrhythmias (≥ grade 3 CTC version 5.0).
19. History of osteoporotic fracture

Diagnostic assessments

20. Known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive or detectable [qualitative] HBV DNA) or known active Hepatitis C virus (defined as HCV Ribonucleic Acid [RNA] [qualitative] is detected) infection.
Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local authority.

21. Known human immunodeficiency virus (HIV). No HIV testing is required unless mandated by local authority.

Prior/Concomitant Therapy

22. Previous (within the last 4 weeks of the planned first dose of study treatment) or concomitant participation in another clinical study with investigational medicinal product(s). Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
23. Systemic steroid therapy within 3 days of the planned first dose of study treatment or chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent). Participants with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
24. Previous treatment with live vaccine within 30 days of planned start of study treatment (seasonal flu vaccines that do not contain a live virus are permitted).
25. Transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte-macrophage-colony stimulating factor [GM-CSF] or recombinant erythropoietin) within 4 weeks prior to planned start of study treatment.
26. Prior treatment with radium-223 dichloride or any therapeutic radiopharmaceutical.
27. Prior radiotherapy within 21 days of planned start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
28. Prior transplantation of human cells, tissues and organs (e.g., liver transplant) or candidates for any type of transplantation.

Other Criteria

29. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial or interfere with the participation for the full duration of the trial
30. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

5.3 Lifestyle Considerations

There are no lifestyle considerations for participants' eligibility for the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who did not subsequently enter in the study.

If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once without the need of re-consent. Only the laboratory tests which are out of range need to be repeated. The laboratory re-tests must be performed within 21 days of the original ICF signature. If the tests cannot be performed or their results will not available within 21 days of the original ICF signature, participant is considered a screening failure.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing

requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened with the following exceptions:

- The participant had successfully passed the screening procedures, but could not start subsequent treatment on schedule, e.g., due to logistical reasons.
- The inclusion/exclusion criteria preventing the participant's initial attempt to participate have been changed (via protocol amendment).

In any case, the investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk.

Diagnostic testing performed as part of the original screening or standard of practice (e.g., CT/MRI scans and bone scintigraphy) will not need to be repeated if performed within 4 weeks of confirmation of eligibility (Phase 1, Phase 2 Cohort 2) or randomization (Phase 2 Cohort 2). However, if CT/MRI scans fall outside of the 28 days allowed period, they will need to be newly acquired.

Re-screening of participants who have failed screening is only allowed once after discussion with the sponsor's designated medical representative and after approval by the sponsor. Sponsor approval of re-screening for a participant must be documented.

The screening failure will be registered to close the patient identification number (PID), and re-screening will start again by signing a new ICF and being assigned a new PID.

6. Study Intervention

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

Participants who satisfy all selection criteria (see Section 5.1 and Section 5.2) will be eligible to start study intervention.

The start of intervention period is defined by the first administration of study intervention. Participants will receive radium-223 dichloride and pembrolizumab combination treatment. If pembrolizumab and radium-223 dichloride are not administered on the same day, the date of pembrolizumab administration is considered start of intervention.

6.1 Study Interventions Administered

A cycle is defined as 3-week interval and starts with every new administration of pembrolizumab.

Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes [-5 min/+10 min]).

Pembrolizumab may be administered up to 3 days before or after the scheduled day of dosing due to administrative reasons.

Dosing interruptions are permitted:

- Up to 3 weeks in the case of medical / surgical events or logistical reasons (i.e. elective surgery, unrelated medical events, participant vacation, holidays) not related to pembrolizumab. Participants should be placed back on pembrolizumab therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant's study record.
- Up to 12 weeks due to treatment related toxicity or need for corticosteroid treatment that cannot be reduced to ≤ 10 mg prednisone or equivalent per day

Pembrolizumab will be administered for a maximum of up to 35 cycles or until PD, death, or withdrawal of consent (whichever occurs first).

Participants who discontinue pembrolizumab due to any reason will also be discontinued from radium-223 dichloride treatment.

Radium-223 dichloride will be administered as a slow bolus IV injection every second cycle of pembrolizumab (every 6 weeks) after initial administration in Cycle 1 for a total of up to 6 administrations or until PD, death, or withdrawal of consent (whichever occurs first). The time window between two radium-223 dichloride administrations should not be less than 4 weeks.

Radium-223 dichloride administration may be delayed by no more than 6 weeks from the date of intended dose (maximum of 12 weeks between 2 doses) for recovery of radium-223 related AEs or any other reason. Continuation of pembrolizumab after stopping radium-223 dichloride can be considered, if this is judged by the investigator to be in the best interest of the participant.

Pembrolizumab and radium-223 should be given on the same day. Radium-223 dichloride must be administered at least 30 minutes post administration of pembrolizumab when study drugs are given on the same day. If not possible, radium-223 dichloride may be administered on a different day following administration of pembrolizumab. The time window between both drug administrations should be as short as possible and not longer than +14 days in C1 and + 7 days thereafter if pembrolizumab and radium-223 are being administered as scheduled. In case of dose delays required for any of the two study drugs, the other study drug can be continued as planned with the aim to again synchronize both drug administrations as soon as possible.

Table 6-1: Study Intervention Administered

Study Intervention	**Radium-223 dichloride (BAY 88-8223)**	**Pembrolizumab**
Type	Drug	Drug
Dose Formulation	Aqueous solution of radium-223 dichloride	Concentrate for solution for infusion 4ml vial (25mg/mL)
Dosage Level(s)	Phase1: RP2D will be determined in Phase 1 part Starting dose is 55 kBq/kg body weight every second cycle after Cycle 1 for 6 injections In case of toxicities, starting dose may be reduced to 33 kBq/kg body weight every 6 weeks	200 mg pembrolizumab Q3W for a maximum of 35 cycles

Table 6-1: Study Intervention Administered

Study Intervention	Radium-223 dichloride (BAY 88-8223)	Pembrolizumab
	No intraindividual dose de-escalation or escalation is allowed Phase 2: RP2D will be administered to all participants	
Route of Administration	slow bolus IV injection (generally up to one minute)	IV infusion
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Vial in lead container and Type A radioactive package. Each vial will be labeled as required per country requirement.	Two vials in a kit box. Each vial will be labeled as required per country requirement.

Abbreviations: IV = intra-venous; kBq = kilo Becquerel; Q3W = every three weeks; RP2D = recommended Phase 2 dose

Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

6.1.1 Radium-223 Dichloride

The sponsor will provide radium-223 dichloride. Radium-223 dichloride is produced according to good manufacturing practice (GMP) and will be delivered with a certified activity. This alpha particle emitting radiopharmaceutical is shipped in a lead container and a Type A radioactive package according to international transportation guidelines for radioactive materials.

Radium-223 dichloride should be received, used and administered only by authorized personnel in designated clinical settings. The receipt, storage, use, transfers and disposal of radium-223 dichloride is subject to the regulations and/or appropriate licenses of the competent official organization.

The volume per vial is 6 mL, corresponding to 6.6 Mega Becquerel (MBq), at the calibration reference day. Radium-223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life is valid for all climate zones I to IV. In addition, it has been shown that the product quality is not jeopardized upon freezing.

The dose should be ordered through IxRS preferably 3 weeks prior to the planned date of administration. The participant's weight taken 3 to 5 days (for US sites) or within 3 days (for ex US sites) before radium-223 dichloride dosing will be submitted with the dose request. The site is not required to perform safety laboratory assessments prior to placing the order.

It is important to note that, in general, in all cases where study drug has been ordered, the time window for administration should be within 3 days of the scheduled radium-223 dichloride dosing day. If administration must be postponed more than 3 days after the scheduled radium-223 dichloride dosing day, replacement of the drug order may be required.

For more details please refer to the Pharmacy Manual.

Written information about radium-223 dichloride and instruction about storage, handling, and injection of radioactive material will be provided to study personnel.

In general, the administration of radioactive drugs involves a potential risk for third parties, due to radiation from the participant and due to possible contamination by spilling urine or feces or vomit. When radium- 223 dichloride has been injected intravenously into a participant, the risk for external radiation exposure to third parties is extremely low, due to the short range of the alpha particles (<100 μm) and the low portion of beta and gamma radiation. For these reasons the product can be administered on an outpatient basis.

To minimize the risk of contamination, the participant and her/his caregivers will be provided with instructions regarding hygiene precautions to abide by after receiving the radioactive drug according to the investigational study site radiation protection guidelines.

6.1.1.1 Dose Calibration

Radium-223 dichloride can be measured in a normal dose calibrator instrument. When all the required written approvals for the use and handling of radium-223 dichloride from the Radiation Protection Agency/Agencies for the specific site have been received by the sponsor, a vial of radium-223 dichloride for technical use may be sent to the study site, if the site is not already a qualified user of radium-223 dichloride.

Different clinical study sites possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from site to site. Consequently, each site must perform the radium-223 dial setting on their relevant dose calibrator(s) if no isotope calibration factor for radium-223 is being provided by the vendor of the dose calibrator. For dial setting, the clinical study site will receive a sealed vial or a prefilled syringe containing a radium-223 solution for calibration only. The vial or syringe is identical to the vials/syringes used for study treatment. The amount of radium-223 in the vial/syringe will be stated on the label. Instructions for the dial setting, including the calibration log form, will be enclosed with the dispatch of the calibration sample.

For clinical study sites in Japan: A radium-223 calibration factor (traceable to the Japanese national radium-223 standard provided by JRIA/AIST) is generally provided by the vendor of the dose calibrator and must be used. If this radium-223 calibration factor cannot be provided by the vendor, the clinical study site needs to perform the dial setting using a sealed calibration-vial containing a radium-223 solution for dial-setting (traceable to National Institute of Standards and Technology [NIST]). This sealed vial will be provided from the sponsor. The investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

6.1.1.2 Dose Handling

Radium-223 dichloride should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides.

The radium-223 dichloride vials or patient ready doses (PRDs) must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production or prior to the expiry date specified for PRDs.

Control measurements of both the radium-223 dichloride vial (before and after dispensing) and syringes (before and after administration) are performed as part of the clinical trial documentation. Since PRDs will be prepared at the country depot, relevant procedures are recorded by the country depot staff. All administrations of radium-223 dichloride will be based on the certified activity of radium-223 at the reference date.

6.1.1.3 Dose calculation

For this study, two dose levels of radium-223 dichloride may be tested:

- 55 kBq/kg body weight
- 33 kBq/kg body weight

The total activity to be injected will be calculated volumetrically using the participant's body weight (kg) within 3 days prior to the dose for ex-US sites or 3 to 5 days prior to the dose for US sites, the dosage level, and the decay correction factor (DK) to correct for physical decay of radium-223 (ex-US sites only). A table with DKs according to physical decay of the study medication will be provided with each vial of radium-223 dichloride (ex-US sites only). The total amount (volume to be drawn into the syringe) to be administered to a participant should be calculated according to the recommended formula below for each dose group:

- 55 kBq/kg

$$\frac{\text{Body Weight (kg)} \times 55\ \text{kBq/kg}}{\text{DK} \times 1{,}100\ \text{kBq/mL}} = \text{volume to be injected (mL)}$$

In case of de- escalation:

- 33 kBq/kg

$$\frac{\text{Body Weight (kg)} \times 33\ \text{kBq/kg}}{\text{DK} \times 1{,}100\ \text{kBq/mL}} = \text{volume to be injected (mL)}$$

Site specific volume calculation methods are acceptable as well, provided that the participant dose is as indicated above.

Data regarding activity, calculations (ex-US sites only), and volume to be injected must be recorded in the Investigational medicinal product (IMP) preparation log and in the study electronic data capture (EDC) tool. This applies to both doses that are prepared at the study site and doses that are prepared by an off-site vendor.

In the US, applicable documentation is required for the country PRD depot. The participant's weight will be obtained only once for each dose. To ensure time for the country PRD depot to prepare and deliver the PRDs to the sites:

- The participant's weight will be obtained 3 to 5 days before the planned dosing date
- This weight will be communicated to the country PRD depot for preparation of the current dose along with a prescription and any other details required by the PRD depot; a record of this information transfer will be retained at the site
- Documentation by the PRD depot of the required activity and volume in the syringe will be retained at the depot with a copy provided to the site

Participants at ex-US sites should be reweighed on the day of dose administration; the final dose to be administered should be determined using that weight. Participants should not be weighed more than once or at different departments on the day of the administration to avoid the potential use of different weights. Participants in the US will receive patient-ready doses based on the participant weight 3 to 5 days before the day of administration. Therefore, no other weight measurement is needed.

6.1.1.4 Dose preparation

Personnel should use appropriate protective clothing and equipment during syringe filling and application to prevent contamination with the radioactive solution (lab coats, medical gloves, protective glasses) and to reduce radiation exposure. Sites should adhere to all relevant radiation safety regulations as prescribed by local authorities administering their site radiation license, including as low as reasonably achievable principles.

Filling of the syringe should take place in a safety bench or similar cabinet in the Radiopharmacy/Nuclear Medicine Department. The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe. The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy. In some countries/study sites, a third party vendor will be used to prepare the injections to be used by the study site.

Radium-223 dichloride should not be diluted or mixed with any solutions. If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a participant.

It is important to note that, in general (unless otherwise agreed, e.g., for sites using PRD depots [Section 6.1.1.2]), in cases where study drug has been ordered, the time window for administration should be within 3 days of the scheduled treatment visit. If administration must be postponed more than 3 days after the scheduled treatment visit, replacement of the drug order may be required.

The study intervention will be administered as a slow bolus IV injection. The actual radioactivity administered must be within the tolerance limits of ± 10% of the calculated radioactivity. After administration, the equipment used in connection with the preparation and administration of drug, are to be treated as radioactive waste and should be disposed in accordance with hospital procedures for the handling of radioactive material and according to local laws. Written information about radium-223 dichloride and instructions for the handling and injection of radioactive material will be provided to study personnel.

For additional information regarding dose preparation, please refer to the Pharmacy Manual.

6.1.2 Dose Limiting Toxicities

In Phase 1, dose-limiting toxicities, using CTCAE version 5.0 for the severity grading, will be monitored for each participant during 6 weeks after the first administration of pembrolizumab (DLT window).

The occurrence of any of the following toxicities during the DLT window will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study treatment administration, excluding toxicities clearly not related to the any of study drugs, i.e. radium-223 dichloride or pembrolizumab, such as disease progression, environmental factors, unrelated trauma, etc.:

1. Grade 4 non-hematologic toxicity.
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with clinically significant bleeding
3. Any non-hematologic AE (excluding laboratory) ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 3 days;

Grade 3 diarrhea, nausea, or vomiting despite use of anti-emetics or anti-diarrheals per standard of care lasting ≤ 3 days; Grade 3 rash without use of systemic corticosteroids or anti-inflammatory agents per standard of care.

4. Any Grade 3 non-hematologic laboratory value if:
   - Clinically significant medical intervention is required to treat the participant, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for >1 week.
5. Liver function tests:
   - Grade 3 abnormality in AST, ALT, or bilirubin in a participant without liver metastases at screening
   - The abnormality results in a Drug-induced Liver Injury (DILI) (see Section 8.3.6)
6. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3 degrees Celsius [°C] (101 degrees Fahrenheit [°F]) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
   - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
7. Prolonged delay (>2 weeks) in initiating Cycle 2 of pembrolizumab due to treatment-related toxicity
8. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1 or 2.
9. Missing >25% of pembrolizumab doses as a result of drug-related AE(s) during the first cycle.
10. Grade 5 toxicity.

For details on dose cohort management and dose de-escalation, please refer to Section 4.1.2.1.

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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).

Further guidance and information for the final disposition of unused study interventions are provided in the Clinical Trial Supply Plan (CTSP) /Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

In Phase 1 and Phase 2 Cohort 2 all participants who meet the inclusion/exclusion criteria will receive radium-223 dichloride plus pembrolizumab. Phase 1 as well as Phase 2 Cohort 2 are uncontrolled and all participants will receive pembrolizumab which is approved for the treatment of NSCLC.

Participants in Phase 2 Cohort 1 will be randomized in a 1:1 ratio to receive either radium-223 dichloride plus pembrolizumab combination or pembrolizumab alone. Pembrolizumab which is approved for the treatment of NSCLC will be given to participants in both arms.
The study is open label, however potential bias will be reduced by central randomization. The specific intervention(s) to be administered to a participant will be assigned using an IxRS. The site will contact the IxRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required.

In order to ensure participants' safety and the integrity of trial, the study will include the same regular safety examinations for all participants as well as appropriate dose modifications.

6.4 Study Intervention Compliance

The administration of radium-223 dichloride and pembrolizumab will be performed at the site as indicated in Section 1.3 and must be recorded in the source data and electronic case report form (eCRF).

Reasons for dose delay, interruption, or discontinuation will also be recorded in the source data and in the eCRF.

Participant compliance with study intervention will be assessed at each visit. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study till EoT (for BHAs until end of long term FU) must be recorded on eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

All participants must be on a BHA treatment, such as bisphosphonates or denosumab treatment unless contraindicated or not recommended per investigator’s judgement.

Administration of contrast media for protocol-specified radiological procedures does not need to be reported, unless there is an AE related to the contrast medium injection (e.g., allergic reaction).

All medication and therapies which are considered necessary for the participant’s welfare, and which are not expected to interfere with the evaluation of the study intervention, may be given

at the discretion of the investigator. The sponsor or representative should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Prohibited Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the sponsor.

The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the sponsor and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- The use of systemic corticosteroid or immunosuppressant before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. Note: replacement therapy such as physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency (in dosing not exceeding 10 mg daily of prednisone equivalent) is not considered a form of systemic treatment as well as inhaled steroids are allowed for management of asthma. Moreover, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions as well as allergy to contrast media.
- Anti-neoplastic therapies, including immunotherapy, chemotherapy, biological therapy or experimental therapies other than radium-223 dichloride and pembrolizumab.
- Radiation therapy

  Note: Radiation therapy to a symptomatic lesion may be allowed after discussion with the sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Live vaccines must not be administered for 90 days after the last dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu - Mist®) are live attenuated vaccines, and are not allowed
- Excessive intake of biotin above the recommended daily dose of 30 µg. Biotin is found in multivitamins, including prenatal multivitamins, biotin supplements, and dietary supplements for hair, skin, and nail growth at levels that may interfere with laboratory tests.

6.5.2 Permitted Concomitant Therapy

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

- Participants who are therapeutically treated with an agent such as warfarin or heparin or novel oral anticoagulants (NOACs) such as dabigatran or rivaroxaban will be allowed to

participate provided that no prior evidence of underlying abnormality in coagulation parameters exists.

- Palliative or supportive care for any underlying illness (e.g., Megestrol acetate (Megace®) as supportive care).
- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all participants on this trial. The use of anti-diarrheal or anti-emetics according to standard practice is strongly encouraged.

All medication and therapies which are considered necessary for the participant's welfare, and which are not expected to interfere with the evaluation of the study intervention, may be given at the discretion of the investigator.

6.5.3 Drug-Drug Interactions Relevant for Pembrolizumab

No formal PK drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

6.6 Dose Modification

6.6.1 Toxicity Management and Dose Modifications Recommendations for Radium-223

Decisions on whether to step down to the lower dose level for radium-223 dichloride of 33 kBq/kg body weight based on DLT are explained in Section 4.1.2.1. Otherwise, intra-participant dose reduction of radium-223 dichloride is not allowed (Section 6.1.1). The dose of pembrolizumab will remain constant at 200 mg Q3W for each dose level, in each cohort and in each participant.

Based on a participant's AE, the investigator will determine which study drug may be related to the toxicity and, therefore, apply the respective dose modification. In case an attribution to radium-223 dichloride or pembrolizumab cannot be determined and conflicting recommendations are provided, the most conservative approach should be followed.

Prior to each dose of radium-223 dichloride, participants must meet the following criteria for study treatment administration:

- Hemoglobin (Hb) level ≥8.0 g/dL
- Platelet count ≥50 x 10^9/L
- ANC ≥1 x 10^9/L
- All non-hematological toxicities resolved to Grade ≤2 or baseline

Every effort will be made to administer the full dosing regimen (6 doses of radium-223 dichloride). Dose adjustment of radium-223 dichloride is not permitted. The minimum time window between 2 doses of radium-223 dichloride must be 4 weeks.

GI toxicity in the form of diarrhea could be very common and potentially serious event caused by radium-223 dichloride and pembrolizumab combination therapy.

The below guidance should be considered in addition to the guidance outlined in Table 6-2.:

- Monitor all patients for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and bowel perforation (e.g., peritoneal signs and ileus)

- For diarrhea G1 and G2:
  - Consider oral fluids, loperamide, avoid high fiber/lactose diet
- For diarrhea ≥ G2, please consider per local institutional guidelines:
  - Blood tests (e.g., hematology and general chemistry including liver function tests (AST, ALT, Bilirubin))
  - Stool examination (e.g., culture, *Clostridium difficile*, cytomegalovirus or other viral etiology, ova and parasite)
  - GI consultation and Imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy)
  - Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper upon AE improving to ≤ G1 and continue to taper over at least 4 weeks
- For severe and life-threatening diarrhea/colitis:
  - Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance
  - Fluid and electrolytes should be administered via IV infusion.
  - Urgent GI consultation and Imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy)
  - IV corticosteroid should be initiated first followed by oral steroid.

6.6.2 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6-2.

Table 6-2: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General instructions:
Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAE v.5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and FU
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion (see Section 6.6.1).
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM)	Newly onset T1DM or	Withhold[a]	Initiate insulin replacement therapy for participants with	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

Table 6-2: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

or Hyperglycemia	Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure		T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis and Stevens-Johnson Syndrome		

Table 6-2: Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

	Grade 4 or recurrent Grade 3	Permanently discontinue		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events; GI = gastrointestinal; irAE = immune-related AE; IV = intravenous; T1-DM = type-1 diabetes mellitus

[a] Withhold or permanently discontinue pembrolizumab at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

6.6.3 Dose Modification and Toxicity Management of Infusion-Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6-3.

Table 6-3: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be premedicated 1.5 hours (± 30 minutes) prior to infusion with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of analgesic).
Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4 Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Abbreviations: CTCAE = common terminology criteria for adverse events; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE v.5.0

6.7 Intervention after the End of the Study

After the end of study, further therapy is at the discretion of the investigator.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Section 6.6 or if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and FU and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Temporary discontinuation of pembrolizumab may be considered for participants who have attained a confirmed complete response (CR), have received at least 8 infusions (24 weeks) of pembrolizumab treatment and had at least 2 infusions with pembrolizumab beyond the date when the initial CR was declared.

No temporary discontinuation of radium-223 is allowed.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant must be withdrawn from the study at any time at his/her own request.

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, and additionally requests destruction of her/his samples taken but not yet tested, the investigator must document this (either destruction by site or request to central lab, as applicable) in the site study records.

In all cases, the reason for withdrawal must be recorded in the eCRF and in the participant's medical record.

Withdrawal from Study Intervention Period

Participants **must** be withdrawn from the intervention period if any of the following occurs:

- If, in the investigator's opinion, continuation of the study intervention would be harmful to the participant's well-being.

- Confirmed radiological disease progression (using iRECIST), unless the investigator in consultation with the sponsor or representative deems that continued treatment is appropriate.
- Clinical progression per investigator judgement.
- Substantial noncompliance with the requirement of the study.
- Pregnancy as confirmed by a urine dipstick test or serum test. Pregnancy will be reported under the same timelines as an SAE.
- Use of illicit drugs or other substances that may, in the opinion of the investigator or their designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Development of any intercurrent illness or situation which may, in the judgment of the investigator, affect assessment of clinical status and study endpoints to a relevant degree.
- Development of a second primary malignancy that requires a different treatment
- Start of a new systemic anti-cancer treatment.
- Unacceptable toxicity, i.e. event requiring permanent discontinuation of pembrolizumab according to dose modification guidance in Section 6.6.2.
- Participants who experience a delay of more than 12 weeks to receive the subsequent pembrolizumab infusion due to treatment related toxicity or need for corticosteroid treatment that cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
- Participants who complete 35 infusions of pembrolizumab (after approximately 2 years of treatment).
- Participants who experience a delay of more than 3 weeks to receive the subsequent pembrolizumab infusion due to medical / surgical events or logistical reasons (i.e. elective surgery, unrelated medical events, participant vacation, holidays) not related to pembrolizumab. Note: participants should be placed back on pembrolizumab therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor.
- Lost to FU
- Withdrawal of consent for study intervention
- Death
- ***Withdrawal of radium-223 only:***
    - Participants who experience a delay of more than 6 weeks to receive the subsequent radium-223 injection due to any reason (more than 12 weeks between 2 doses)

Withdrawal from active follow-up

Participants must be withdrawn from active FU if any of the following occurs:

- Radiologically (using iRECIST) or clinically confirmed PD is observed.
- Start of subsequent anti-cancer treatment

- Lost to FU
- Withdrawal of consent to efficacy FU visits
- Death

Participants **may** be withdrawn from active FU if any of the following occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance).

Withdrawal from long-term FU

Participants must be withdrawn from long-term FU if any of the following occurs:

- Lost to follow-up
- Withdrawal of consent to long-term FU
- Death

Participants may be withdrawn from long-term FU if any of the following occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance).

7.3 Lost to Follow-up

A participant will be considered lost to FU 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to FU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to FU.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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.

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 and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

The RECIST v1.1 and iRECIST criteria will be used for efficacy evaluation of response and disease control (for details see 10.7). Participants who show evidence of radiological PD by RECIST 1.1 and are clinically stable may continue on study treatment until repeat imaging is obtained and confirmation of progression is documented according to iRECIST criteria. For further guidance please refer to Section 10.7.2. Participants who continue to receive study drug after confirmed disease progression as defined by iRECIST must sign a written informed consent prior to receiving any additional dose of study drug. In addition, treatment beyond progression should not delay an imminent intervention to prevent serious complications of disease progression (i.e. central nervous system [CNS] metastases).

Radiological tumor assessments will be performed locally by the investigator/radiologist. Tumor imaging should be performed by CT or MRI with contrast enhancement. At FU CT or MRI can be done, as an exception, without use of contrast media if this is contraindicated. For chest examination, CT is strongly recommended and preferred. A bone scan (i.e. whole-body technetium-99m bone scan) is mandatory at baseline only. If in the opinion of the investigator, the bone scan is not considered appropriate, whole-body FDG-PET or FDG-PET/CT scan is acceptable. Bone metastases detected by bone scan should be confirmed by MRI (preferable) or CT. All scans should be interpreted by the same radiologist/investigator during the study, where at all possible.

The first radiological tumor evaluation will be conducted during the screening period. Images that were obtained prior to the signing the ICF as part of normal clinical FU of the participant's tumor can be used as long as they were performed within 28 days of randomization or confirmation of eligibility and meet the requirements for the study.

Tumor evaluation must include chest, abdomen and pelvis, and bone. Head CT or MRI will be done in participants with known active or suspected central nervous system metastases and/or carcinomatous meningitis at baseline (screening) and throughout the study treatment period.

Tumor assessments during the study intervention and active follow-up periods include the same anatomic areas as baseline and will be done until radiological disease progression or the end of the study.

Evaluations are to be performed at screening, and every 6 weeks (± 7 days) following Cycle 1 Day 1 for the first 36 weeks, thereafter every 9 weeks (±7 days) up to 2 years, after 2 years every 3 months (±14 days). The evaluations will end when confirmed disease progression by iRECIST is documented.

For participants who discontinue study intervention without radiological disease progression, subsequent tumor assessments will be obtained during active FU.

All scans should be done with the same modality (CT or MRI) and the equivalent technique (e.g., slice thickness, field of view) to those obtained at baseline.

Scan data should be stored in DICOM (Digital Imaging and Communications in Medicine) format until the end to the trial (either in the radiology department or in the investigator site file on applicable storage media, e.g., CD/DVD and made available to the sponsor upon request.

8.2 Safety Assessments

Safety will be assessed by monitoring and recording all AEs and SAEs, cardiac, hematologic, and blood chemistry parameters, vital signs, ECOG PS, and any abnormal findings observed during the performance of physical examinations.

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

A complete physical examination will include, at minimum, assessments of the Cardiovascular, Respiratory, GI, and Neurological systems. Height and weight will also be measured and recorded (Section 1.3).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Body temperature, pulse rate, and blood pressure will be assessed.
- Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse

8.2.3 Electrocardiograms (ECGs)

- Single12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).

8.2.4 Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
    - The investigator must review the laboratory report, document this 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory are considered clinically significant by the investigator, then these also need to be reported as SAE or AE.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the EoT visit after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the protocol and the SoA.

8.2.5 ECOG Performance Status

An ECOG PS score of 0 or 1 is required for study inclusion (see Section 5.1). Assessment of ECOG performance is carried out during screening, on Day 1 of each cycle, and at the EoT visit as indicated in the SoA (Section 1.3).

Grading definitions for ECOG PS are given in Table 8-1 below.

Table 8-1: Definitions for ECOG PS Grading

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status

8.2.6 Patient Reported Outcome

Patient reported outcomes are administered to both Cohort 1 and Cohort 2 in Phase 2 to assess health condition of the participants. For participants in Cohort 1, PROs are administered within 7 days before study intervention and thereafter, on Day 1 of every second cycle. It is strongly recommended that PROs are completed prior to study drug administration, adverse event evaluation, and disease status assessment. For participants in Cohort 2, PROs are administered only within 7 days before study intervention.

EORTC QLQ-C30 (version 3.0) and a supplementary questionnaire module (EORTC QLQ-LC13) are administered to participants. The EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects and is the most widely used cancer-specific Health Related Quality of Life (HRQoL) instrument. It contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) and global health and quality of life. The global health and quality of life scale uses a 7 point scale scoring with anchors (1=very poor and 7=excellent); the other items are scored on a 4 point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much).

The EORTC QLQ-LC13 (Bergman et al. 1994) , a supplemental lung cancer-specific module used in combination with QLQ-C30 (Aaronson et al. 1993), comprises multi-item and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy and alopecia). It is scored on a 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much).

Detailed scoring approach for the PROs is presented in Section 10.5 (Appendix 5).

8.2.7 Pregnancy Test

A serum pregnancy test is performed at screening. From Cycle 1 onwards, either a urine or serum pregnancy test may be used. The frequency of pregnancy tests may be higher, if required by local regulations.

8.2.8 Baseline Characteristics

Demographics

Baseline participant data pertaining to demographic information should be documented accordingly in the appropriate eCRF including the following:

- Date of birth (year, age) if allowed according to local law
- Gender
- Race, if legally allowed
- Ethnicity, if legally allowed
- Weight (weight is also measured at other time points indicated in the SoA, Section 1.3)
- Height

Medical History

Medical history findings (including co-existing disease, prior non cancer related surgery, and allergy history) and smoking history meeting all criteria listed below will be collected as available to the investigator.

- Started before signing the ICF
- Considered relevant for the participant's study eligibility.

Other Baseline Characteristics

Other baseline characteristics will be collected, including but not limited to:

- Baseline cancer characteristics, including cancer type, date of initial diagnosis, histology, tumor stage, and tumor mutations, date of most recent progression, prior cancer therapies and procedures, and radiotherapy
- ECOG-PS
- All medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 21 days prior to the study intervention.

All the population characteristic data should be recorded in the eCRF. Detailed instructions on baseline characteristics can be found in the eCRF completion guidelines.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative or health care professional not involved in the study).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for following up SAEs, or AEs, considered related to the study intervention or study procedures, or those that caused the participant to discontinue the study intervention or the study (see Section 7). Events of Special Interest have to be followed up regardless of causality or relationship to study intervention.

Investigators should refer to the current radium-223 dichloride and pembrolizumab IB for the expected side effects. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs, whether or not related to the study drugs, will be collected from the signing of the ICF until the EoT visit after the last dose of the study intervention at the time points specified in the SoA (Section 1.3); all AE/SAEs must be fully documented in the participant's records and on the respective CRF pages by the investigator.

An AE/SAE (irrespective of causal relationship) not completely resolved at the EoT visit must be followed up until resolution (chronicity, baseline grade or complete resolution) or until the investigator considers the event will not improve further.

In addition, during the FU period participants will be followed for:

- Study intervention related AEs/SAEs
- All SAEs regardless of the investigator's causality assessment, per pembrolizumab requirements, with an onset up to 90 days after cessation of study intervention or up to EoT visit (30 [+ 7] days following cessation of study intervention) if the participant initiates new anticancer therapy, whichever is earlier, need to be documented.
- All occurrences of leukemia, myelodysplastic syndrome, aplastic anemia, and primary bone cancer or any other new primary malignancy; regardless of the investigator's causality assessment.
- Any anti-cancer treatment and BHA
- All bone fractures and bone associated events (e.g., osteoporosis) need to be reported as either AEs or SAEs if the criteria of SAE were met, regardless of the investigator's causality assessment.
- Radium-223 dichloride-related occurrences of febrile neutropenia or hemorrhage will also be collected.
- *Only during Active FU of Phase 2*: SSEs need to be collected as either AEs or SAEs regardless of the investigator's causality assessment.

Medical occurrences that begin before obtaining informed consent will be recorded on the medical history section of the eCRF.

Medical findings (e.g., ECG or radiological findings), that conceivably started before signing of informed consent, will be recorded as medical history.

Medical conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE section of the eCRF.

Medical occurrences that started before but deteriorated after obtaining informed consent will be recorded as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to FU (as defined in Section 7.3). Further information on FU procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected at least 6 months after the last dose of study intervention

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4). The participant will be withdrawn from the study.

If a participant becomes pregnant while on treatment, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor.

Radium-223 dichloride and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period and up to 6 months after the last dose of radium-223 dichloride or up to 120 days after the last dose of pembrolizumab, whichever is later. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

For a pregnancy in the partner of a male study participant, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

8.3.6 Adverse Events of Special Interest

Selected non-serious and serious AEs are also known as AEs of Special Interest (AESI) and must be reported to the sponsor **(within 24 hours of the investigator's awareness)**:

AESI - Pembrolizumab

- Pembrolizumab overdose defined as ≥1000 mg (5 times the study dose) of pembrolizumab.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing (per DILI criteria).

AESI – Radium-223

- All bone fractures (including asymptomatic radiologic fractures)
- Osteonecrosis of the jaw (ONJ)

8.4 Treatment of Overdose

Radium-223 dichloride

There have been no reports of inadvertent overdose of radium-223 dichloride solution during clinical studies.

There is no specific antidote. In the event of an inadvertent overdose, general supportive measures, including monitoring for potential hematological and GI toxicity should be undertaken.

Single doses up to 276 kBq (0.00746 milli Curie [mCi]) per kg b.w. were evaluated in a Phase 1 clinical trial and no dose-limiting toxicities were observed.

Pembrolizumab

An overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥ 5 times the indicated dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

General guidance

In the event of an overdose, the investigator should:

1. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 120 days for pembrolizumab).
2. Obtain a serum sample for PK analysis (for pembrolizumab PK in case of a pembrolizumab overdose) within 3 days from the date of the last dose of study intervention if requested by the sponsor (determined on a case-by-case basis). In case the overdose is identified during a clinical visit, then a serum PK sample should be collected during that visit (if no scheduled PK sampling is planned).
3. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.
4. AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF.
5. Appropriate supportive treatment should be provided if clinically indicated.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

For detailed guidance on overdosing please refer to the most current version of the IBs for radium-223 dichloride and pembrolizumab.

8.5 Pharmacokinetics

In all participants enrolled, serial blood (serum) samples will be collected at the time points shown in the SoA Table 1-2, to assess PK of pembrolizumab.

Wherever possible, all efforts should be made to adhere to the blood sampling schedule as given in Section 1.3. Samples for PK will be collected at pre-dose on Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter and at EoT. The PK sampling beyond Cycle 8 might be discontinued after sponsor agreement, if no additional benefit or knowledge will be expected.

A decision to analyze PK samples for pembrolizumab will be made during the course of the study. Until that time, samples will be held by the central lab.

When the PK assessments coincide with the ECG recording and/or the measurement of vital signs (blood pressure and heart rate), participants' ECG and vital signs will be measured before collection of the PK sample. If this sequence is not feasible, then the investigating site should obtain the PK sample at the planned time, followed by 5-10 minutes period of quiet rest in supine or semi-recumbent position, then the ECG and finally the vital signs.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

The date and time of actual blood sampling will have to be documented in the eCRF. The actual dosing start and stop date and time will have to be documented in the eCRF.

Instruction for the collection, processing, storage, and shipment of PK samples will be provided separately by the sponsor (sample handling sheets and Biosample Management Plan).

For this trial, PK parameters will not be calculated/reported by the sponsor; the samples may be used for separate PK analyses under separate cover.

8.6 Pharmacodynamics

Refer to Section 8.8.

8.7 Genetics

Refer to Section 8.8.

8.8 Biomarkers

8.8.1 Biomarker Overview

For all participants, archival or fresh tumor material has to be collected during screening. For participants eligible for first line treatment and enrolled in Phase 1 or Phase 2 Cohort 1, PD-L1 expression has be determined prior to enrollment to confirm eligibility. If a PD-L1 testing result is available (based on an approved or appropriately validated test) at screening and has

been performed in line with the protocol requirements, this can be used to confirm eligibility of the participant and does not need to be repeated. For all other participants (Phase 1 ≥ 2nd line treatment and Phase 2 Cohort 2) , the PD-L1 test result is not required to be available before enrollment and will be determined retrospectively in a central laboratory.

Tumor samples are to be collected for all participants and will further be used to determine TMB by Next Generation Sequencing (NGS) as well as to determine the inflammatory status of a tumor.

Pharmacodynamic biomarker evaluations will be conducted for all participants enrolled in the study using circulating markers. Biomarker samples will be collected from participants as specified in the SoA and as described below, and will include the following:

- Serum/urine samples will be used to assess baseline and post-dose levels of bone formation (e.g., B-ALP, PINP) or bone resorption markers (e.g., bCTX , NTX).
- Plasma will be used for evaluations of circulating tumor DNA, and circulating protein markers such as cytokines
- Whole blood will be collected for immune cell analysis.

Blood, serum/urine, and plasma samples will be collected on Day 1 (predose) and Day 15 of Cycle 1, thereafter on Day 1 (predose) of subsequent cycles, and during the EoT visit. Samples will be tested for bone biomarkers and circulating proteins or tumor DNA.

Details on collection, processing, storage and shipment of samples are described in a separate document (e.g., sample handling sheets or laboratory manual).

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of biomarker responses to pembrolizumab.

8.8.2 Immunogenicity Assessments

Antibodies to pembrolizumab will be evaluated in serum samples collected from all participants according to the SoA. Samples will be collected at pre-dose on Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter and at EoT. Immunogenicity sampling beyond Cycle 8 might be discontinued after sponsor agreement, if no additional benefit or knowledge will be expected (Section 8.5).

A decision to analyze immunogenicity samples for pembrolizumab will be made during the course of the study. Until that time, samples will be held by the central lab.

Serum samples will be screened for antibodies binding to pembrolizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to pembrolizumab and/or further characterize the immunogenicity of pembrolizumab.

Instructions for the collection, processing, storage and shipment of IM samples will be provided separately by the sponsor (e.g., sample handling sheets or laboratory manual).

For this trial Immunogenicity results will not be reported by the sponsor; the samples may be used for separate analyses and reported under a separate report.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses

9.1.1 Phase 1

No formal statistical hypotheses will be tested. Analysis will be descriptive and exploratory. All data will be pooled, and descriptive analyses will be summarized and listed by dosing cohort at the end of Phase 1.

9.1.2 Phase 2 Efficacy

The primary objective of Phase 2 is to assess the efficacy of the combination of radium-223 dichloride and pembrolizumab (compared with pembrolizumab alone in Cohort 1 only).

The primary endpoint, ORR as determined by RECIST 1.1, will be tested using the chi-square test in Cohort 1, and the exact binomial test in Cohort 2.

In Cohort 1, the population of inference is patients with treatment-naïve Stage IV non-small cell lung cancer with PD-L1 TPS ≥ 50%. The null and alternative hypotheses for Cohort 1 are:

$$H_0: p_1 \leq p_2 \text{ versus } H_1: p_1 > p_2$$

where p_1 is the true response rate fto treatment with pembrolizumab and radium-223 in this population, and p_2 is the true response rate to treatment with pembrolizumab monotherapy in this population.

In Cohort 2, the population of inference is patients with Stage IV non-small cell lung cancer of any PD-L1 status who progressed following a prior line of treatment with an immune checkpoint inhibitor. The null and alternative hypotheses for Cohort 2 are:

$$H_0: p \leq 0.1 \text{ versus } H_a: p > 0.1$$

Where p is the true response rate to treatment with the pembrolizumab and radium-223 combination in this population, and 0.1 is the assumed historical ORR for patients in this population.

Both hypotheses will be tested at the one-sided α 0.1 level.

The tests for Cohorts 1 and 2 are assumed independent. There will be no adjustment for multiplicity in this Phase 2 study. There will be no other formal statistical testing in this study.

9.1.3 Phase 2 Safety

There will be no formal hypothesis testing of safety in either cohort of Phase 2.

9.2 Sample Size Determination

9.2.1 Phase 1

Phase 1 is designed to determine the tolerable dose of radium-223 dichloride in combination with standard dose of pembrolizumab (200 mg pembrolizumab Q3W) in participants with NSCLC. The dose de-escalation will follow ‘3+3” design. No formal sample size calculation was performed. It is planned to treat up to 10 participants evaluable for DLT at each dose level, and it expected that 10 to 20 participants will be treated in Phase 1, not including replacements for those who do not complete the DLT assessment window.

9.2.2 Phase 2

In both Cohort 1 and 2, sample size is calculated based on the primary endpoint: ORR, which is determined by RECIST v1.1 (as defined in Section 9.4.1).

Cohort 1:

Assuming the control group (pembrolizumab alone) ORR is 45%, in order to detect a 25% increase in ORR in the experimental group (radium-223 dichloride + pembrolizumab), a total of 104 participants are required to achieve 90% power, based on a test with 1-sided $\alpha = 0.1$ and a randomization ratio of 1:1 between the 2 groups (experimental and control groups).

Cohort 2:

The null hypothesis of the true ORR is 0.10 will be tested against a 1-sided alternative hypothesis of the true ORR is greater than 0.1. By utilizing Simon's 2-stage Min-Max design, a total of 40 participants are required to achieve 90% power with 1-sided $\alpha=0.1$ when the true ORR is 0.25. In the first stage, 27 participants will be accrued. If there are 2 or fewer responses in these 27 participants, the cohort will be stopped early for futility. Otherwise, another 13 participants will be accrued to reach the total number of 40 participants in the second stage. The null hypothesis will be rejected if 7 or more responses are observed in the 40 participants.

9.3 Populations for Analyses

9.3.1 Phase 1

The **DLT Population** will be used for evaluation of the number of participants experiencing DLTs in Phase 1. The DLT analysis population will include all the following participants:

- Participants who experienced a DLT during the DLT observation window, which is defined as the time from the first dose of study treatment through 6 weeks after administration of the first dose of pembrolizumab.
- Participants who did not experience a DLT, and who were compliant with treatment administration during the DLT observation window.

The **Safety Population (SAF)** will be used for summaries of safety data. The Safety Population will consist of all participants who received at least 1 administration of study treatment. Participants who were replaced for evaluation of DLT in Phase 1 will still be included in the Safety Population, if they received at least 1 administration of any study treatment (any component of the combination).

The **Efficacy population (EFF)** will be used for assessment of antitumor activity. The efficacy population will include all participants who received at least 1 administration of planned dose of any study treatment.

9.3.2 Phase 2

The **Full Analysis Set (FAS)** will include all participants treated in Cohort 2 or randomized in Cohort 1 regardless of whether any study treatment was received. Participants in Cohort 1 will be analyzed for efficacy in the treatment groups they were randomized to even if a participant received, partially or completely, the wrong study treatment. Participants in Cohort 2 must have received at least 1 administration of planned dose of any study treatment. This is the primary analysis population for efficacy. The FAS definition for Cohort 1 is identical to the traditional definition for an Intent-to-Treat population.

The **Safety Population (SAF)** will be used for summaries of safety data. The Safety Population will consist of all participants who received at least 1 administration of any study treatment. The analysis will be performed using actual treatment received. For patients in Cohort 1, to be assigned to the combination arm, a participant must have received at least one administration (any non-zero amount) of any study treatment.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy Analyses

9.4.1.1 Phase 1 Efficacy Variables

Secondary efficacy variables in the Phase 1 will include ORR, DCR, DoR.

Exploratory efficacy variables in the Phase 1 will include PFS, OS, iORR, iDCR, iPFS, and iDoR.

Phase 1 efficacy variables will have the same definition as described for the corresponding Phase 2 efficacy variables. See Section 9.4.1.2.

9.4.1.2 Phase 2 Efficacy Variables

The efficacy objectives in the Phase 2 will be demonstrated by the following endpoints:

Primary endpoint:

- ORR, as determined by RECIST v1.1, is defined as the proportion of participants in the analysis population who have best overall response of CR or partial response (PR) during the course of the study. A CR or PR must be confirmed by a second assessment of CR/PR at least 4 weeks apart.

Secondary endpoints:

- PFS is defined as the time from the Reference Date (see below) to the date of earliest radiological progression per RECIST 1.1 or death due to any cause, whichever occurs first. Additional details including censoring rules will be defined in the SAP.
- OS is defined as the time from the Reference Date (see below) to death due to any cause. Participants who are alive at the time of database cut-off will be censored at the last date known to be alive.
- DoR is defined as the time interval from the date of first response (CR or PR) to the date of disease progression (as determined by RECIST 1.1 response criteria) or death, whichever comes first. Only responders (participants with confirmed CR or PR per RECIST 1.1) will be included in the analysis.
- DCR is defined as the proportion of participants in the analysis population who have CR or PR, or SD per RECIST 1.1 for at least 6 weeks from the first study treatment.

Tertiary/Exploratory endpoints:

- iORR as determined by iRECIST, is defined as the proportion of participants in the analysis population who have best overall response (iBOR) of iCR or iPR during the course of the study. iCR or iPR must be confirmed by a second assessment of iCR/iPR at least 4 weeks apart.

- iPFS is defined as the time from the Reference Date (see below) to the date of radiological progression per iRECIST criteria or death, whichever occurs first. Additional details including censoring rules will be defined in the SAP.
- iDoR is defined as the time interval from the date of first response (iCR or iPR) to the date of disease progression per iRECIST or death, whichever comes first. Only responders (participants with confirmed iCR or iPR per iRECIST) will be included in the analysis. Additional details including censoring rules will be defined in the SAP.iDCR is defined as the proportion of participants in the analysis population who have iCR or iPR, or iSD per iRECIST for at least 6 weeks from the first study treatment. Assessments of iCR, iPR, or iSD occurring following unconfirmed progression per iRECIST will count as continuous disease control for purposes of this endpoint.
- SSE-FS is defined as the time from the Reference Date (see below) to the earliest occurrence of one of the following:
    - the use of EBRT to relieve skeletal symptoms
    - the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral)
    - the occurrence of spinal cord compression
    - a tumor related orthopedic surgical intervention
    - Death from any cause
- Patient reported outcome (PRO) (Phase 2 Cohort 1 only):

  The EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects and is the most widely used cancer-specific HRQoL instrument. It contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) and global health and quality of life. The global health and quality of life scale uses a 7 point scale scoring with anchors (1=very poor and 7=excellent); the other items are scored on a 4 point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much).

  The EORTC QLQ-LC13 (Bergman et al. 1994), a supplemental lung cancer-specific module used in combination with QLQ-C30 (Aaronson et al. 1993), comprises multi-item and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy and alopecia). It is scored on a 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much) and has been translated and validated into more than 60 languages.
    - Time to deterioration of Global heath (TTDGH) is defined, as time from the Reference Date (see below) to deterioration from the baseline EORTC QLQ-C30 global/health quality of life scale score or death, whichever occurs first. Details included the score change required for deterioration and censoring rules will be defined in the SAP.
    - Time to deterioration of dyspnea (TTDD) is defined, as time from the Reference Date (see below) to deterioration from the baseline EORTC QLQ-LC13 dyspnea scale score or death, whichever occurs first. Details included the score change required for deterioration and censoring rules will be defined in the SAP.

- Change from baseline in EORTC QLQ-C30 symptom scale scores (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and item scores is defined, for each symptom scale and each item score at each post-baseline assessment timepoint, as the change in the applicable score from baseline to the timepoint.
- Change from baseline in EORTC QLQ-LC13 symptom scale scores (dyspnea, pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis) and item scores is defined, for each symptom scale and each item score at each post-baseline assessment timepoint, as the change in the applicable score from baseline to the timepoint.

The Reference Date is defined as the date of randomization (Phase 2 Cohort 1) or date of first dose of pembrolizumab (Phase 1 and Phase 2 Cohort 2).

9.4.1.3 Statistical Methods for Phase 1 Efficacy Analyses

The analysis of Phase 1 efficacy variables will be descriptive.

The ORR and DCR will be summarized in the EFF by dose cohort and overall. Confidence intervals (CI) will be provided overall and for each dose cohort with at least 10 participants. The number and types of responses will be listed and summarized separately, as appropriate.

DoR will be summarized descriptively for each dose cohort (if there will be dose de-escalation), if data warrant, using Kaplan-Meier medians and quartiles.

Details will be described in the SAP

9.4.1.4 Statistical Methods for Phase 2 Efficacy Analyses

The ORR in Cohort 1 will be tabulated based on the number and percentage of participants attaining either a CR or PR for each treatment group in the FAS. The chi-square test will be performed for differences between treatment groups. The observed treatment difference and its 80% and 95% CIs will be reported. Binomial exact 80% and 95% CIs for ORR will be provided for each treatment group.

The ORR in Cohort 2 will be tabulated based on the number of percentage of participants attaining either a CR or PR in the SAF. An exact binomial test will be performed. The null hypothesis will be rejected if at least 7 responders are observed. Binomial exact 80% and 95% CIs for ORR will be provided.

Additional details, including details for calculating the p-value, will be described in the SAP.

Secondary endpoints:

PFS will be summarized descriptively, by treatment group in Cohort 1 and overall in Cohort 2, using Kaplan-Meier quantile estimates and graphic displays. Details will be described in the SAP including rules for censoring. DoR will be summarized descriptively for by treatment group in Cohort 1 and overall in Cohort 2, if data warrant, using Kaplan-Meier medians and quartiles. Details on rules for censoring will be provided in the SAP.

The DCR will be analyzed as specified for ORR, except that no hypothesis test will be performed.

OS will be summarized, by treatment group in Cohort 1 and overall in Cohort 2, using Kaplan-Meier quantile estimates and graphic displays. For the analysis of OS, the last date of known contact will be used for those participants who have not died at the time of analysis; such participants will be considered censored. Further details on rules for censoring will be provided in the SAP.

Tertiary/Exploratory endpoints:

iORR and iDCR will be analyzed as specified for ORR.

iDoR will be summarized in the same manner as DoR.

iPFS, SSE-FS, TTDGH, and TTDD will be summarized in the same manner as PFS.

Change in baseline in EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scale and item scores will be summarized with descriptive statistics at baseline and each post-baseline timepoint. Plots of change over time may be provided for selected scores. Details will be provided in the SAP.

9.4.2 Safety Analyses

All safety analyses for Phase 1 and Phase 2 will be performed on the Safety Population. Safety data will be presented in tabular and/or graphical format and summarized descriptively.

All collected safety endpoints (e.g., laboratory tests, vital signs, ECG) will be summarized according to the scheduled, nominal visits at which they were collected. Complete details will be provided in the SAP.

AEs will be coded using the latest Medical Dictionary for Drug Regulatory Affairs (MedDRA) version. AEs will be graded by the investigator according to the NCI-CTCAE v.5.0.

Events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment and dose modification. AEs, if listed in the NCI-CTCAE v.5.0, will be summarized by the maximum grade.

DLTs will be listed for Phase 1 participants and summarized by dose cohort (if there is dose de-escalation).

Any AEs of special interest will be summarized. An analysis of time to bone fracture will be performed. Details will be described in the SAP.

The incidence of deaths and primary cause of death will be summarized and listed.

Laboratory abnormalities will be summarized by severity and, where applicable, by dose cohort or treatment group. Frequency and incidence rates will be provided. Frequency tables will also be provided for changes in severity from baseline to worst value post-baseline. Laboratory test results outside the reference ranges will be summarized using proportions. Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in ‘worse case post baseline’ summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the SAP.

Data for vital signs and ECGs will be summarized based on predetermined criteria identified to be of potential clinical concern. Further details will be provided in the SAP.

9.4.3 Other Analyses

The pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock, Additional exploratory analyses may be described in documents separate from the study SAP. The pharmacodynamic analyses will be presented separately from the main clinical study report. In case the PK samples are going to be analyzed, the analyses will be described and results will be presented separately from the main clinical study report.

9.5 Interim Analyses

In Phase 2 Cohort 1, an interim analysis will be performed when 52 participants are randomized and then treated for at least 12 weeks or have PD. The analysis will be delayed pending confirmation of response if a participant has unconfirmed response at 12 weeks. A Hwang-Shih-DeCani (Hwang et al. 1990) futility boundary with γ=-2 will be used for interim efficacy assessment and the type II error spent at the interim analysis is about 2.7%. If the futility boundary is crossed based on the interim analysis results, Cohort 1 will be stopped for futility.

At the time of interim analysis, Cohort 1 is stopped for futility if the difference in ORR (radium-223 dichloride plus pembrolizumab - pembrolizumab) is < -0.8% or 1-sided P-value is > 0.524. This actual threshold for P-value or treatment difference might change based on the actual number of participants at the time of interim analysis. There is no plan to stop the study at the interim analysis due to superiority of the combination arm. Accrual will not be paused for the interim analysis.

In Phase 2 Cohort 2, a look will be performed when 27 participants are enrolled. If there are 2 or fewer responses at the time the 27th participant is treated, accrual will be paused until all participants have the Week 12 tumor assessment or have PD. If at the Week 12 assessment there are 2 or fewer confirmed responses and a participant has unconfirmed response, the analysis will be delayed pending confirmation of response. If there are still 2 or fewer responses, then Cohort 2 will be stopped for futility.

9.5.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be instituted for this study in order to ensure ongoing safety of study participants in the Phase 2 portion of this study, and to conduct the planned formal futility analysis of Cohort 1.

Safety data will be monitored by DMC periodically and the DMC may recommend that the study can be stopped for any safety findings. The DMC will conduct risk/benefit assessments during each periodic data review meeting and provide a formal recommendation for continuation/termination of each cohort of the study.

An independent unblinded Statistical Analysis Center will conduct the planned formal Cohort 1 futility analysis. The DMC will review results and provide a formal recommendation for continuation/termination of the Cohort 1 portion of the study.

Only the DMC and the independent Statistical Analysis Center will have access to unblinded study results of Phase 2 Cohort 1 prior to the study database being locked for the final analysis. Details on the responsibilities and operations of the DMC will be given in a separate DMC charter.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

All relevant documentation will be filed in the trial master file.

10.1.3 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[1] and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative[1] (if acceptable per local law) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

[1] Note: For Germany, participants who are not capable of providing informed consent will not be included in this study.

- 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative[1].

Participants who are rescreened are required to sign a new ICF (Section 5.4).

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. 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 authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical trials in drug development Phases II, III, and IV and Phase I trials in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases." In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and European Union (EU) Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the US and EU on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH for good clinical practice (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 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

- Source Documents Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the eCRF or entered in the eCRF 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.
- Definition of what constitutes source data can be found in a separate document.

10.1.8 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 study-site closure visit has been performed.

The investigator may initiate study-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 but are not limited to:

- 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 study intervention development

10.1.9 Publication Policy

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 the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with 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 mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory at time points specified in the SoA (Section 1.3).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing is detailed in Section 8.2.7.

Table 10-1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hb Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean cell Hb (MCH) Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood urea nitrogen (BUN) or urea	Potassium	AST/ Serum Glutamic-Oxaloacetic Transaminase (SGOT) Lipase	Total bilirubin
	Creatinine	Sodium	ALT/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Albumin
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	
		Chloride Magnesium Phosphorus		
Coagulation	• International Normalized Ratio (INR) or Prothrombin time (PT) • Activated partial thromboplastin time (aPTT)			
Calculation of	• By Cockcroft Gault			

Table 10-1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
eGFR	GFR [ml/min per 1.73 m²] = (140-age) x weight (kg) [x 0.85 if female] / (72 x serum creatinine [mg/dl])
Thyroid Function	• Thyroid stimulating hormone (TSH) • Free T3 • Free T4
Other Screening Tests	• At screening: highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[a] • From cycle 1 onwards: either urine or serum pregnancy test The results of each test must be entered into the eCRF.

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eCRF = electronic case report form; eGFR =estimated glomerular filtration rate; Hb = hemoglobin; hCG = human chorionic gonadotropin; INR = international normalized ratio; MCV = mean corpuscular volume; PT = prothrombine time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid stimulating hormone; WBC = white blood cell count

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after signature of informed consent even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs

hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and FU of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Bayer (the sponsor). In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and grade each event using NCI-CTCAE, version 5.0.

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Action taken with study intervention

The study intervention action should be recorded separately for each study intervention as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of FU information and send an SAE FU report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

FU of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized FU period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see below) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see below) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the investigator file.

SAE Reporting to Bayer via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the investigator file.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

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

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

Women in the following categories are not considered women of childbearing potential:

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

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. 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 women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females 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 they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the FU will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect FU information on the participant and the neonate, after obtaining the signed informed consent from both parents of the neonate, unless local law or specific circumstances of the respective case allow otherwise, and the information will be forwarded to the sponsor. Generally, FU will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 Appendix 5: Patient Reported Outcome: EORTC QLQ-C30 and EORTC QLQ-C13

EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not At All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not At All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

	During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ-LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body? If yes, where _____	1	2	3	4
43.	Did you take any medicine for pain? **1 No 2 Yes** If yes, how much did it help?	1	2	3	4

10.6 Appendix 6: Participant Identification Number

The Participant Identification Number is a 9-digit number consisting of:

Digit 1 to 5 = Unique center number

Digit 6 to 9 = Current participant number with the center

10.7 Appendix 7: Response Evaluation Criteria in Solid Tumors (RECIST) and iRECIST

10.7.1 RECIST

The RECIST v1.1 criteria, based on the measurement of the longest diameter of tumor lesions, were designed and validated to assess treatment response in solid tumors (Eisenhauer et al. 2009).

Measurable Disease:

Non-nodal tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of:

- 10 mm by CT scan or MRI (slice thickness no greater than 5 mm). If scans with slice thicknesses greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest x-ray
- 10 mm calliper measurement by clinical examination will not qualify as target lesion in this study, but can be considered as non-target lesions

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan or MRI (slice thickness recommended to be no greater than 5 mm). At baseline and in FU, only the short axis will be measured and followed.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to < 15mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/ abdominal organomegaly identified by physical examination that are not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesion with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for *all target lesions* will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are > 5 measurable lesions, those not selected as target lesions will be considered together with non-measurable disease as non-target lesions.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions,* including pathological lymph nodes (with

short axis ≥10 mm and < 15 mm), should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent" or in rare cases "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g.; 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Best Response

The best overall response is the best response recorded from the start of the study treatment until the end of active FU. The participant's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

All participants will have their BEST RESPONSE on study classified as outlined below:

Complete Response: Disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm.

Partial Response: At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non target lesions and no appearance of new lesions.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute PD. Ascites or pleural effusion will be recorded as disease progression only if proven malignant.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm.

To achieve unequivocal progression in participants with measurable disease on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal.

Table 10-2: RECIST v1.1: Response for participants with target and non-target lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented at least 6 weeks from start of treatment
Not all evaluated	Non-PD	no	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease
Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment.

Response duration

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

Stable disease duration

Stable disease is measured from **treatment allocation** until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during FU. All measurements must be recorded in millimeters (or decimal fractions of centimeters), if applicable.

Clinical Lesions - Clinical lesions will not be considered measurable disease in this study.

Chest X-ray - Lesions on chest X-ray will not be considered measurable disease in this study. If new lesions are identified by chest X-ray in the course of the study, confirmation by CT or MRI is advised.

CT / MRI - CT scans and MRI should be performed with cuts of 5 mm or less in slice thickness. When slice thickness are greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. This applies to all anatomical regions.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases. When effusions are known to be a potential adverse effect of treatment, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

10.7.2 iRECIST

iRECIST is RECIST v1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs (Table 10-3). iRECIST will be used by site investigator/local radiology review to make treatment decisions. This data will be collected in the clinical database

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at screening and Prior to RECIST v1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST v1.1 Progression

For participants who show evidence of radiological PD by RECIST v1.1, the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained using iRECIST for participant management (see Table 10-3). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Evidence of clinical benefit (defined as the stabilization or improvement of disease related symptoms) as assessed by the investigator
- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- Absence of tumor progression at critical anatomical sites (i.e., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated at least 4 weeks, but no longer than 8 weeks later to confirm PD by iRECIST, per investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

- Note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD and iCPD (confirmed PD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST v1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
- For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared with any prior iUPD time point
- For non-target lesions, worsening is any significant growth in lesions overall, compared with any prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1

For new lesions, worsening is any of these:

- An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
- Visible growth of new non-target lesions
- The appearance of additional new lesions

Any new factor appears that would have triggered PD by RECIST v1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND

- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST v1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset”. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in this protocol (see Section 8.1)

Detection of Progression at Visits after Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

Target lesions

- Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.

Non-target lesions

- If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
- If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

New lesions

- New lesions appear for the first time
- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour et al. 2017).

Table 10-3: Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging 4 -8 weeks later at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging 4-8 weeks later to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging 4 -8 weeks later to confirm PD.	Continue study treatment at the investigator's discretion.	Repeat imaging 4-8 weeks later to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion provided criteria for dose delay per protocol are met.

Abbreviations: iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified response evaluation criteria in solid tumors 1.1 for immune-based therapeutics; iPR = iRECIST partial response; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; N/A = not applicable; PD = progressive disease; RECIST v1.1 = response evaluation criteria in solid tumors, version 1.1

10.8 Appendix 8: New York Heart Association Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Abbreviations: NYHA = New York Heart Association
Source (National Heart Lung and Blood Institute 2004)

10.9 Appendix 9: Line of Treatment

Line of treatment: A line of treatment is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of treatment starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of treatment also starts when a planned period off treatment is interrupted by a need for additional treatment for the disease (Rajkumar et al. 2011).

10.10 Appendix 10: Definition of PD/L1 refractory

This is only applicable to participants eligible for ≥2nd line treatment in Phase 1 and in Phase 2 Cohort 2.
Participants must have progressed on treatment with an anti-PD-1/L1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD/L1 treatment progression is defined by meeting all of the following criteria:

a) Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

b) Has demonstrated disease progression after PD-1/L1 as defined by RECIST v1.1. The initial evidence of PD is to be confirmed by a second assessment no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression.

c) PD has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.

1. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics (Seymour et al. 2017).

2. This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.

10.11 Appendix 11: Abbreviations

AAP	abiraterone acetate plus prednisone/prednisolone
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AIST	National Institute of Advanced Industrial Science and Technology
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AQA	analgesic quantification algorithm
AST	aspartate aminotransferase
B-ALP	bone alkaline phosphatase
BCG	Bacillus Calmette-Guérin
bCTX	B-carboxyl-terminal cross-linking telopeptide of type I collagen
BHA	bone health agent
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BUN	blood urea nitrogen
C	cycle
°C	degree Celsius
CD	cluster of differentiation
CFR	code of federal regulations
CI	confidence interval
CIOMS	council for international organizations of medical sciences
CNS	central nervous system
CR	complete response
CRPC	castration resistant prostate cancer
CT	computed tomography
CTCAE	common terminology criteria for adverse events (v.5.0)
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte associated protein 4
CTSP	clinical trial supply plan
DCR	disease control rate
DICOM	digital imaging and communications in medicine
DILI	drug induced Liver Injury
DK	decay correction factor
DL	dose level
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
EBRT	external beam radiotherapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) case report form
EDC	electronic data capture
e.g.	exempli gratia / for example
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EoT	end of treatment
EU	European Union
°F	degree Fahrenheit
FACS	fluorescence activated cell sorting
FAS	full analysis set
FDG	2-deoxy-[^{18}F]fluoro-D-glucose
FSH	follicle-stimulating hormone

FU	follow-up
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte- macrophage colony-stimulating factor
GMP	good manufacturing practice
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IB	investigator's brochure
iBOR	immune best overall response
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune confirmed progressive disease
iCR	immune complete response
ICTP	C-telopeptide pyridinoline crosslinks of type I collagen
iDCR	immune disease control rate
iDoR	immune duration of response
i.e.	Id est (that is)
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IO	immune oncology
iPFS	immune progression-free survival
iPR	immune partial response
irAEs	immune-related AEs
IRB	institutional review board
iRECIST	immune response evaluation criteria in solid tumors, version 1.1
iSD	immune stable disease
ITT	intent-to-treat (population)
IUD	Intrauterine device
iUPD	immune unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IxRS	interactive voice/web response system
JRIA	Japan Radioisotope Association
kBq	kilo Becquerel
LET	linear energy transfer
mAb	monoclonal antibody
MBq	mega Becquerel
MCH	mean cell hemoglobin
mCi	milli Curie
mCRPC	metastatic castration resistant prostate cancer
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	magnetic resonance imaging
nABs	neutralizing antibodies
NCI	National Cancer Institute
NE	not evaluated
NGS	next generation sequencing
NIST	National Institute of Standards and Technology
NOAC	novel oral anticoagulants
NSAIDs	nonsteroidal anti-inflammatory drugs

NSCLC	non-small cell lung cancer
NTX	amino-terminal cross-linking telopeptide of type I collagen
NYHA	New York Heart Association
OME	oral morphine equivalents
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PBPK	Physiologically Based Pharmacokinetic Modeling
PD-1	programmed cell death protein 1
PD	progressive disease
PD-L1	programmed cell death protein ligand 1
PD-L2	programmed cell death protein ligand 2
PET	positron emission tomography
PFS	progression-free survival
PID	patient identification number
PINP	procollagen-type-I-N-terminal propeptide
PK	pharmacokinetics
PR	partial response
PRD	patient-ready dose
PRO	patient reported outcome
PS	performance status
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ	Quality of Life Questionnaire
RBC	red blood cell count
RECIST	response evaluation criteria in solid tumors, version 1.1
RNA	ribonucleic acid
ROS	reactive oxygen species
RP2D	recommended Phase 2 dose
rPFS	radiological progression free survival
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoA	schedule of activities
SSE	symptomatic skeletal event
SSE-FS	symptomatic skeletal event-free survival
T	thyroxine
T1-DM	type 1 diabetes mellitus
$T_{1/2}$	half-life
T3	triiodothyronine
T4	thyroxine
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
TMDD	target-mediated drug disposition
TPS	tumor protein score
TSH	thyroid stimulating hormone
TTDD	time to deterioration of dyspnea
TTDGH	time to deterioration of global heath
ULN	upper limit of normal
US(A)	United States of America
WBC	white blood cell count

10.12 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (29 OCT 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

Overall rationale: This protocol amendment was prepared to clarify and strengthen guidance on tumor assessment, eligibility criteria, toxicity management and DLT criteria, in line with Health Authorities' requests.

Section # and name	Description of change	Brief rationale
1.3 Schedule of Activities, 8.1 Efficacy Assessments	Clarification was made on bone scan requirement at screening.	Change made to ensure the extent of bone disease is accurately diagnosed/documented at screening.
5.1 Inclusion Criteria, 6.5 Concomitant Therapy	Bisphosphonates or denosumab usage was made mandatory.	Precautionary measure to align with other radium-223 studies.
5.2 Exclusion Criteria	History of osteoporotic fracture was added to the exclusion criteria.	Precautionary measure to align with other radium-223 studies.
6.1.2 Dose Limiting Toxicities	Addition of DLT criterion for grade 3 liver toxicity in participants without liver metastases at screening.	To extend DLT criteria for liver toxicity in participants without liver metastases at screening.
6.1.2 Dose Limiting Toxicities	The DLT criterion for non-hematologic toxicities was modified to also include any grade 4 laboratory event.	Update made since the CTCAE definition for most grade 4 laboratory abnormalities includes "life-threatening consequences."

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