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Title page

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

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

Bayer study drug	BAY 88-8223 / radium-223 dichloride / Xofigo®		
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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ADA	anti-drug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
BOR	best objective response
BRAF	v-RAF murine sarcoma viral oncogene homolog B
CI	confidence interval
CR	complete response
CRF	case report form
CSP	clinical study protocol
CTC	Common Terminology Criteria
DCR	disease control rate
DLT	dose limiting toxicity
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFF	efficacy population
EGFR	epidermal growth factor receptor
EoT	end of treatment
GCP	good clinical practice
iBOR	immune best objective response
ICH	International Council for Harmonisation
iDCR	immune disease control rate
iDoR	immune duration of response
iPFS	immune progression-free survival
irAE	immune-related adverse event
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRR	infusion related reaction
kBq	kilo Becquerel
LKAD	last known alive date
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
nABs	neutralizing antibodies
NCI	National Cancer Institute
NE	not evaluated
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PFS	progression free survival
PID	participant identification number
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	reactive oxygen species
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SOC	System Organ Class

TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMB	tumor mutational burden
TNM	TNM Classification of Malignant Tumors
TPS	tumor protein score
ULOQ	upper limit of quantification

1. Introduction

This Statistical Analysis Plan (SAP) is based on the Phase 1 part for Clinical Study Protocol (CSP) BAY 88-8223 / 19781, Global Amendment 2 dated 18 SEP 2020.

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 non-small cell lung cancer (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.

The study consists of two phases, including a safety run-in as well as two distinct cohorts to assess the efficacy of the combination of radium-223 dichloride and pembrolizumab.

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) and establish the safety of the combination.

In JAN 2021, Bayer decided to not further pursue the NSCLC study. At the time of the decision 10 participants were enrolled in the treatment refractory group and none in the treatment naïve group; 7 of the 10 participants were treated. This decision was mainly based on strategic considerations, also acknowledging the recruitment challenges for the first line population encountered during the Phase 1 part of the study. No safety issues were observed for the combination and data observed so far are consistent with the known safety profile of both drugs. As a consequence of this decision, some analyses are not being done and some data are being displayed in listings rather than summarized.

2. Study Objectives

2.1 Primary objective

The primary objective of Phase 1 of this study is:

- To assess the safety of the combination of radium-223 dichloride and pembrolizumab and to determine the RP2D:
    - Adverse event (AE) assessments using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (v 5.0) and incidence of dose limiting toxicities (DLT)

2.2 Secondary objective

The secondary objective of Phase 1 of this study is:

- 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

2.3 Exploratory objectives

The exploratory objectives of Phase 1 of this study are:

- To evaluate predictive, prognostic and pharmacodynamic biomarkers:
  - Programmed cell death protein ligand 1 (PD-L1), tumor mutational burden (TMB), bone markers, immune cell analysis and circulating protein markers
- To assess the pharmacokinetics (PK) and immunogenicity of the combination of radium-223 dichloride and pembrolizumab (if applicable):
  - Trough PK concentrations and titers for anti-drug antibodies (ADAs) and neutralizing antibodies (nABs) for pembrolizumab (if applicable)
- To explore efficacy of the combination of radium-223 dichloride and pembrolizumab
  - ORR per a modified RECIST 1.1 for immune-based therapeutics (iRECIST) [iORR]
  - DoR per iRECIST (iDoR)
  - DCR per iRECIST (iDCR)
  - Progression-free survival (PFS) per RECIST 1.1 and iRECIST
  - Overall survival (OS)

3. Study Design

This is an open-label, multicenter, Phase 1/2 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.

The Phase 1 part consists of 4 phases: screening, treatment, active-follow-up and long-term follow-up periods:

- The screening period is defined as the period from informed consent to start of any study treatment.
- The treatment period is defined as the period from start of any study treatment to end of treatment visit.
- The active follow-up period is defined as the period from end of treatment visit to day of last protocol stipulated procedure.
- The long-term follow period is defined as the period from the day after the last protocol stipulated procedure (in case of completion of active follow-up) to at least 2 years after last dose of radium-223.

Participants receiving treatment beyond progression will still be classed as being in the treatment period until the end of treatment visit.

The Phase 1 part of the study will include participants with stage IV NSCLC either treatment naïve (PD-L1 tumor protein score [TPS] $\geq$ 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).

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).

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.

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

Dose de-escalation decision

The starting dose will be the monotherapy dose approved for castration resistant prostate cancer, 55 kilo Becquerel (kBq)/kg body weight of radium-223 dichloride. In case of DLTs, the radium-223 dichloride dose may be reduced by one dose level to 33 kBq/kg body weight (see Table 3–1).

Table 3–1: Planned dose Levels

Dose Sequence	Dose Level
1	55 kBq/kg (starting dose)
2	33 kBq/kg (lowest planned dose)

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.

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

Phase 1 should include a minimum of 3 participants refractory to prior therapy with immune checkpoint inhibitors (irrespective of PD-L1 TPS) 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 2 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 RP2D 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).

4. General Statistical Considerations

4.1 General principles

The statistical evaluation will be performed using the software package SAS release 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Unless otherwise specified:

- Continuous variables will be summarized using amount of available data (n), mean, standard deviation, minimum, median, maximum and missing (provided it exceeds 0).
- Categorical variables will be summarized using n and percentages.
- For the time to event endpoints, the product limited estimates of the survival distribution function using Kaplan-Meier will be presented for each dose cohort: N, total failed, total censored, time to event (medians) with the associated 80% and 95% CIs), range (with or without censored), probability of event-free survival at pre-specified months, such as 3, 6, 9, etc. months. Kaplan-Meier curves will be generated by dose, if necessary.

4.2 Handling of dropouts

4.2.1 Screen failures and rescreening

Screen failures are defined as participants who consent to participate in the clinical study but do not meet the eligibility criteria. Participants may be rescreened under the following criteria:

- 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).

Screen failures will be registered to close the participant identification number (PID). After Sponsor approval of re-screening a new informed consent form will be signed and the participant will be assigned a new PID. A map between the original and the new PID will be maintained. For other reporting purposes, the participant will be identified by the rescreened PID, and the reported date of the rescreened informed consent. Rescreened participants will appear once in disposition summaries utilizing the rescreened PID.

4.2.2 Dropout

Dropouts are eligible participants who withdraw during the DLT observation window (see Section 6.4.1) for reasons other than experiencing a DLT and who have not completed both 1 dose of radium-223 dichloride and 2 cycles of pembrolizumab. Dropouts will be replaced. Dropouts will not be included in the DLT analysis set but will be included in the Safety and efficacy population (see Section 5).

4.2.3 Replacement

In this study, "replacement" indicates the enrollment and treatment of additional participants to ensure that the required number of participants are eligible for the DLT population.

According to the protocol, subjects not completing the DLT observation window will be replaced if they discontinued for a reason other for a DLT. Replaced subjects will be included in all other analyses for which they meet validity criteria. I.e., All treated subjects will be included in the safety analysis regardless of replacement for other purposes.

4.3 Handling of missing data

In order to achieve the goal of a well-conducted clinical trial according to International Council for Harmonisation Good Clinical Practice (ICH-GCP), every effort should be made to collect all data. However, despite best efforts, it may be inevitable that missing or incomplete data are reported.

All missing or partially missing data will be presented in the participant data listings as they are recorded on the case report form (CRF). Such listings will include reasons that data was not collected, was invalid, etc. where it has been collected in the eCRF.

Except as otherwise specifically noted, missing data will not be imputed or carried forward in any statistical analysis.

When appropriate, the following rules will be implemented so as not to exclude participants from summaries due to missing or incomplete data:

4.3.1 Efficacy variables

Last known alive date (LKAD) and death date for efficacy variables will be imputed according to the following rules:

- If partial date has day and month missing, then the date will not be imputed.
- If partial date has missing day only, then the first day of the month will be assigned to the missing day.
- If the imputed first of the month is before the treatment start date, then the date will be imputed as the treatment start date.

4.3.2 Safety variables

When only partial dates are available, the following rules will be used for the derivation of treatment-emergence:

- If AE partial date has day and month missing, date will not be imputed. Such events, recorded on the AE CRF, will be deemed treatment-emergent with indeterminable start and duration.
- If partial date has missing day only, then the first day of the month will be assigned to the missing day.
- If the imputed first of the month is before the treatment start date, then the date will be imputed as the treatment start date.
- If the imputed first of the month places stop date before start date, then use start date.

4.3.3 Laboratory values

For laboratory values below the lower limit of quantification (LLOQ) like "< xxx" or "≤ xxx", or above the upper limit of quantification (ULOQ) like "> xxx" or "≥ xxx", LLOQ or ULOQ (xxx) as applicable will be imputed for purposes of calculating descriptive statistics. The original laboratory values ("< xxx", "≤ xxx", "> xxx" or "≥ xxx") will be presented in a listing.

4.4 Interim analyses and Data Monitoring Committee

Except for the dose de-escalation decisions described in Section 3 of this SAP, neither interim analysis nor a data monitoring committee are planned for Phase 1 of this study. The safety of study participants will be monitored regularly by investigators and sponsor experts. Monitoring activities, including dose decision meetings described in Section 3, will be based on clinical data management reports.

4.5 Data rules

Generally, for each date stored in the database, a set of organizational variables will be derived in order to describe the temporal context of that date in the specific study: phase of study treatment (radium-223 dichloride or pembrolizumab) (screening, treatment or follow-up), day relative to the start of study treatment, day relative to the end of study treatment. Additional contextual variables may be created in analysis datasets.

Unless otherwise specified, the baseline value for safety or efficacy data is defined as the last non-missing value on or prior to first administration date of any study treatment (radium-223 dichloride or pembrolizumab). Any unscheduled (repeated) assessments/evaluations will be included in the determination of the baseline value.

The duration for the time-to-event variables in days is calculated by (event/censoring date – reference date + 1). Time-to-event analysis reference date is the start of any study treatment date. Time-to-event variables may be converted to months for reporting as specified in this SAP. The unit will be noted in the Tables, Figures and Listings specifications. Conversion to months will divide by 30.4375.

4.6 Final data review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets required by protocol

Dose Limiting Toxicity (DLT) population

The DLT population will be used for evaluation of the number of participants experiencing DLTs. The DLT population will include all the following participants:

- Participants who experienced a DLT during the DLT observation window (see Section 6.4.1)
- Participants who did not experience a DLT, and who were not dropouts as defined in Section 4.2.

Safety population (SAF)

The SAF will be used for summaries of safety data. The SAF will consist of all participants who received at least 1 administration of study treatment. Participants who were replaced for evaluation of DLT will still be included in the SAF, if they received at least 1 administration of the study treatment.

Efficacy population (EFF)

The EFF will be used for assessment of antitumor activity. In Phase 1, the EFF will include all participants who received at least 1 administration of planned dose of any study treatment.

5.2 Assignment of other analysis sets

Enrolled population

All participants who signed informed consent will be considered part of the enrolled population. Rescreened participants will be included in the enrolled population once and identified by the rescreened PID.

6. Statistical Methodology

No formal statistical hypotheses will be tested in the Phase 1 portion of the study. Analysis will be descriptive and exploratory. Descriptive analyses at the end of Phase 1 will be summarized and listed by dosing cohort. In the event that the RP2D is determined separately for the 2 patient populations (treatment naïve and treatment refractory participants), the analysis will be presented by dosing cohort for each patient population, as applicable.

6.1 Population characteristics

6.1.1 Disposition

The number and percentage of enrolled participants who did not complete screening, assigned to treatment, were never treated, and who started treatment, and treated participants who terminated treatment, and who are ongoing with treatment will be presented. The number and percentage of treated participants who started, completed or are ongoing with active follow-up, and long-term follow-up will also be presented. The number and percentage of participants with each reason for terminating screening, treatment, terminating active follow-up, and terminating long-term follow-up, will also be presented. The number and percentage of participants in each analysis set together with reasons for non-inclusion will be tabulated.

Participants who discontinued will also be listed.

The number and percentage of participants in each protocol required analysis set together with reasons for non-inclusion will be tabulated.

6.1.2 Demographic and baseline disease characteristics

Descriptive summaries of demographics and baseline disease characteristics will be presented by dosing cohort and overall for the SAF.

The following demographic data will be summarized:

- Sex (Female, Male, Not reported)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not reported, Multiple)
- Age at Screening (years)
- Age group (< 65, ≥ 65, $65 – 74$, $75 – 84$, ≥ 85 years)
- Weight at Baseline (kg)

The following baseline disease characteristics will be summarized:

- Cigarette smoking status (never, former, current)
- Patient population (treatment naïve, treatment refractory)
- Prior systemic lines of therapy
- PD-L1 TPS treatment refractory (< 1%, 1 – 19%, 20 – 49%, ≥ 50%)
- Any of EGFR, ALK, or ROS mutation (Yes, No)
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) Score (0 vs 1)
- NSCLC histology (squamous cell carcinoma, large cell carcinoma, non-squamous cell carcinoma)
- Stage at initial diagnosis (TNM classification)
- Stage at study entry (TNM classification)
- Grading (American Joint Committee on Cancer [AJCC]) at initial diagnosis
- Time from initial diagnosis to first study treatment (months) (simple summary statistics, standard means)
- Time from most recent progression/ relapse to first study treatment (months) (simple summary statistics, standard means)

Demographics and baseline disease characteristics will be listed.

6.1.3 Treatment duration of study drug

Treatment duration of radium-223 dichloride and pembrolizumab respectively will be summarized by presenting descriptive statistics of overall time under treatment (including interruptions/delays), number of injections of radium-223 dichloride (6-week interval) and number of cycles of pembrolizumab (3-week interval). Number of injections of radium-223 dichloride and number of cycles will be presented using both descriptive statistics and categorically. Cycles for pembrolizumab will be split into the following categories (0, 1 to < 3, 3 to < 5, 5 to < 9, 9 to ≤ 12, and > 12).

Overall time under treatment (weeks) will be calculated as:

$$\frac{\text{day of last dose} - \text{day of first dose} + 1}{7}$$

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

Exposure to radium-223 dichloride and pembrolizumab will be listed.

6.2 Efficacy

Efficacy data will be listed for participants in the EFF.

6.2.1 Objective response rate

Objective response rate, as determined by RECIST v1.1, accessed by investigator, is defined as the proportion of participants in EFF who have best overall response of complete response (CR) or partial response (PR) during the course of the study. Participants whose best overall tumor response is CR or PR will be considered as responders while other participants will be considered as non-responders.

Best objective response (BOR) is defined as the best timepoint response per RECIST v1.1 (ordered CR, PR, stable disease [SD], progressive disease [PD], non-evaluated [NE]) over all post-treatment assessments on or prior to first progression or any new systemic anticancer therapy, subject to the following additional rules:

- Time point responses of CR require confirmation by a consecutive CR at least 4 weeks later, with no intervening assessment of PR, SD or PD.
- Time point responses of PR require confirmation by a subsequent PR or CR at least 4 weeks later with no intervening SD or PD.
- Time point assessments of SD must occur at least 6 weeks following first treatment. A time point assessment of SD occurring prior to 6 weeks will be classified as NE for purposes of calculating BOR.
- Unconfirmed assessments of CR or PR, if meeting the timing requirements for SD, will be classified as SD.
- If the requirements of CR, PR, SD or PD are not met, the BOR is NE.

RECIST response assessments over time and best overall response will be listed.

6.2.2 Duration of response

Duration of response 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 due to any cause, whichever comes first. Only responders will be included in the analysis. Details of censoring rules have been provided in Table 6–1 and details for two consecutive missed tumor assessments have been provided in Table 6–2.

Duration of response will not be provided due to study termination.

Table 6–1: Duration of response and progression free survival censoring rules

Situation	End date	Outcome	Reason for censoring	Applicable analysis
PD (without two or more consecutive missing or inadequate tumor assessments [a])	Date of first PD	Event [b]	Not applicable	DoR and PFS
Death (without two or more consecutive missing or inadequate tumor assessment) without radiological PD assessment before death	Date of death	Event [b]	Not applicable	DoR and PFS
No baseline or post-baseline radiological tumor assessment	Treatment start date	Censored	No baseline or post-baseline radiological assessment.	PFS
Death during the study before first radiological assessment	Treatment start date	Censored	No radiological progression observed	PFS

Table 6–1: Duration of response and progression free survival censoring rules

Situation	End date	Outcome	Reason for censoring	Applicable analysis
Death or PD after more than 1 missed radiological assessment	Date of last adequate radiological assessment before missed assessment	Censored	Missed more than 1 tumor assessment	DoR and PFS
Participant discontinuation from study due to a reason other than PD	Last adequate radiological assessment date without PD	Censored	Participant discontinued from study due to a reason other than PD	DoR and PFS
Participant discontinued from study due to PD, but no documented date of PD	Date of last adequate radiological assessment before discontinuation	Censored	Participant discontinued from study due to PD, but no documented date of PD	DoR and PFS
Participants still on study at the time of data cutoff without PD	Last adequate radiological assessment before data cutoff	Censored	Participant is still alive without PD	DoR and PFS
New anticancer treatment started	Date of last adequate radiological assessment before starting new systemic anticancer treatment	Censored	New systemic anticancer treatment started	DoR and PFS

PFS or DoR = (End Date – treatment start date +1)/30.4375

[a] Two consecutive missing radiological assessments are defined as being when the time interval between last adequate tumor assessment to either event date or cut-off date is more than the allowed time frame.

[b] The earliest end date in the table is used in calculating the PFS or DoR.

Table 6–2: Two consecutive missed tumor assessments

Scheduled tumor assessments	Scheduled data from treatment start date	Time windows for two consecutive missed tumor assessments
Before Week 36	Every 6 weeks	2 * (6 + 1) = 14 weeks
Week 45 to Week 108	Every 9 weeks	2 * (9 + 1) = 20 weeks
After Week 108	Every 3 months	7 months

6.2.3 Disease control rate

DCR, as determined by RECIST v1.1, is defined as the proportion of participants in the EFF who have CR, PR or SD for at least 6 weeks from the start of study treatment.

DCR will not be reported due to study termination.

6.2.4 Progression free survival

PFS is defined as the time from start of any study treatment to the date of radiological progression per RECIST 1.1 and iRECIST or death due to any cause, whichever occurs first. Details of censoring have been provided in Table 6–1 and details for two consecutive missed tumor assessments have been provided in Table 6–2.

PFS will not be reported due to study termination.

6.2.5 Overall survival

Overall survival is defined as the time from start of any study treatment to the date of 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 or the database cut-off date, whichever occurs first.

Overall survival analysis will not be reported due to study termination.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

With the exception of DLTs, all safety analyses will be performed on the SAF. DLTs will be presented using the DLT analysis set.

6.4.1 Dose limiting toxicities

A DLT is defined as any AE listed in Section 6.1.2 of the CSP, occurring within 6 weeks after the first administration of pembrolizumab (DLT observation window), if assessed by the investigator to be possibly, probably, or definitely related to study treatment administration.

Section 3 of this SAP describes the dose de-escalation process as well as rules for finding the RP2D.

Participants experiencing DLTs will be presented by System Organ Class (SOC) and Preferred Term (PT). Dose limiting toxicities will be presented in participant listings.

6.4.2 Adverse events

6.4.2.1 Adverse event definitions

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

Treatment-emergent Adverse Events

The treatment period for this study for reporting purposes of AEs, extends from the initiation of study treatment until:

- 90 days after the cessation of study treatment for serious adverse events (SAE) (regardless of causality) or until the end of treatment (EoT) visit if the participant initiates new anti-cancer therapy, whichever is earlier.
- EoT visit for all other AEs.
- Participants with treatment beyond progression will still be classed as treatment emergent if it is within the treatment period.

All AEs starting or worsening within the treatment period will be considered treatment-emergent adverse events (TEAE), for example:

- Events that started on or after the first dose and within the treatment period and are not a continuation of a pre-treatment event.
- Events that started before the first dose and worsened on or after the first dose and on or before the end of the treatment period.

Pre-treatment AEs

Pre-treatment AEs will be defined as AEs that started and either stopped before the first dose of study treatment or continued after and did not worsen in intensity (i.e. increase in CTCAE grade or became serious) during the treatment period.

Post-treatment AEs

Post-treatment AEs will be defined as AEs that started or worsened after the treatment period.

6.4.2.2 Adverse event summaries

An overall summary of TEAEs will be provided by dose cohort and overall presenting the number and percentage of participants with:

- Any TEAE,
- Any TEAE by maximum CTCAE grade,
- Any study treatment-related TEAE,
- Any study treatment-related TEAE by maximum CTCAE grade,
- Any TEAE related to procedures required by the CSP,
- Any TEAE leading to discontinuation of study treatment,
- Any TEAE leading to discontinuation of radium-223 dichloride,
- Any TEAE leading to discontinuation of pembrolizumab,
- Any TEAE leading to dose modification of radium-223 dichloride,
- Any TEAE leading to dose modification of pembrolizumab,
- Any treatment-emergent SAE (TESAE),
- Any study treatment-related TESAE,
- Any TESAE related to procedures required by the CSP,
- Any TESAE leading to discontinuation of study treatment,
- Any TESAE leading to discontinuation of radium-223 dichloride,
- Any TESAE leading to discontinuation of pembrolizumab,
- Any TESAE leading to dose modification of radium-223 dichloride,
- Any TESAE leading to dose modification of pembrolizumab,
- Any TEAE of special interest,
- Any treatment-emergent bone fractures, and
- TEAEs with outcome death,

where study treatment refers to either radium-223 dichloride or pembrolizumab.

TEAEs will be summarized by presenting frequency and percentage of participants by SOC, PT, and worst CTCAE grade. For each participant, multiple occurrences of the same event will be counted once at their maximum severity within an SOC and PT. Tables will be sorted alphabetically by SOC. Preferred terms will be sorted by descending overall total frequency within an SOC.

- All TEAEs

Data listings will be produced for all AEs recorded in the study.

6.4.3 Deaths

Deaths will be reported in participant listings.

6.4.4 Clinical laboratory evaluations

Selected laboratory abnormalities will be summarized by severity (based on the most abnormal result during the treatment period including any unscheduled visits) and by dose cohort (and overall). Frequency and incidence rates will be provided.

The following laboratory parameters will be summarized:

Hematology:

- Hemoglobin (g/dL)
    - Increase
        - > 0 – 2 g/dL change from upper limit of normal (ULN)
        - > 2 – 4 g/dL change from ULN
        - > 4 g/dL change from ULN
        - Total increased change from ULN
    - Decrease
        - < lower limit of normal (LLN) – 10.0 g/dL
        - < 10.0 – 8.0 g/dL
        - < 8.0 g/dL
        - Total decreased
        - All (participants with at least one non-missing post-baseline value)
- Neutrophils (GIGA/L)
    - Decrease
        - < LLN – 1.5 GIGA/L
        - < 1.5 – 1.0 GIGA/L
        - < 1.0 – 0.5 GIGA/L
        - < 0.5 GIGA/L
        - Total decreased
        - All (participants with at least one non-missing post-baseline value)
- Platelets (GIGA/L)
    - Decrease
        - < LLN – 75.0 GIGA/L
        - < 75.0 – 50.0 GIGA/L

- < 50.0 – 25.0 GIGA/L
- < 25.0 GIGA/L
- Total decreased
- All (participants with at least one non-missing post-baseline value)

Chemistry:

- Alanine aminotransferase (U/L)
  - Increase (Baseline Normal)
    - > ULN – 3.0 x ULN
    - > 3.0 – 5.0 x ULN
    - > 5.0 – 20.0 x ULN
    - > 20.0 x ULN
    - Total Increased with Baseline Normal
    - All with Baseline Normal (participants who have a normal baseline and at least one non-missing post baseline value)
  - Increase (Baseline Abnormal)
    - ≥ 1.5 – 3.0 x Baseline
    - > 3.0 – 5.0 x Baseline
    - > 5.0 – 20.0 x Baseline
    - > 20.0 x Baseline
    - Total Increased with Baseline Abnormal
    - All with Baseline Abnormal (participants who have an abnormal baseline and at least one non-missing post baseline value)
    - All with Baseline (participants with non-missing baseline and at least one non-missing post-baseline result)
- Alkaline phosphatase (U/L)
  - Increase (Baseline Normal)
    - > ULN – 2.5 x ULN
    - > 2.5 – 5.0 x ULN
    - > 5.0 – 20.0 x ULN
    - > 20.0 x ULN
    - Total Increased with Baseline Normal
    - All with Baseline Normal (participants who have a normal baseline and at least one non-missing post baseline value)
  - Increase (Baseline Abnormal)
    - 2.0 – 2.5 x Baseline
    - > 2.5 – 5.0 x Baseline
    - > 5.0 – 20.0 x Baseline
    - > 20.0 x Baseline
    - Total Increased with Baseline Abnormal

        - All with Baseline Abnormal (participants who have an abnormal baseline and at least one non-missing post baseline value)
        - All with Baseline (participants with non-missing baseline and at least one non-missing post-baseline result)
- Aspartate aminotransferase (U/L)
    - Increase (Baseline Normal)
        - > ULN – 3.0 x ULN
        - > 3.0 – 5.0 x ULN
        - > 5.0 – 20.0 x ULN
        - > 20.0 x ULN
        - Total Increased with Baseline Normal
        - All with Baseline Normal (participants who have a normal baseline and at least one non-missing post baseline value)
    - Increase (Baseline Abnormal)
        - 1.5 – 3.0 x Baseline
        - > 3.0 – 5.0 x Baseline
        - > 5.0 – 20.0 x Baseline
        - > 20.0 x Baseline
        - Total Increased with Baseline Abnormal
        - All with Baseline Abnormal (participants who have an abnormal baseline and at least one non-missing post-baseline value)
        - All with Baseline (participants with non-missing baseline and at least one non-missing post-baseline result)
- Bilirubin (mg/dL)
    - Increase (Baseline Normal)
        - > ULN – 1.5 x ULN
        - > 1.5 – 3.0 x ULN
        - > 3.0 – 10.0 x ULN
        - > 10.0 x ULN
        - Total Increased with Baseline Normal
        - All with Baseline Normal (participants who have a normal baseline and at least one non-missing post baseline value)
    - Increase (Baseline Abnormal)
        - 1.0 – 1.5 x Baseline
        - > 1.5 – 3.0 x Baseline
        - > 3.0 – 10.0 x Baseline
        - > 10.0 x Baseline
        - Total Increased with Baseline Abnormal
        - All with Baseline Abnormal (participants who have an abnormal baseline and at least one non-missing post baseline value)

        - All with Baseline (participants with non-missing baseline and at least one non-missing post-baseline result)
- Creatinine (mg/dL)
    - Increase
        - > ULN – 1.5 x ULN
        - > 1.5– 3.0 x ULN
        - > 3.0 – 6.0 x ULN
        - > 6.0 x ULN
        - Total Increased
        - All (participants with at least one non-missing post-baseline value)

Other laboratory parameters (TSH, T3 and T4) not included in the above list will be presented using shifts from baseline to worst post-baseline value based on normal range categories (low, normal, high).

6.4.5 Biomarkers

Not applicable.

6.4.6 Other safety endpoints

Not applicable.

7. Document history and changes in the planned statistical analysis

- Approval of the SAP for Phase 1 version 4.0 dated 31 JAN 2023.
  Rationale for updates:
    - Section on patient replacement added to Section 4.2.3
    - Prior systemic lines of therapy added to baseline characteristics
    - Removed analysis on treatment related AEs for pembrolizumab and radium-223 dichloride and kept the combinations
    - Separated AEs leading to dose modification to include radium-223 dichloride and pembrolizumab
- Approval of the SAP for Phase 1 version 3.0 dated 22 FEB 2021.
  Rationale for updates:
    - Strategic considerations and recruitment challenges has led to the study no longer being pursued. This SAP update contains adjustments for the synopsis CSR.
- Approval of the SAP for Phase 1 version 2.0 dated 11 DEC 2020.
  Rationale for updates:
    - Protocol amendment 2 updates impacting the SAP
    - Study objectives updated to include the endpoints
    - Study design updated to include the study periods
    - Enrolled set included in the analysis set section
    - Demographic and baseline characteristics updated

- Treatment duration updated with the details of the categories for pembrolizumab
- Description added for time to event analysis, response rates and rescreened participants
- Listing added for rescreened participants
- Censoring rules added for DoR and PFS
- Overall AEs now include irAE, IRR, additional primary malignancy and bone fractures.

- Approval of the SAP for Phase 1 version 1.0 dated 02 JUN 2020

8. References

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13. https://doi.org/10.1093/biomet/26.4.404