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

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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49669

Source
ToetsingOnline

Brief title
Study of radium-223 dichloride in combination w/ pembrolizumab

Condition

- Other condition

Synonym
Non-small cell lung cancer; Radium-223

Health condition

niet-kleincellige longkanker

Research involving
Human

Sponsors and support

Primary sponsor: Bayer Consumer Care AG
Source(s) of monetary or material Support: Farmaceutisch industrie

Intervention

Keyword: Non-small cell lung cancer, Open-label, Radium-223 dichloride

Outcome measures

Primary outcome

Phase 1

* 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)

Phase 2

* ORR per RECIST v1.1

Secondary outcome

Phase 1

* Objective response rate (ORR) per Response Evaluation Criteria in Solid

Tumors (RECIST) v1.1 and iRECIST

* Duration of response (DOR) per RECIST v1.1 and iRECIST

* Disease control rate (DCR) per RECIST v1.1 and iRECIST

Phase 2

* ORR per iRECIST

* DOR per RECIST v1.1 and iRECIST

* DCR per RECIST v1.1 and iRECIST

* Progression free survival (PFS) per RECIST v1.1 and iRECIST

* OS

* AE assessments using NCI CTCAE (v.5.0)

Study description

Background summary

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 pathoabbrelogical 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*) 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. 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.

Study objective

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.

Study 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.

Intervention

Pembrolizumab will be administered every 3 weeks for up to 35 cycles or until progressive disease (PD), death, or withdrawal of consent (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, or withdrawal of consent (whichever occurs first).

Study burden and risks

The study medication may improve the medical condition of the patient, but this is not certain.
The information collected in this study will help the study sponsor and doctors learn more about the study drug. This information may help future patients.

Disadvantages of participation in the study may be
- possible side effects/complications of the study medication
- possible side effects/discomforts of the evaluations in the study
- You might need to stop taking other medicines

Participation in the study also means:
- additional time;
- additional or longer hospital stays;
- additional tests;
- instructions you need to follow;

The participation of the patient will last about 12 months.
However, this may be longer based on how well the patient respond to the treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Histologically or cytologically confirmed diagnosis of stage IV NSCLC. Phase 2 Cohort 1: no Epidermal Growth Factor Receptor (EGFR) sensitization (activating) mutation or anaplastic lymphoma kinase (ALK)/ROS1 rearrangement. Treatment naïve (no prior systemic therapy) for their metastatic NSCLC. Phase 2 Cohort 2: progression on prior treatment with an immune checkpoint inhibitor. Phase 1 includes participants meeting either Cohort 1 or Cohort 2 criteria.
- Measurable disease per RECIST v1.1.
- At least 2 skeletal metastases.
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.
- Adequate bone marrow and organ function.

Other criteria
- 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.

Exclusion criteria

- Previous or concurrent cancer within 3 years prior to enrollment.
- 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. Phase 2 Cohort 2: was discontinued from that treatment due to a Grade 3 or higher immune-related AEs (irAEs).
- Known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, clinically stable, and without requirement of steroid treatment for at least 14 days prior to first

dose of study treatment.
- Active autoimmune disease that has required systemic treatment in the past 2 years.
- History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Known history or presence of osteonecrosis of jaw.
- Ongoing infection >Grade 2 NCI-CTCAE v.5.0 requiring systemic therapy.
- 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.
- Prior treatment with radium-223 dichloride or any therapeutic radiopharmaceutical.
- Prior radiotherapy within 21 days of planned start of study treatment.
- History of osteoporotic fracture

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-06-2020
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Radium-223 dichloride
Generic name:	Xofigo®

Ethics review

Approved WMO Date:	21-08-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-02-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-03-2020
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-04-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003704-39-NL
ClinicalTrials.gov	NCT03996473
CCMO	NL70314.031.19