臺北醫學大學附設醫院
TAIPEI MEDICAL UNIVERSITY HOSPITAL

藥物不良反應工作小組藥物安全警訊通告 107.08

歐洲藥物管理局(EMA)用藥安全資訊風險溝通：
限制攝護腺癌藥物Xofigo® (radium-223 dichloride)之治療策略

摘要說明：

Xofigo® 目前於衛生福利部、美國食品藥物管理署及歐洲藥物管理局之核准適應症為治療去勢抗性攝護腺癌(castration-resistant prostate cancer)病患，其合併有症狀的骨轉移且尚未有臟器轉移者。

EMA 建議 Xofigo® 應限制用於已經兩次治療轉移性前列腺癌（前列腺癌已經擴散到骨骼）或無法接受其他治療之患者。

ERA-223 為隨機雙盲第三期臨床試驗，顯示與 Zytiga (abiraterone acetate)、prednisone 或 prednisolone 併用相較於安慰劑組會有增加骨折(試驗組 28.6% vs.安慰劑組 11.4%)及降低存活率(試驗組 30.7 個月 vs.安慰劑組 33.3 個月)的風險，故禁止併用。特別在有骨質疏鬆病史的骨轉移數量低病患中發生骨折的風險較高。Xofigo® 僅用於單一治療或與 LHRH 衍生物合併治療外，不建議同時接受其他化療。

另外，在 ALSYMPCA 隨機雙盲第三期臨床試驗中，研究結果顯示骨轉移數量低 (osteoblastic bone metastases)或 ALP <220 U/L 的病患族群在統計學上沒有顯著的臨床效益。

醫療人員注意事項：

1) Xofigo® 禁止與 Zytiga (abiraterone acetate)、prednisone 或 prednisolone 併用。上述併用藥品最後一次服用應至少五天後再開始 Xofigo® 治療。
2) Xofigo® 為單一治療或合併 LHRH 衍生物用於已經兩次治療轉移性前列腺癌（前列腺癌已經擴散到骨骼）或無法接受其他治療之患者。在最後一次 Xofigo® 治療後至少 30 天內不應接受的全身性癌症治療。
3) 骨轉移數量低的病患和僅有無症狀骨轉移的病患，不建議使用 Xofigo。。
4) Xofigo® 療程開始前及治療期間應評估病患的骨質狀態(如:骨密度測量)及危險因子(如:骨質疏鬆症、骨轉移數量、併用藥物及 BMI 指數等)並提醒病患應注意的事項。應監測至少 24 個月。
5) 現已發現同時併用雙磷酸鹽或 denosumab 可以降低 Xofigo® 引起骨折的風險。
6) 醫療人員若懷疑病人因為使用藥品導致不良反應發生時，請立即線上通報藥物不良反應及登入於藥物過敏/不良反應記錄中。

院內品項：

Xofigo® (radium-223 dichloride) 6000 kBq/vial 鐳治骨

北醫藥物不良反應工作小組 敬啟
臨床藥學組 呂懷恩 藥師
(分機 8443/8444)

27 July 2018
EMA/500948/2018

EMA restricts use of prostate cancer medicine Xofigo

Medicine to be used only after two previous treatments or when other treatments cannot be taken

The European Medicines Agency has concluded its review of the cancer medicine Xofigo (radium-223 dichloride), and has recommended restricting its use to patients who have had two previous treatments for metastatic prostate cancer (prostate cancer that has spread to the bone) or who cannot receive other treatments.

Xofigo must also not be used with the medicines Zytiga (abiraterone acetate) and the corticosteroid prednisone or prednisolone. Xofigo should not be used with other systemic cancer therapies, except for treatments to maintain reduced levels of male hormones (hormone therapy). The medicine should also not be used in patients who have no symptoms, in line with the current indication; in addition, the use of Xofigo is not recommended in patients with a low number of bone metastases called osteoblastic bone metastases.

The review of Xofigo was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) after data from a clinical study suggested that patients given Xofigo in combination with Zytiga and prednisone/prednisolone could be at risk of dying earlier and had more fractures than patients given placebo (a dummy treatment) with Zytiga and prednisone/prednisolone. The study included patients with no or only mild symptoms, whereas Xofigo is only authorised in patients with symptoms. In addition, the combination used in this study is now contraindicated. In the study, patients given the combination with Xofigo died on average 2.6 months earlier than those given the combination with placebo. In addition, 29% of patients who received the Xofigo combination had fractures, compared with 11% of patients given the placebo combination.

It is thought that Xofigo, which is taken up by the bone, accumulates at sites where the bone is already damaged, for example by osteoporosis or micro-fractures, increasing the risk of fracture. However, the reasons for a possible earlier death seen in this study are not fully understood. The company that markets Xofigo will have to conduct studies to further characterise these events and clarify the mechanisms behind them.

The PRAC's recommendations have now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP) and will be sent to the European Commission for a final legal decision.

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Information for patients

- The prostate cancer medicine Xofigo can increase the risk of having fractures. Also, having Xofigo together with the cancer medicine Zytiga and a corticosteroid medicine (prednisone or prednisolone) for prostate cancer could possibly increase the risk of death.
- Your doctor will not use the combination of Xofigo and the other two medicines for prostate cancer. In addition Xofigo, used on its own or with medicines called 'luteinising hormone releasing hormone (LHRH) analogues', will be reserved for patients who have had at least two previous treatments for prostate cancer that has spread to the bone, or who cannot receive other treatments.
- Xofigo is authorised for use only when the spreading cancer is causing symptoms; depending on how the cancer has spread to the bone, your doctor will decide whether Xofigo is the right treatment for you.
- Before, during, and after treatment with Xofigo your doctor will carry out tests to check the health status of your bones. Depending on the results of these tests, Xofigo may be interrupted or stopped, and you may be given an alternative treatment.
- Before starting and during treatment with Xofigo, your doctor may also give you a medicine to protect your bones from fractures.
- If you experience any new or unusual bone pain or swelling before, during or after your treatment with Xofigo, you should consult your doctor.
- If you have any questions or concerns about your treatment, speak to your doctor or pharmacist.

Information for healthcare professionals

- The use of Xofigo is associated with an increased risk of fractures. A possible increased risk of death was also observed in a clinical trial investigating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer.
- Xofigo should only be used as monotherapy or in combination with an LHRH analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, who are in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.
- Xofigo is contraindicated in combination with abiraterone acetate and prednisone/prednisolone. In addition, Xofigo should not be started in the first 5 days following the last dose of abiraterone and prednisone/prednisolone. Subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of Xofigo.
- Xofigo is not recommended in patients with a low level of osteoblastic bone metastases and in patients with only asymptomatic bone metastases. It is also not recommended in combination with systemic cancer therapies other than LHRH analogues.
- In mildly symptomatic patients, the benefit of treatment should be carefully assessed against its risks, considering that high osteoblastic activity is likely to be required for treatment benefit (see below for more information).

- Before starting and during treatment with Xofigo, an assessment of patients' bone status (e.g. by scintigraphy, bone mineral density measurement) and risk of fractures (e.g. osteoporosis, fewer than 6 bone metastases, medication increasing fracture risk, low body mass index) should be performed. Monitoring should continue for at least 24 months.
- In patients with a high baseline risk of fracture, carefully consider the benefit of treatment against the risks.
- Concurrent use of bisphosphonates or denosumab has been found to reduce the incidence of fractures in patients treated with Xofigo. Therefore such preventive measures should be considered before starting or resuming treatment with Xofigo.

The Agency's recommendations are based on the assessment of data from a randomised, double blind, placebo controlled phase III trial (ERA-223), which showed that there was an increased incidence of fractures (28.6% vs 11.4%), a possible reduction in median overall survival (30.7 months vs 33.3 months, HR 1.195, 95% confidence interval (CI) 0.950 - 1.505, p=0.13) and an increased risk of radiological non-bone progression (HR 1.376 [95% CIs 0.972, 1.948], p=0.07) among patients receiving Xofigo in combination with abiraterone acetate plus prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone (n=405). An increased fracture risk was found particularly in patients with a medical history of osteoporosis and in patients with fewer than 6 bone metastases.

In another randomised, double blind, placebo controlled phase III trial (ALSYMPCA), a statistically significant overall survival benefit of treatment with Xofigo could not be demonstrated in the subgroups of patients with fewer than 6 metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 - 1.466], p=0.674) or a baseline total alkaline phosphatase (ALP) <220 U/L (HR 0.823 95% CI 0.633-1.068, p=0.142), indicating that efficacy may be diminished in patients with a low level of osteoblastic activity from their bone metastases.

More about the medicine

Xofigo is currently used to treat adult men with cancer of the prostate (a gland of the male reproductive system). It is authorised for use when medical or surgical castration (stopping the production of male hormones in the body using medicines or surgery) does not work, and when the cancer has spread to the bones and is causing symptoms such as pain but is not known to have spread to other internal organs.

Xofigo was authorised in the European Union in November 2013. More information on Xofigo is available on the EMA website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports

More about the procedure

The review of Xofigo was initiated on 1 December 2017 at the request of the European Commission, Article 20 of Regulation (EC) No 726/2004.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. In March 2018, the

PRAC recommended contraindicating the use of Xofigo with Zytiga and prednisone/prednisolone, as an interim measure, while the review was ongoing.

The final PRAC recommendations were adopted on 12 July 2018 and then sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

Radium-223 Dichloride and Abiraterone Acetate Compared to Placebo and Abiraterone Acetate for Men With Cancer of the Prostate When Medical or Surgical Castration Does Not Work and When the Cancer Has Spread to the Bone, Has Not Been Treated With Chemotherapy and is Causing no or Only Mild Symptoms (ERA 223)

ClinicalTrials.gov Identifier: NCT02043678

Recruitment Status: Active, not recruiting
First Posted: January 23, 2014
Last Update Posted: July 12, 2018

Sponsor:
Bayer

Collaborator:
Janssen Research & Development, LLC

Information provided by (Responsible Party):
Bayer

Tracking Information

First Submitted Date ICMJE	January 21, 2014
First Posted Date ICMJE	January 23, 2014
Last Update Posted Date	July 12, 2018
Actual Study Start Date ICMJE	March 30, 2014
Actual Primary Completion Date	February 15, 2018 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE **(submitted: April 4, 2018)**	Symptomatic skeletal event free survival (SSE-FS). [Time Frame: At 4 years]
Original Primary Outcome Measures ICMJE **(submitted: January 21, 2014)**	Symptomatic skeletal event free survival (SSE-FS) [Time Frame: At 3 years]
Change History	Complete list of historical versions of study NCT02043678 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE **(submitted: April 4, 2018)**	• Overall Survival [Time Frame: At 4 years for interim and at 6 years for final.] • Time to opiate use for cancer pain [Time Frame: At 4 years] • Time to pain progression [Time Frame: At 4 years]

	• Time to cytotoxic chemotherapy [Time Frame: At 4 years] • Radiological progression free survival (rPFS) [Time Frame: At 4 years] • Number of participants with adverse events as a measure of safety and tolerability. [Time Frame: Up to 4 years]
Original Secondary Outcome Measures ICMJE **(submitted: January 21, 2014)**	• Overall Survival [Time Frame: At 3 years for interim and at 6 years for final] • Time to opiate use for cancer pain [Time Frame: At 3 years] • Time to pain progression [Time Frame: At 3 years] • Time to cytotoxic chemotherapy [Time Frame: At 3 years] • Radiological progression free survival (rPFS) [Time Frame: At 3 years] • Number of participants with adverse events as a measure of safety and tolerability [Time Frame: Up to 3 years]
Current Other Outcome Measures ICMJE	*Not Provided*
Original Other Outcome Measures ICMJE	*Not Provided*

Descriptive Information

Brief Title ICMJE	Radium-223 Dichloride and Abiraterone Acetate Compared to Placebo and Abiraterone Acetate for Men With Cancer of the Prostate When Medical or Surgical Castration Does Not Work and When the Cancer Has Spread to the Bone, Has Not Been Treated With Chemotherapy and is Causing no or Only Mild Symptoms
Official Title ICMJE	A Phase III Randomized, Double-blind, Placebo-controlled Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone/Prednisolone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-naïve Subjects With Bone Predominant Metastatic Castration-resistant Prostate Cancer(CRPC)
Brief Summary	To determine if the addition of radium-223 dichloride to standard treatment is able to prolong life and to delay events specific for prostate cancer which has spread to the bone, such as painful fractures or bone pain which needs to be treated with an X-ray machine.
Detailed Description	This study is a phase III multinational, multicenter,randomized, double blind, placebo controlled, study with a randomization allocation ratio of 1:1 (radium-223 dichloride plus abiraterone acetate plus prednisone/prednisolone: placebo plus abiraterone acetate plus prednisone/prednisolone).The study period will consist of screening/randomization, treatment, active follow-up with clinic visits, active follow-up without clinic visits, and long-term follow-up phases. In this study, subjects will receive study treatment (radium-223 dichloride or placebo in addition to abiraterone acetate plus prednisone/prednisolone for the first 6 cycles followed by abiraterone acetate plus prednisone/prednisolone thereafter) until an on-study symptomatic skeletal event (SSE) occurs (or other withdrawal criteria are met). Follow-up will continue for up to 7 years or until the subject dies, is lost to followup, or withdraws informed consent and actively objects to collection of further data.This study will be conducted at approximately 150 investigative study centers and approximately 800 subjects will be enrolled.
Study Type ICMJE	Interventional
Study Phase	Phase 3
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Condition ICMJE	Prostatic Neoplasms

Intervention ICMJE	• Drug: Radium-223 dichloride (Xofigo, BAY88-8223) 50 kBq/kg body weight, intravenous injection (IV-slow bolus), every 4 weeks for 6 cycles. (nominal change to 55 kBq/kg after implementation of National Institute of Standards and Technology (NIST) update) • Drug: Matching placebo (normal saline) Intravenous injection (IV-slow bolus), every 4 weeks for 6 cycles • Drug: Abiraterone All study subjects will receive treatment with oral abiraterone acetate (1000 mg once daily),with best supportive care • Drug: Prednisone/Prednisolone All study subjects will receive treatment with oral prednisone/prednisolone (5 mg twice daily), with best supportive care
Study Arms	• Experimental: Radium-223 dichloride Radium-223 dichloride +abiraterone+prednisone/prednisolone All study subjects will receive treatment with oral abiraterone acetate (1000 mg once daily), oral prednisone/prednisolone (5 mg twice daily), with best supportive care Interventions: ◦ Drug: Radium-223 dichloride (Xofigo, BAY88-8223) ◦ Drug: Abiraterone ◦ Drug: Prednisone/Prednisolone • Placebo Comparator: Placebo Placebo+abiraterone+prednisone/prednisolone All study subjects will receive treatment with oral abiraterone acetate (1000 mg once daily), oral prednisone/prednisolone (5 mg twice daily), with best supportive care Interventions: ◦ Drug: Matching placebo (normal saline) ◦ Drug: Abiraterone ◦ Drug: Prednisone/Prednisolone
Publications *	*Not Provided*

*** Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.**

Recruitment Information

Recruitment Status ICMJE	Active, not recruiting
Actual Enrollment ICMJE **(submitted: September 22, 2016)**	806
Original Estimated Enrollment ICMJE **(submitted: January 21, 2014)**	800
Estimated Study Completion Date	December 23, 2019
Actual Primary Completion Date	February 15, 2018 (Final data collection date for primary outcome measure)
Eligibility Criteria ICMJE	Inclusion Criteria:

	• Histologically confirmed adenocarcinoma of the prostate • Male subjects of age ≥ 18 years • Prostate cancer progression documented by prostate specific antigen according to the Prostate Cancer Working Group 2 (PCWG2) criteria or radiological progression according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. • Two or more bone metastases on bone scan within 4 weeks prior to randomization with no lung, liver, other visceral and/or brain metastasis. • Asymptomatic or mildly symptomatic prostate cancer. • Subjects who received combined androgen blockade with an anti-androgen must have shown PSA(prostate specific antigen) progression after discontinuing the anti-androgen prior to enrollment. • Medical or surgical castration with testosterone less than 50 ng/dL (1.7nmol/L). • Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 Exclusion Criteria: • Prior cytotoxic chemotherapy for the treatment of CRPC, including taxanes, mitoxantrone and estramustine • Any chronic medical condition requiring a higher dose of corticosteroid than 5 mg prednisone/prednisolone bid. • Pathological finding consistent with small cell carcinoma of the prostate • History of visceral metastasis, or presence of visceral metastasis detected by screening imaging examinations • History of or known brain metastasis. • Malignant lymphadenopathy exceeding 3 cm in short-axis diameter. • Blood transfusion or erythropoietin stimulating agents prior 4 weeks of screening and during the whole screening period before randomization • Imminent spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI). Subjects with history of spinal cord compression should have completely recovered • Use of opiate analgesics for cancer-related pain, including codeine and dextropropoxyphene, currently or anytime during the 4- week period prior to randomization.
Sex/Gender	Sexes Eligible for Study: Male
Ages	18 Years and older (Adult, Older Adult)
Accepts Healthy Volunteers	No
Contacts ICMJE	*Contact information is only displayed when the study is recruiting subjects*
Listed Location Countries ICMJE	Australia, Belgium, Brazil, Canada, Finland, France, Germany, Israel, Italy, Japan, Netherlands, Norway, Poland, Russian Federation, Singapore, Spain, Sweden, United Kingdom, United States
Removed Location Countries	

Administrative Information

NCT Number ICMJE	NCT02043678
Other Study ID Numbers ICMJE	15396 2013-003438-33 (EudraCT Number)
Has Data Monitoring Committee	Yes

U.S. FDA-regulated Product	Studies a U.S. FDA-regulated Drug Product: Yes Studies a U.S. FDA-regulated Device Product: No
IPD Sharing Statement	*Not Provided*
Responsible Party	Bayer
Study Sponsor ICMJE	Bayer
Collaborators ICMJE	Janssen Research & Development, LLC
Investigators ICMJE	Study Director: Bayer Study Director Bayer
PRS Account	Bayer
Verification Date	July 2018

ICMJE **Data element required by the International Committee of Medical Journal Editors and the World Health Organization ICTRP**

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Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

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ABSTRACT

BACKGROUND

Radium-223 dichloride (radium-223), an alpha emitter, selectively targets bone metastases with alpha particles. We assessed the efficacy and safety of radium-223 as compared with placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases.

METHODS

In our phase 3, randomized, double-blind, placebo-controlled study, we randomly assigned 921 patients who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, to receive six injections of radium-223 (at a dose of 50 kBq per kilogram of body weight intravenously) or matching placebo; one injection was administered every 4 weeks. In addition, all patients received the best standard of care. The primary end point was overall survival. The main secondary efficacy end points included time to the first symptomatic skeletal event and various biochemical end points. A prespecified interim analysis, conducted when 314 deaths had occurred, assessed the effect of radium-223 versus placebo on survival. An updated analysis, when 528 deaths had occurred, was performed before crossover from placebo to radium-223.

RESULTS

At the interim analysis, which involved 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs. 11.2 months; hazard ratio, 0.70; 95% confidence interval [CI], 0.55 to 0.88; two-sided $P=0.002$). The updated analysis involving 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; $P<0.001$). Assessments of all main secondary efficacy end points also showed a benefit of radium-233 as compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer adverse events.

CONCLUSIONS

In this study, which was terminated for efficacy at the prespecified interim analysis, radium-223 improved overall survival. (Funded by Algeta and Bayer HealthCare Pharmaceuticals; ALSYMPCA ClinicalTrials.gov number, NCT00699751.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Parker at the Royal Marsden Hospital, Academic Urology Unit, Downs Rd., Sutton, Surrey SM2 5PT, United Kingdom, or at chris.parker@rmh.nhs.uk.

*Additional investigators in the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study are listed in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa1213755

More than 90% of patients with metastatic castration-resistant prostate cancer have radiologic evidence of bone metastases, which are a major cause of death, disability, decreased quality of life, and increased treatment cost among these patients.[1,2] Unlike deaths from many other types of cancer, deaths from prostate cancer are often due to bone disease and its complications.[3] Current bone-targeted therapies have not been shown to improve survival, and the benefits derived from bisphosphonates, denosumab, and existing radioisotope treatments are primarily limited to pain relief and delay of skeletal events.[4-13]

Radium-223 dichloride (radium-223) is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 μm).[14] As a bone-seeking calcium mimetic, radium-223 is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases.[15,16] The high-energy alpha-particle radiation induces mainly double-stranded DNA breaks that result in a potent and highly localized cytotoxic effect in the target areas.[10,15,17,18] The short path of the alpha particles also means that toxic effects on adjacent healthy tissue and particularly the bone marrow may be minimized.[16,19,20]

Radium-223 has been reported to have a favorable safety profile, with minimal myelotoxicity, in phase 1 and 2 studies involving patients with bone metastases.[21,22] Phase 2 studies have shown that radium-223 reduces pain and improves disease-related biomarkers (e.g., bone alkaline phosphatase and prostate-specific antigen [PSA]),[22-24] and they have suggested a survival benefit among patients with castration-resistant prostate cancer and bone metastases.[22] To evaluate the effect of radium-223 on survival, we conducted the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study, a phase 3, randomized, double-blind, multinational study comparing the efficacy and safety of radium-223 versus placebo in patients with castration-resistant prostate cancer and bone metastases.

A Quick Take animation is available at NEJM.org

Methods

Study Oversight and Conduct

The study was designed, conducted, and analyzed by employees of Algeta and Bayer HealthCare Pharmaceuticals, the sponsors, in collaboration with the study investigators. The blinded database was held at a third-party contract clinical research organization that provided data to the independent data and safety monitoring committee, assembled by the sponsors. After the independent data and safety monitoring committee recommended unblinding of the data, analyses were performed as defined in the statistical-analysis plan by statisticians employed by the sponsors, and the results were reviewed by the authors. The study investigators signed time-limited confidentiality agreements with the sponsors regarding publishing of the study data. Assistance in writing the first draft of the manuscript was provided by a professional medical writer paid by Bayer HealthCare Pharmaceuticals. All authors wrote the manuscript, made the decision to submit it for publication, and assume responsibility for the completeness and integrity of the data and adherence of the study to the protocol. The protocol and statistical-analysis plan are available with the full text of this article at NEJM.org.

The institutional review board at each participating center approved the study, which was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation.

Patients

Patients were eligible to participate in the study if they had histologically confirmed, progressive castration-resistant prostate cancer with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases; were receiving the best standard of care; and had received docetaxel, were not healthy enough or declined to receive it, or it was not available. Castration-resistant disease was defined as a serum testosterone level of 50 ng per deciliter or lower (≤1.7 nmol per liter) after bilateral orchiectomy or during maintenance treatment consisting of androgen-ablation therapy with a luteinizing hormone–releasing hormone agonist or polyestradiol phosphate. Patients with castration-resistant disease during maintenance treatment were required to continue that treatment throughout the study. Patients were required to have symptomatic disease with regular use of analgesic medication or treatment with external-beam radiation therapy required for cancer-related bone pain within the previous 12 weeks. Additional eligibility criteria included a baseline PSA level of 5 ng per milliliter or higher with

evidence of progressively increasing PSA values (two consecutive increases over the previous reference value); an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a scale of 0 to 5, with 0 indicating no symptoms and full activity and higher scores indicating greater functional compromise[25]) (see the definitions of ECOG performance-status scores in the Supplementary Appendix, available at NEJM.org); a life expectancy of 6 months or longer; and adequate hematologic, renal, and liver function.

Patients were excluded if they had received chemotherapy within the previous 4 weeks or had not recovered from adverse events due to chemotherapy. Additional exclusion criteria were previous hemibody external radiotherapy, systemic radiotherapy with radioisotopes within the previous 24 weeks, a blood transfusion or use of erythropoietin-stimulating agents within the previous 4 weeks, a malignant lymphadenopathy that was more than 3 cm in the short-axis diameter, a history of or the presence of visceral metastases, and imminent or established spinal cord compression. All patients provided written informed consent.

STUDY DESIGN AND REGIMEN

Patients were stratified according to previous use or nonuse of docetaxel, baseline alkaline phosphatase level (<220 U per liter vs. ≥220 U per liter), and current use or nonuse of a bisphosphonate. They were randomly assigned in a 2:1 ratio to receive six intravenous injections of radium-223 (at a dose of 50 kBq per kilogram of body weight) or matching placebo; one injection was administered every 4 weeks (see Fig. S1A and the description of radium-223 radiation safety in the Supplementary Appendix). The best standard of care was defined as the routine care provided at each center (e.g., local external-beam radiation therapy or treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine). Chemotherapy, hemibody external radiotherapy, and other systemic radionuclides were not permitted during the period from the first injection of the study drug to 4 weeks after the last injection of the study drug. The planned follow-up period was 3 years.

The primary end point was overall survival, defined as the time from randomization to the date of death, regardless of cause. The main secondary efficacy end points were the time to an increase in the total alkaline phosphatase level (defined as an increase of ≥25% from baseline at ≥12 weeks, in patients with no decrease from baseline, or as an increase of ≥25% above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline), a total alkaline phosphatase response (defined as a reduction of ≥30% from the baseline value, confirmed ≥4 weeks later), the time to the first symptomatic skeletal event (defined as the first use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or nonvertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention), normalization of the total alkaline phosphatase level (defined as a return to a value within the normal range at 12 weeks [confirmed by two consecutive measurements ≥2 weeks apart] in patients with total alkaline phosphatase values above the upper limit of the normal range at baseline), and the time to an increase in the PSA level (defined as a relative increase of ≥25% from the baseline level and an absolute increase of ≥2 ng per milliliter at ≥12 weeks, in patients with no decrease in the PSA level from baseline, or a relative increase of ≥25% and an absolute increase of ≥2 ng per milliliter above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline). Other secondary end points included additional efficacy end points (listed in Table S1 in the Supplementary Appendix), safety end points, and quality of life.

STUDY ASSESSMENTS

Efficacy assessments included survival status, clinically evaluated symptomatic skeletal events, and total alkaline phosphatase and PSA concentrations. Safety was assessed on the basis of adverse events, hematologic values, clinical laboratory variables, and findings on electrocardiography and physical examination. All adverse events that occurred after randomization and within 12 weeks after the last injection of the study drug were reported and evaluated for their potential relationship to the study drug. Adverse events that occurred more than 12 weeks after the final injection of the study drug were reported only if they were determined to be related to the study drug by the investigator. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire.[26]

STATISTICAL ANALYSIS

A sample of 900 patients was required to provide a statistical power of 90% to detect a hazard ratio of 0.76 for the risk of death in the radium-223 group versus the placebo group with a two-sided alpha significance level of 0.05. The final overall survival analysis would be conducted after approximately 640 deaths had occurred. One formal interim analysis was planned after approximately 50% of the deaths (i.e., 320 deaths) had occurred, to assess the effect of radium-223 on the primary end point (overall survival). As prespecified in the protocol, the Lan–DeMets alpha spending approach[27] was applied with O'Brien–Fleming stopping boundaries[28] to evaluate the difference in overall survival between the two groups. On the basis of the actual number of deaths at the time of the interim analysis (314), a two-sided alpha significance level of 0.0028 or lower was required to support early termination of the study for efficacy. An independent data and safety monitoring committee was responsible for evaluating the results of the interim analysis. On the basis of this evaluation, which showed a survival advantage with radium-223 and an acceptable safety profile, the committee recommended early discontinuation of the trial and crossover from placebo to radium-223. We report here the results of an updated descriptive analysis of the efficacy and safety data, performed when 528 deaths had occurred, before any crossover treatment with radium-223 was administered.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Radium-223 (N=614)	Placebo (N=307)
Age		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	575 (94)	290 (94)
Total alkaline phosphatase — no. (%)		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)
Any previous use of docetaxel — no. (%)		
Yes	352 (57)	174 (57)
No	262 (43)	133 (43)
ECOG performance-status score — no. (%)‡		
0	165 (27)	78 (25)
1	371 (60)	187 (61)
≥2	77 (13)	41 (13)
WHO ladder for cancer pain — no. (%)§		
1	257 (42)	137 (45)
2	151 (25)	78 (25)
3	194 (32)	90 (29)
Extent of disease — no. (%)		
<6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
>20 metastases	195 (32)	91 (30)
Superscan¶	54 (9)	30 (10)

Table 1. (Continued.)

Characteristic	Radium-223 (N=614)	Placebo (N=307)
External-beam radiation therapy within 12 wk after screening — no. (%)		
Yes	99 (16)	48 (16)
No	515 (84)	259 (84)
Median biochemical values (range)‖		
Hemoglobin — g/dl	12.2 (8.5–15.7)	12.1 (8.5–16.4)
Albumin — g/liter	40 (24–53)	40 (23–50)
Total alkaline phosphatase — U/liter	211 (32–6431)	223 (29–4805)
Lactate dehydrogenase — U/liter	315 (76–2171)	336 (132–3856)
PSA — μg/liter	146 (3.8–6026)	173 (1.5–14500)

* Percentages may not sum to 100 due to rounding.
† Race was self-reported.
‡ The Eastern Cooperative Oncology Group (ECOG) scores the performance status of patients with respect to activities of daily living as follows: 0, fully active and able to carry out all predisease activities without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature; 2, ambulatory and up and about for more than 50% of waking hours and capable of self-care but unable to carry out work activities; 3, capable of only limited self-care and confined to a bed or chair for more than 50% of waking hours; 4, completely disabled; and 5, dead.
§ A total of 12 patients in the radium-223 group (2%) and 2 patients in the placebo group (1%) had no pain or analgesic use at baseline. A World Health Organization (WHO) score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use.
¶ Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity.
‖ The normal ranges are as follows: hemoglobin, 13.4 to 17.0 g per deciliter; albumin, 36 to 45 g per liter; total alkaline phosphatase, 35 to 105 U per liter; lactate dehydrogenase, 115 to 255 U per liter; and prostate-specific antigen (PSA), 0 to 3.999 μg per liter.

The stratified log-rank test was used as the primary analysis for survival; subgroup analyses were performed to assess whether the treatment effect was consistent across subgroups. The main secondary efficacy end points were analyzed with the use of a gatekeeping procedure to control for the overall type I error rate; an end point was tested at a two-sided significance level of 0.05 only if the two-sided P value for all higher-ranking end points was 0.05 or lower. The intention-to-treat population included all randomly assigned patients, and the safety population was composed of patients who received at least one injection of a study drug.

After unblinding of the data, inconsistencies were noted between the total number of symptomatic skeletal events as reported on the case-report form and the number in the listings of adverse events. Thus, a post hoc sensitivity analysis was performed after resolution of these inconsistencies with the study sites. As shown in Figure S2 and Table S2 in the Supplementary Appendix, these inconsistencies did not affect the results of the original analysis to any meaningful degree.

RESULTS

PATIENTS AND STUDY REGIMEN

From June 2008 through February 2011, a total of 921 patients were enrolled (614 in the radium-223 group and 307 in the placebo group) at 136 study centers in 19 countries and were included in the intention-to-treat population (Fig. S1B in the Supplementary Appendix). The safety population included 901 patients (600 in the radium-223 group and 301 in the placebo group). Baseline clinical and demographic characteristics were well balanced between the study groups (Table 1). The planned interim analysis was based on data from 809 enrolled patients (541 in the radium-223 group and 268 in the placebo group) (Table S3 in the Supplementary Appendix).

Overall, as of this writing, 532 of 921 patients (58%) had received all six injections of the study drug (387 patients in the radium-223 group [63%] and 145 in the placebo group [47%]). The median number of injections was six in the radium-223 group and five in the placebo group.

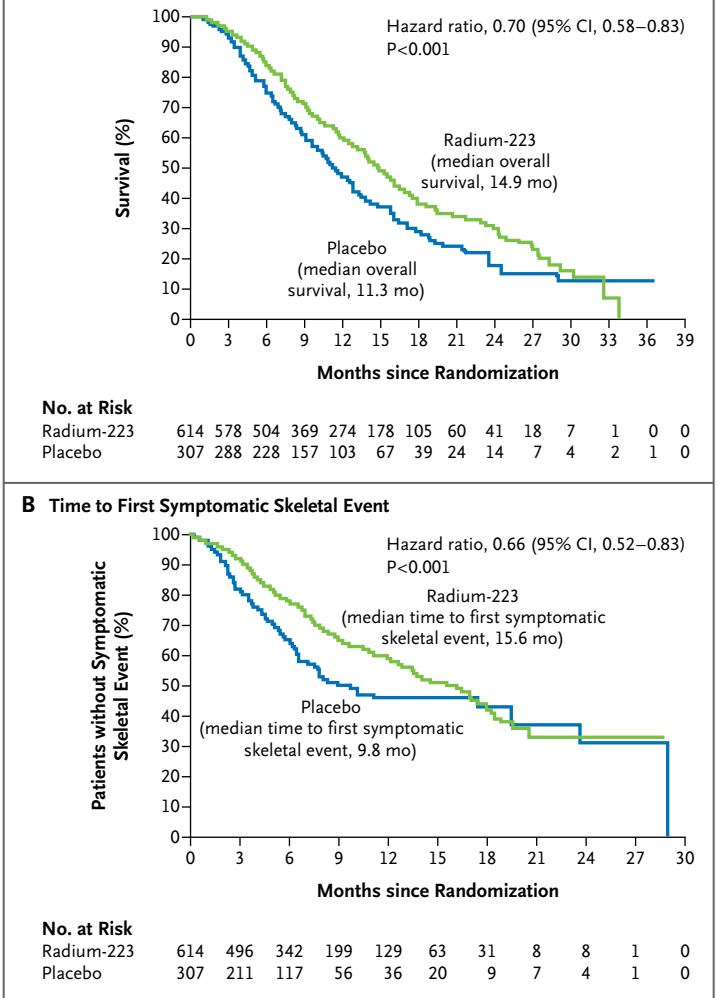

Figure 1. Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event.

EFFICACY

At the interim analysis, the median overall survival was 14.0 months in the radium-223 group and 11.2 months in the placebo group (Fig. S3A in the Supplementary Appendix). Radium-223, as compared with placebo, was associated with a 30% reduction in the risk of death (hazard ratio, 0.70; 95% confidence interval [CI], 0.55 to 0.88; two-sided P=0.002). In the intention-to-treat population, 314 patients died. In the radium-223 group, 191 of 541 patients died (35%), and in the placebo group, 123 of 268 patients died (46%). The effect of radium-223 on overall survival was consistent across all subgroups (Fig. S3B in the Supplementary Appendix), and radium-223, as compared with placebo, was not associated with significantly more grade 3 or 4 toxic effects (Table S4 in the Supplementary Appendix). On the basis of these data, the independent data and safety monitoring committee recommended termination of the trial.

In the updated analysis, the median overall survival was 14.9 months in the radium-223 group and 11.3 months in the placebo group (Fig. 1A). The updated analysis confirmed the 30% reduction in the risk of death among patients in the radium-223 group as compared with the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001). A total of 528 patients in the intention-to-treat population died. In the radium-223 group, 333 of 614 patients died (54%), and in the placebo group, 195 of 307 patients died (64%). The effect of radium-223 on overall survival was consistent across all subgroups (Fig. 2).

All main secondary efficacy end points provided support for the benefit of radium-223 plus the best standard of care over placebo plus the best standard of care (Table 2). Radium-223, as compared with placebo, significantly prolonged the time to the first symptomatic skeletal event (median, 15.6 months vs. 9.8 months; hazard ratio, 0.66; 95% CI, 0.52 to 0.83; P<0.001) (Fig. 1B), the time to an increase in the total alkaline phosphatase level (hazard ratio, 0.17; 95% CI, 0.13 to 0.22; P<0.001) (Fig. S4A in the Supplementary Appendix), and the time to an increase in the PSA level (hazard ratio, 0.64; 95% CI, 0.54 to 0.77; P<0.001) (Fig. S4B in the Supplementary Appendix). Increases in the alkaline phosphatase and PSA levels, as defined in the protocol, were assessed after 12 weeks; a post hoc analysis of alkaline phosphatase and PSA levels from the start of study-drug administration is shown in Figure S4C and S4D in the Supplementary Appendix, respectively. In addition, a significantly higher proportion of patients in the radium-223 group than in the placebo group had a response according to the total alkaline phosphatase level (≥30% reduction, P<0.001) and normalization of this level (P<0.001). A 30% or greater reduction in PSA blood levels at week 12 was achieved in 16% of patients in the radium-223 group and in 6% of patients in the placebo group (P<0.001). This reduction was sustained 4 weeks after the last injection in 14% of patients in the radium-223 group and in 4% of patients in the placebo group (P<0.001).

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)

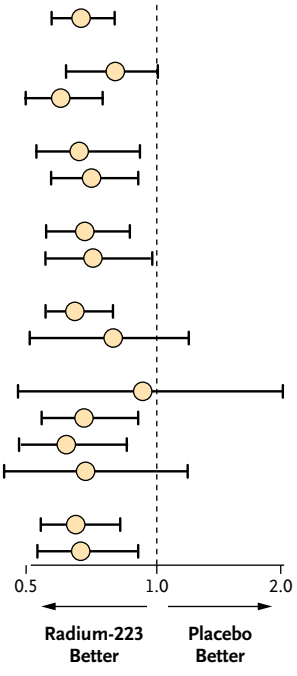

Figure 2. Subgroup Analysis of Hazard Ratios for Death in the Two Study Groups.

The Eastern Cooperative Oncology Group (ECOG) scores the performance status of patients with respect to activities of daily living as follows: 0, fully active and able to carry out all predisease activities without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature; 2, ambulatory and up and about for more than 50% of waking hours and capable of self-care but unable to carry out work activities; 3, capable of only limited self-care and confined to a bed or chair for more than 50% of waking hours; 4, completely disabled; and 5, dead. The category for use of opioids includes patients with a score of 2 or 3 on the World Health Organization "ladder" for cancer pain (a score of 1 indicates mild pain and no opioid use, 2 indicates moderate pain and occasional opioid use, and 3 indicates severe pain and regular daily opioid use). The category for nonuse of opioids includes patients without pain or opioid use at baseline and patients with a score of 1 on the WHO ladder for cancer pain. Superscan refers to a bone scan showing diffuse, intense skeletal uptake of the tracer without renal and background activity. ALP denotes alkaline phosphatase, and NE not evaluated.

SAFETY

The number of patients who had adverse events after they received the study drug was consistently lower in the radium-223 group than in the placebo group for all adverse events (558 of 600 patients [93%] vs. 290 of 301 patients [96%]), grade 3 or 4 adverse events (339 patients [56%] vs. 188 patients [62%]), serious adverse events (281 patients [47%] vs. 181 patients [60%]), and study-drug discontinuation because of adverse events (99 patients [16%] vs. 62 patients [21%]).

Hematologic and nonhematologic adverse events that occurred in at least 5% of patients in either study group are shown in Table 3. Overall, no clinically meaningful differences in the frequency of grade 3 or 4 adverse events were observed between the study groups. Grade 3 febrile neutropenia was reported in one patient (<1%) in the radium-223 group and in one patient (<1%) in the placebo group. Only one grade 5 hematologic adverse event was considered to be possibly related to the study drug: thrombocytopenia in a patient in the radium-223 group, who died from pneumonia with hypoxemia, with no evidence of bleeding. For serious adverse events that occurred in at least 5% of patients in the radium-223 group or the placebo group, the respective frequencies were as follows: disease progression (11% and 12%), bone pain (10% and 16%), anemia (8% and 9%), and spinal cord compression (4% and 5%).

A significantly higher percentage of patients who received radium-223, as compared with those

Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Radium-223 (N=614)	Placebo (N=307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

* Only patients who had elevated total alkaline phosphatase levels at baseline are included.

who received placebo, had a meaningful improvement in the quality of life according to the FACT-P total score (i.e., an increase in the score of ≥10 points on a scale of 0 to 156, with higher scores indicating a better overall quality of life) during the period of study-drug administration (25% vs. 16%, P=0.02). The mean change in the FACT-P total score from baseline to week 16 significantly favored the radium-223 group, as compared with the placebo group (–2.7 vs. −6.8, P=0.006).

DISCUSSION

In this phase 3 study, radium-223 significantly prolonged overall survival in patients who had castration-resistant prostate cancer and bone metastases, with a 30% reduction in the risk of death, as compared with placebo. In the updated analysis, the median survival was longer among patients who received radium-223 than among those who received placebo, by 3.6 months. All main secondary efficacy end points were significant and favored treatment with radium-223, including the clinically defined end point of the time to the first symptomatic skeletal event, which was significantly prolonged among patients who received radium-223. Whereas other trials included asymptomatic fractures — detected by means of periodic radiologic review — as skeletal events, in this study, only symptomatic pathologic bone fractures were included as symptomatic skeletal events.

The highly targeted nature of radium-223, with alpha particles of short range (<100 μm), minimizes myelosuppression and has limited effects on normal tissue. The overall incidence of adverse events was consistently lower in the radium-223 group than in the placebo group for adverse events of all grades, grade 3 or 4 adverse events, and serious adverse events. The number of patients who discontinued the study drug because of adverse events was also lower in the radium-223 group. No clinically meaningful differences in the frequency of hematologic adverse events were observed between the study groups.

A distinctive feature of the study was the liberal definition of the best standard of care permitted with both study drugs (radium-223 and placebo); this allowed patients to be treated with standard therapies chosen by the treating physician. Consequently, findings from this study may be generalizable to routine clinical practice, since the control group consisted of patients who received placebo with the best standard of care. The study also has high external validity because it used liberal inclusion criteria that are representative of the general population of patients with castration-resistant prostate cancer. One limitation was the exclusion of patients with visceral metastases, which may occur in up to 25% of patients with castration-resistant prostate cancer.[1,29]

Many patients with castration-resistant prostate cancer and bone metastases do not receive docetaxel because they are too frail (ECOG performance-status score >2), they have coexisting conditions that preclude its use, or they simply decline treatment. Our study addressed this important group by including patients who were not

Table 3. Adverse Events That Occurred in at Least 5% of Patients in Either Study Group in the Safety Population.

Adverse Event	Radium-223 (N=600)				Placebo (N=301)			
	All Grades	Grade 3	Grade 4	Grade 5*	All Grades	Grade 3	Grade 4	Grade 5*
	number of patients (percent)							
Hematologic								
Anemia	187 (31)	65 (11)	11 (2)	0	92 (31)	37 (12)	2 (1)	1 (<1)
Thrombocytopenia	69 (12)	20 (3)	18 (3)	1 (<1)	17 (6)	5 (2)	1 (<1)	0
Neutropenia	30 (5)	9 (2)	4 (1)	0	3 (1)	2 (1)	0	0
Nonhematologic								
Constipation	108 (18)	6 (1)	0	0	64 (21)	4 (1)	0	0
Diarrhea	151 (25)	9 (2)	0	0	45 (15)	5 (2)	0	0
Nausea	213 (36)	10 (2)	0	0	104 (35)	5 (2)	0	0
Vomiting	111 (18)	10 (2)	0	0	41 (14)	7 (2)	0	0
Asthenia	35 (6)	5 (1)	0	0	18 (6)	4 (1)	0	0
Fatigue	154 (26)	21 (4)	3 (1)	0	77 (26)	16 (5)	2 (1)	0
Deterioration in general physical health	27 (4)	9 (2)	2 (<1)	5 (1)	21 (7)	8 (3)	2 (1)	2 (1)
Peripheral edema	76 (13)	10 (2)	0	0	30 (10)	3 (1)	1 (<1)	0
Pyrexia	38 (6)	3 (1)	0	0	19 (6)	3 (1)	0	0
Pneumonia	18 (3)	9 (2)	0	4 (1)	16 (5)	5 (2)	2 (1)	0
Urinary tract infection	47 (8)	7 (1)	0	0	28 (9)	4 (1)	1 (<1)	1 (<1)
Weight loss	69 (12)	4 (1)	0	0	44 (15)	5 (2)	0	0
Anorexia	102 (17)	9 (2)	0	0	55 (18)	2 (1)	0	0
Decreased appetite	35 (6)	2 (<1)	0	0	13 (4)	0	0	0
Bone pain	300 (50)	120 (20)	5 (1)	0	187 (62)	74 (25)	3 (1)	0
Muscular weakness	9 (2)	2 (<1)	1 (<1)	0	17 (6)	6 (2)	0	0
Pathologic fracture	22 (4)	13 (2)	0	0	15 (5)	8 (3)	1 (<1)	0
Progression of malignant neoplasm	77 (13)	9 (2)	4 (1)	55 (9)	44 (15)	4 (1)	1 (<1)	33 (11)
Dizziness	43 (7)	2 (<1)	0	0	26 (9)	2 (1)	0	0
Spinal cord compression	25 (4)	14 (2)	6 (1)	1 (<1)	23 (8)	16 (5)	1 (<1)	0
Insomnia	27 (4)	0	0	0	21 (7)	1 (<1)	0	0
Hematuria	30 (5)	7 (1)	0	0	15 (5)	3 (1)	0	0
Urinary retention	25 (4)	9 (2)	0	0	18 (6)	6 (2)	0	0
Dyspnea	49 (8)	10 (2)	1 (<1)	1 (<1)	26 (9)	7 (2)	0	3 (1)

* Only one grade 5 hematologic adverse event was considered to be possibly related to the study drug: thrombocytopenia in one patient in the radium-223 group.

thought to be eligible to receive chemotherapy or who chose not to receive it. It is possible that some of these men could have received chemotherapy at other institutions or in other studies; however, at least 20 to 40% of patients with castration-resistant prostate cancer and bone metastases never receive chemotherapy,[30-32] so our study addresses an important unmet need in a population that is not served by current therapies.

The treatment of prostate cancer has evolved since the trial began, with new data on the use of cabazitaxel,[29] abiraterone,[33] and enzalutamide[34] in patients who have received docetaxel. The excellent safety profile of radium-223 and the nonover-

lapping mechanism of action make radium-223 potentially suitable for use either sequentially or in combination with these other agents. A phase 1–2 trial of radium-223 combined with docetaxel in patients with castration-resistant prostate cancer and bone metastases is currently ongoing (ClinicalTrials.gov number, NCT01106352).

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APPENDIX

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鐳治骨® 注射液
Xofigo® solution for injection

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本藥限由醫師使用

1. 藥品名稱

鐳治骨®注射液

2. 組成

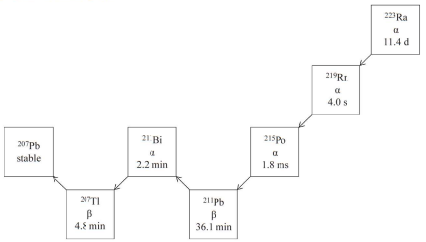
於參照日期時，每mL溶液含有1100 kBq鐳-223二氯化物(Radium-223 dichloride)，相當於含0.58 mg鐳-223。鐳以游離離子的形式存在於溶液中。

每小瓶含有6 mL溶液(鐳-223二氯化物於參照日期為6.6 MBq)。

鐳-223為α粒子放射，半衰期為11.4天，比活度為1.9 MBq/ng。

鐳-223到鉛-207的6階段衰變中產生短暫存在子代(daughters)，並伴造不同能量與放射概率的α、β及γ放射線。鐳-223及其衰變子代放射α粒子的能量介率佔95.3%（能量範圍5.0至7.5 MeV）。放射β粒子的能量分率佔3.6%（平均能量為0.445 MeV及0.492 MeV），而放射γ粒子的能量分率佔1.1%（能量範圍0.01至1.27 MeV）。

圖1：鐳-223衰變鏈、自然半衰期及衰變模式：



賦形劑

每mL溶液含有0.194 mmol（相當於4.5 mg)的鈉。

完整的賦形劑，請參閱第6.1節。

3. 劑型

注射液劑。

澄清、無色的等滲透壓溶液，酸鹼值(pH)介於6.0和8.0間。

4. 臨床特性

4.1 治療適應症

本品用於治療去勢抗性攝護腺癌(castration-resistant prostate cancer)病人，其合併有症狀的骨轉移且尚未有臟器轉移者。

4.2 劑量與給藥方式

Xofigo應於合格醫師之病人評估後，由處理放射性藥物的合格人員在指定的臨床場所(請參閱第6.6節)進行給藥。

劑量

Xofigo的劑量療程為每公斤體重給予55 kBq的放射活性，每隔4週給予，共6劑注射。

尚未針對注射Xofigo超過6劑的安全性與療效進行研究。

計算給藥體積的詳細說明請參閱第8節。

老年病人

在第III期試驗的600位以Xofigo治療的病人中，447位病人(74.5%)為65歲以上，同時196位病人(22.7%)為75歲以上。

在第III期試驗中，並未觀察到老年病人(年齡≥ 65歲)和年輕病人(年齡< 65歲)的安全性或療效有整體上的差異。老年病人不認為需要調整劑量。

肝功能不全病人

尚未在肝功能受損病人中針對Xofigo的安全性及療效進行過試驗。

由於鐳-223既不是由肝臟代謝，也不及經由膽汁排除，因此並不預期肝功能受損會影響到氡化鐳-223的藥動學。

腎功能不全病人

尚未在肌酐廓清試驗中，在輕度腎功能受損(肌酸酐廓清率[CLCR]：50至80 ml/min)與腎功能正常的病人間，並未觀察到安全性或療效的相關差異。在中度(CLCR：30至50 ml/min)及重度(CLCR：< 30 ml/min)腎功能受損病人中的資料有限，並無末期腎病病人的相關資料。然而，由於尿液均弱除器官，且主要排除途徑是經由糞便，因此腎功能受損預期不會影響氡化鐳-223的藥動學。

兒童族群

尚未在兒童和18歲以下青少年中針對Xofigo的安全性與療效進行研究。在攝護腺癌適應症中，本藥品並無相關使用於兒童族群中。

給藥方式

Xofigo供靜脈注射使用，必須以緩慢注射(通常為1分鐘)的方式給藥。

Xofigo注射前及注射後，必須以等滲過濾的氯化鈉9 mg/mL (0.9%)注射用溶液沖洗靜脈輸注管路及導管。

關於使用本藥品的額外說明，請參閱第6.6和第8節。

4.3 禁忌症

Xofigo的使用上並無已知的禁忌症。

4.4 特殊警語與使用注意事項

骨髓抑制

接受Xofigo治療的病人中曾有骨髓抑制的通報，特別是血小板減少症、嗜中性白血球減少症、白血球減少症及全血球減少症(請參閱第4.8節)。

因此，必須在基期及每一劑Xofigo治療前對病人進行血液學評估。第1次給藥前，絕對嗜中性白血球計數(ANC)應≥ 1.5 x 10^9/l、血小板計數≥ 100 x 10^9/l且血紅素≥ 10.0 g/dl。而後，後續注射給藥前，ANC應≥ 1.0 x 10^9/l且血小板計數≥ 50 x 10^9/l。若在投予最後一劑Xofigo後6週內，即使接受標準照護這些數值仍未恢復，則只有在仔細評估效益/風險後才應繼續Xofigo治療。

有臨及骨髓功能證據(如先前接受細胞毒性化學治療和/或放射治療[EBRT]之後)的病人或晚期骨髓受性浸潤到骨頭(EOD4：superscan)的攝護腺癌病人，治療時應特別小心，在第III期試驗中，觀察到這些病人的血液學不良反應(例如嗜中性白血球減少症及血小板減少症)發生率升高(請參閱第4.8節)。

Xofigo治療後進行細胞毒性化學治療仍療效與安全性尚未確立。現有的有限資料顯示，於Xofigo治療後接受化學治療的病人與安慰劑治療後接受化學治療的病人相較，同者的血液學概況相似(請參閱第5.1節)。

克隆氏症與潰瘍性結腸炎

尚未在克隆氏症與潰瘍性結腸炎病人中針對Xofigo的安全性與療效進行研究。由於Xofigo為經血管便排除，因此放射線可能導致急性發炎性腸道疾病的病情加劇，在急性發炎性腸道疾病病人中，只有在仔細評估效益/風險後才應投予Xofigo治療。

脊髓壓迫

在未治療血即將發生或已確認為脊髓壓迫的病人中，應於開始或重新開始Xofigo治療前完成標準照護治療。

骨折

在骨折病人中，應於開始或重新開始Xofigo治療前完成骨折的骨科固定。

顎骨壞死

在接受雙磷酸鹽類物與Xofigo治療的病人中，無法排除有顎骨壞死(ONJ)風險增加的情況。在第II期試驗中，Xofigo組曾有0.67%的病人(4/600)通報ONJ案例。相較於安慰劑組(曾有0.33%的病人(1/301)。然而，所有發生ONJ的病人先前承有使用或正併用雙磷酸鹽藥物(例如：zoledronic acid)以及先前接受化學治療(例如：docetaxel)。

繼發性惡性腫瘤

Xofigo會增加病人長期累積的整體放射線暴露量。因此，長期累積的放射線暴露可能與癌症及遺傳缺陷的風險增加具有相關性，尤其是骨肉瘤、骨髓增生異常症候群及白血病的風險可能會增加。於臨床試驗中，長達3年的追蹤期間並無Xofigo誘發癌症的案例通報。

腻形壓

依據給藥體積，本藥品每次劑量可能含有高達2.35 mmol (54 mg)的鈉。對控制鈉飲食的病人應考量到這點。

4.5 與其他藥品的交互作用，以及其他形式的交互作用

尚未進行臨床藥物交互作用的研究。

由於無法排除與鈣和磷酸鹽的交互作用，應考慮於開始Xofigo治療前幾天提暫停使用這些物質和/或維生素D的補充劑。

Xofigo合併化學治療可能產生骨髓抑制的加成效果(請參閱第4.4節)。尚未確立Xofigo併用化學治療的安全性與療效。

4.6 生殖力、懷孕與哺乳

男性避孕

不曾針對Xofigo進行動物內生殖研究。

由於存放射線對精子生成均潛在影響，應告知男性病人於Xofigo治療期間以及治療後6個月內使用有效的避孕方式。

懷孕與哺乳

Xofigo不適用於女性病人。Xofigo不會用於已經懷孕、可能懷孕或正在哺乳的女性。

生殖力

關於Xofigo對生殖力的影響，目前並無人體資料。

根據動物試驗，Xofigo產生的放射線可能有造成生殖力不良反應的潛在風險(請參閱第5.3節)。男性病人在治療前應尋求關於精子保存的醫學建議。

4.7 對駕駛與操作機械能力的影響

並無證據及不預期Xofigo會影響駕駛或操作機械的能力。

4.8 不良反應

安全性概況摘要

Xofigo的整體安全性概況是以第III期試驗中接受Xofigo治療的600位病人資料作為基礎。接受Xofigo治療內病人中最常觀察到的不良反應(≥ 10%)為腹瀉、噁心、嘔吐及血小板減少症。而最嚴重的不良反應則為血小板減少症及嗜中性白血球減少症(請參閱第4.4節與後述的「特定不良反應說明」)。

不良反應列表

Xofigo治療中觀察到的不良反應如下表所示(請參閱表1)。這些不良反應為根據系統器官類別予以分類。使用最適當的MedDRA詞彙以描述特定反應及其同義詞和相關病況。

臨床試驗中的不良反應依其發生頻率分類。頻率定義如下：非常常見(≥ 1/10)、常見(≥ 1/100至< 1/10)、不常見(≥ 1/1000至< 1/100)。在各頻率組別內，其不良反應為依嚴重度遞減的順序排列。

表1：病人接受Xofigo治療的臨床試驗中所通報的不良反應

系統器官類別 (MedDRA)	非常常見 (≥ 1/10)	常見 (≥ 1/100到< 1/10)	不常見 (≥ 1/1,000到< 1/100)
血液與淋巴系統疾患	血小板減少症	嗜中性白血球減少症、 全血球減少症、 白血球減少症	淋巴球減少症
胃腸道疾患	腹瀉、 嘔吐、 噁心		
全身性疾患與給藥部位症狀		注射部位反應	

特定不良反應說明

血小板減少症及嗜中性白血球減少症

有11.5%接受Xofigo治療的病人，以及5.6%接受安慰劑治療的病人發生血小板減少症(所有級別)，有6.3%受接Xofigo治療的病人以及2%接受安慰劑治療的病人，觀察到第3和第4等級的血小板減少症(請參閱第4.4節)。整體而言，關於第3和第4等級的血小板減少症，相較於先前曾接受docetaxel治療的病人(接受Xofigo治療的病人為8.9%，接受安慰劑治療的病人為2.9%)　先前未接受docetaxel治療的病人發生類率較低(接受Xofigo治療的病人為2.8%，接受安慰劑治療的病人為0.8%)。在ERADICATE ("supersum")病人中，有19.6%接受Xofigo治療的病人以及6.7%接受安慰劑治療的病人，通報有血小板減少症(所有級別)，有5.9%接受Xofigo治療的病人以及6.7%接受安慰劑治療的病人，觀察到第3和第4等級的血小板減少症(請參閱第4.4節)。

有5%接受Xofigo治療的病人以及1%接受安慰劑治療的病人，通報嗜中性白血球減少症(所有級別)，有2.2%接受Xofigo治療的病人以及0.7%接受安慰劑治療的病人，觀察到第3和第4等級的嗜中性白血球減少症。整體而言，關於第3和第4等級的嗜中性白血球減少症，相較於先前曾接受docetaxel治療的病人(接受Xofigo治療的病人為3.2%，接受安慰劑治療的病人為0.4%)。先前未接受docetaxel治療的病人發生類率較低(接受Xofigo治療的病人為0.8%，接受安慰劑治療的病人為0.1%)。

在一項第1期試驗中，嗜中性白血球及血小板計數最低值發生於單劑量靜脈給予Xofigo後第2至第3週。

注射部位反應

有1.2%接受Xofigo治療的病人以及0%接受安慰劑治療的病人，通報有第1和第2等級的注射部位反應，例如紅斑、疼痛及腫脹。

繼發性惡性腫瘤

Xofigo會增加病人長期累積的整體放射線暴露量，長期累積的放射線暴露可能與癌症及遺傳缺陷的風險增加具有相關性，尤其是骨肉瘤、骨髓增生異常症候群及白血病的風險可能會增加。於臨床試驗中，長達3年的追蹤期間並無Xofigo誘發癌症的案例通報。

通報疑似不良反應

醫療藥品取得核准後之通報疑似不良反應非常重要。此為能持續監測醫療藥品的效益/風險平衡。任何的疑似不良反應須通報至全國藥物不良反應通報中心。

4.9 過量

臨床試驗期間並無不慎使用Xofigo過量的通報案例。Xofigo無特定解毒劑。不慎使用過量時，應採取一般性的支持措施，包括監測潛在的血液學及胃腸道毒性。

曾在一項第1期臨床試驗中評估過單劑量給予每公斤體重含有高達276 kBq放射活性的Xofigo劑量，並未觀察到任何劑量限制毒性。

5. 藥理特性

5.1 藥效學特性

藥物治療類別：各種治療用放射性藥物，ATC碼：V10XX03

作用機轉

Xofigo為治療用的α粒子放射藥品。其活性組成鐳-223 (鐳-223二氯化物)為類似鈣離子，與骨礦物質經基雙取名形成複合物而選擇性作用於骨質，特別是骨轉移區域。其鐳α放射線的高強性能重轉移(50 keV/很大)，會導致鄰近腫瘤細胞中高頻率的雙股去氧核糖核酸(DNA)斷裂，產生強效的細胞毒殺性效果。對於腫瘤微環境的額外效果(包括成骨細胞和脈管細胞)亦促及其活體內療效。鐳-223放射的α粒子範圍小於100微米(小於10個細胞直徑)，因此可將周圍正常組織受到的傷害減至最低。

藥效學效果

在一項第1期隨機分配試驗中，研究5項骨代謝的血清生物標記(骨形成標記：bone alkaline phosphatase [ALP]、total ALP、procollagen I N propep:ide [PINP]，骨吸收標記：C-terminal crosslinking telopeptide of type I collagen [S-CTX-I]、type I collager crosslinked C-telopeptide [ICTP])，顯示Xofigo組均發於安慰劑且達到顯著差異。

臨床療效與安全性

在一項雙盲、隨機分配、多次劑量的第III期多中心臨床試驗(ALSYMPCA)中，對具有症狀性骨轉移的去勢抗性攝護腺癌病人進行Xofigo的臨床安全性與療效評估。該試驗排除臟器轉移及急性脈巴結病變超過3 cm的病人。

主要療效指標為整體存活期。次要指標包括出現有症狀骨骼事件(SSE)發生時間、出現ALP及PSA惡化的時間。

在預定期中分析(檢證分析)的資料截止日期時，共有809位病人以2：1的比例隨機分配至接受每4週靜脈注射Xofigo 55 kBq/kg共6個週期合併最佳標準照護治療(N = 541)，或相對應接受安慰劑合併最佳標準照護治療(N = 268)。最佳標準照護治療包括局部體外放射線治療、雙膦酸鹽藥物、皮質類固醇、抗雄性素、睾酮素、estramustine和ketoconazole的使用。

在先前轉換治療(亦即提出安慰劑組病人接受Xofigo治療的機會)前，共有921位隨機分配病人完成安全性與整體存活期的最新截述性分析。

本試驗排除患有克隆氏疾、潰瘍性結腸炎、臟器轉移、先前接受半身性放射治療以及具有未癒置之骨髓惡造危險或確定為骨髓壓迫的病人。

Xofigo及安慰劑兩組間的人口統計學與基期疾病特徵(期中分析族群)相似，下方為列出Xofigo組的資料：

- 病人的平均年齡為70歲(範圍49至90歲)。
- 87%的納入病人具美國東岸癌症臨床研究合作組織(ECOG)功能狀態的分數為0至1分。
- 41%病人曾接受雙磷酸鹽類物。
- 42%的病人因不符資格未拒絕接受docetaxel治療，而先前未接受docetaxel治療。
- 46%的病人無疼痛，或疼痛程度為世界衛生組織(WHO)量表的1分(無症狀或輕微症狀)，有54%病人的疼痛嚴度為WHO量表的2至3分。
- 16%的病人主骨轉移小於6處，44%的病人具有6至20處骨轉移，另40%的病人具有多於20處骨轉移或為超組影像(superscar)。

在治療期間，83%的病人接受過促黃體素釋放激素促進劑(LHRH agonist)的治療，而26%的病人接受過抗雄性素合併治療。

期中分析及最新分析兩者的結果顯示接受Xofigo加上最佳標準照護治療的病人，其整體存活期顯著長於接受安慰劑加上最佳標準照護治療的病人(請參閱表2、圖2及圖3)。在兩個資料庫中，根據危險比，整體存活期的改善為44%。

在期中分析中，觀察到Xofigo加上最佳標準照護治療的OS中位數較安慰劑加上最佳標準照護治療增加2.8個月(HR = 0.695 (95%信賴區間[CI] 0.552/0.875)，p = 0.00185，OS中位數：分別為14.0個月和11.2個月)，死亡風險降低超過30%。

在最新分析中，觀察到Xofigo加上最佳標準照護治療的整體存活期中位數較安慰劑加上最佳標準照護治療增加3.6個月(HR = 0.695 (95% CI 0.581/0.832)，OS中位數分別為14.9個月和11.3個月)。

表2：第III期ALSYMPCA試驗得到的存活結果

療效參數	Xofigo	安慰劑
期中分析	**N=541**	**N=268**
死亡數(%)	191 (35.3%)	123 (45.9%)
整體存活期中位數(月) (95% CI)	14.0 (12.1 – 15.8)	11.2 (9.0 – 13.2)
p值[a] (雙尾)	0.00185	
危險比[b] (95% CI)	0.695 (0.552 - 0.875)	
最新分析	**N=614**	**N=307**
死亡數(%)	333 (54.2%)	195 (63.5%)
整體存活期中位數(月) (95% CI)	14.9 (13.9 – 16.1)	11.3 (10.4 – 12.8)
危險比[b] (95% CI)	0.695 (0.581 - 0.832)	

CI =信賴區間，HR =危險比(Xofigo相較於安慰劑)

[a] 期中分析後，即因療效因素而停止這項第III期試驗(ALSYMPCA)。由於最新分析僅為敘述性分析，因此並未提供p值。

[b] 危險比< 1，以Xofigo較佳。

圖2：Kaplan-Meier整體存活曲線(期中分析)

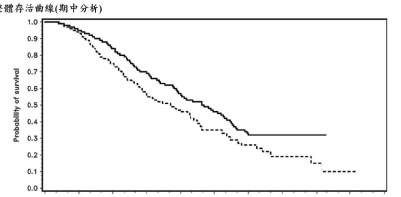
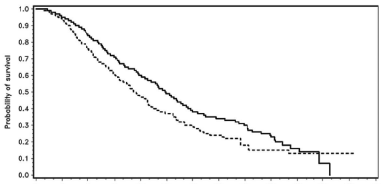


圖3：Kaplan-Meier整體存活曲線(最新分析)



期中分析和最新分析的結果亦證實Xofigo加中所有主要次要試驗指標均較安慰劑組達到顯著似改善(請參閱表3、表4及5)。

接受Xofigo治療的病人中症狀性骨骼事件(SSE，定義為發生任何下方事件：以外照射放射療去緩和疼痛、或病理性骨折、或脊髓壓迫，或建廠相關骨科手術介入治療)療生時間較接受安慰劑治療的病人顯著延緩(期中分析：HR = 0.610，95% CI 0.461-0.807，p = 0.00046；至SSE發生時間中位數：Xofigo組13.5個月和安慰劑組8.4個月；最新分析：HR = 0.658，95% CI 0.522-0.830，SSE發生時間中位數= Xofigo組15.6個月和安慰劑組9.8個月)。

- Xofigo治療中至SSE發生時間延長主要是源自於至以外照射放射療法(EBRT)緩和疼痛的時間達到統計顯著性的延長(期中分析：HR = 0.649，95% CI 0.483/0.871，p = 0.00375，中位數(月) = Xofigo組17.0個月和安慰劑組10.4個月；最新分析：HR = 0.670，95% CI 0.525/0.854，中位數(月) = Xofigo組17.1個月和安慰劑組17.5個月)。安慰劑組中亡故的病人已例較高，導致安慰劑組中EBRT事件較少，因而導致最新分析對生EBRT時間中位數較支的誤差。
- 在接受Xofigo治療的病人中觀察到至骨髓壓迫時間較接受安慰劑治療的病人延長(期中分析：HR = 0.443，95% CI 0.223/0.877，p = 0.01647，中位數(月)無法估算，因資料截止日期時尚未達到中位數)；最新分析：HR = 8.516，95% CI 0.286/0.931，中位數(月)無法估算，因資料截止日期時尚未達到中位數)。
- 在接受Xofigo治療的病人中觀察到至手術介入治療時間較接受安慰劑治療的病人延長(期中分析：HR = 0.801，95% CI 0.267/2.398，p = 0.6904，中位數(月)無法估算，因資料截止日期時尚未達到中位數)；最新分析：HR = 8.715，95% CI 0.280/1.821，中位數(月)無法估算，因資料截止日期時尚未達到中位數)。
- 在接受Xofigo治療的病人中觀察到至骨折時間較接受安慰劑治療的病人延長(期中分析：HR = 0.450，95% CI 0.236/0.856，p = 0.01255，中位數(月)無法估算，因資料截止日期時尚未達到中位數)；最新分析：HR = 8.620，95% CI 0.351/1.093，中位數(月)無法估算，因資料截止日期時尚未達到中位數)。

Xofigo治療延長至總ALP惡化時間(定義為較基期/最低值增加≥ 25%)的效果優於安慰劑(期中分析：HR = 0.162，95% CI 0.120/0.220，p < 0.00001，中位數(月)無法估算，因資料截止日期時尚未達到中位數；最新分析：HR = 0.167，95% CI 0.129/0.217，中位數(月) = Xofigo組7.4個月和安慰劑組3.8個月)。

第12週時Xofigo組中達到總ALP反應(證實較基期下降≥ 30%)的病人百分比高於安慰劑組(期中分析：Xofigo組46.2%，安慰劑組2.5%，p < 0.001；最新分析：Xofigo組46.9%，安慰劑組3.3%)。

第12週時Xofigo組中達到總ALP正常化(定義為總ALP數值回復到正常範圍內)的病人百分比高於安慰劑組(期中分析：Xofigo組32.9%，安慰劑組0.9%，p < 0.001；最新分析：Xofigo組34.0%，安慰劑組1.4%)。

接受Xofigo治療的病人生PSA惡化時間(定義為較基期/最低值增加≥ 25%且絕對數值增加≥ 2 ng/mL)也較接受安慰劑治療的病人顯著延長(期中分析　HR = 0.671，95% CI 0.546/0.826，p = 0.00015，中位數(月) = Xofigo組3.6個月和安慰劑組3.4個月；最新分析：HR = 0.643，95% CI 0.539/0.768，中位數(月) = Xofigo組3.6個月和安慰劑組3.4個月)。

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表3：ALSYMPCA試驗得到的次要試驗指標：至症狀性骨骼事件時間(SSE)、至外照射放射療法(EBRT)時間、至骨髓壓迫時間、至手術介入治療時間以及至骨折時間

	症狀性骨骼事件 (SSE)[a]		SSE構成事件							
			以EBRT緩和疼痛		脊髓壓迫		手術介入治療		骨折	
	Xofigo	安慰劑	Xofigo	安慰劑	Xofigo	安慰劑	Xofigo	安慰劑	Xofigo	安慰劑
期中分析 (Xofigo組：N = 541位病人；安慰劑組：N = 268位病人)										
發生率	132	82	122	72	117	16	9	5	20	18
[病人數(%)]	(24.4%)	(30.6%)	(22.6%)	(26.9%)	(3.1%)	(6.0%)	(1.7%)	(1.9%)	(3.7%)	(6.7%)
至事件時間分析 (95% CI)	13.4	8.4	17.0	10.8	NE	NE	NE	NE	NE	NE
[中位數(月)]	(12.2– 9.6)	(7.2 –NE[b])	(12.9-NE)	(7.9-NE)						
p值[b] (雙尾)	0.00046		0.00375		0.01647		0.69041		0.01255	
HR[c] (95% CI)	0.610		0.649		0.443		0.801		0.450	
	(0.461 – 0.807)		(0.483 – 0.871)		(0.223 – 0.877)		(0.267 – 2.398)		(0.236 – 0.856)	
最新分析 (Xofigo組：N = 614位病人；安慰劑組：N = 307位病人)										
發生率	202	116	186	105	25	21	12	7	32	20
[病人數(%)]	(32.9%)	(37.8%)	(30.3%)	(34.2%)	(4.1%)	(6.8%)	(2.0%)	(2.3%)	(5.2%)	(6.5%)
至事件時間分析 (95% CI)	15.3	9.8	17.1	17.5	NE	NE	NE	NE	NE	NE
[中位數(月)]	(13.5 –18.0)	(7.3 – 23.7)	(14.1 – 19.8)	(7.5 – 29.0[d])						
HR[c] (95% CI)	0.658		0.670		0.516		0.715		0.620	
	(0.522 – 0.830)		(0.525 – 0.854)		(0.286 – 0.931)		(0.280 – 1.821)		(0.351 – 1.093)	

CI＝信賴區間、EBRT＝外照射放射療法、HR＝危險比(Xofigo相對於安慰劑)
[a] SSE定義為發生任何下方事件：以外照射放射療法緩和疼痛，或病理性骨折，或脊髓壓迫，或脛瘤相關骨科手術介入治療
[b] 期中分析後，與固療效因素而停止這項第III期試驗(ALSYMPCA)。由於最新分析僅為敘述性分析，因此並未提供p值。
[c] 危險比<1，以Xofigo較佳。
[d] NE：無法估算，即資料截止時尚未達到中位數。
[e] 安慰劑組中亡故的病人比例較高，導致安慰劑組中EBRT事件較少，因而導致最新分析時至EBRT時間中位數較長的誤差。

表4：ALSYMPCA試驗得到的次要試驗指標：至總鹼性磷酸酶(ALP)惡化時間以及至前列腺特異性抗原(PSA)惡化時間

	總ALP惡化[a]		PSA惡化[b]	
	Xofigo	安慰劑	Xofigo	安慰劑
期中分析 (Xofigo組：N = 541位病人；安慰劑組：N = 268位病人)				
事件數	79 (14.6%)	116 (43.3%)	288 (53.2%)	141 (52.6%)
惡化時間(95% CI) [中位數(月)]	NE[c]	3.7 (3.5 – 4.1)	3.6 (3.5 – 3.7)	3.4 (3.3 – 3.5)
p值[a] (雙尾)	< 0.00001		0.00015	
危險比[c] (95% CI)	0.162 (0.120 – 0.220)		0.671 (0.546 – 0.826)	
最新分析 (Xofigo組：N = 614位病人；安慰劑組：N = 307位病人)				
事件數	106 (17.3%)	151 (49.2%)	388 (63.2%)	193 (62.9%)
惡化時間(95% CI) [中位數(月)]	7.4 (7.1 – NE[f])	3.8 (3.6–4.2)	3.6 (3.5–3.8)	3.4 (3.3 – 3.5)
危險比[c] (95% CI)	0.167 (0.129 – 0.217)		0.643 (0.539 – 0.768)	

CI＝信賴區間、HR＝危險比(Xofigo相較於安慰劑)
[a] 定義為較基期/最低值增加≥ 25%。
[b] 定義為較基期/最低值增加≥ 25%且絕對數值增加≥ 2 ng/mL。
[c] NE：無法估算，即期中分析資料截止時尚未達到中位數。
[d] 期中分析後，與固療效因素而停止這項第III期試驗(ALSYMPCA)。由於最新分析僅為敘述性分析，因此並未提供p值。
[e] 危險比<1，以Xofigo較佳。
[f] NE：無法估算，即因中位數後事件數不足。

表5：ALSYMPCA試驗得到的次要試驗指標：總鹼性磷酸酶(ALP)反應以及總ALP正常化

	第12週時的總ALP反應[a]		第12週時的總ALP正常化[b]	
	Xofigo	安慰劑	Xofigo	安慰劑
期中分析 (Xofigo組：N = 541位病人；安慰劑組：N = 268位病人)				
病人數(%)	176/381[c] (46.2)	4/160[c] (2.5)	83/252[d] (32.9)	1/107[d] (0.9)
p值[e] (雙尾)	< 0.001		< 0.001	
最新分析 (Xofigo組：N = 614位病人；安慰劑組：N = 307位病人)				
病人數(%)	233/497[c] (46.9)	7/211[c] (3.3)	109/321[c] (34.0)	2/140[d] (1.4)

[a] 定義為證實較基期下降≥ 30%
[b] 定義為基期時總ALP偏高的病人其總ALP數值回復到正常範圍內
[c] 同時具有基期與第12週總ALP表值的病人數
[d] 基期時總ALP數值偏高的病人數
[e] 期中分析後，與固療效因素而停止這項第III期試驗(ALSYMPCA)。由於最新分析僅為敘述性分析，因此並未提供p值。

次群組存活分析

次群組存活分析結果顯示Xofigo治療具一致性的存活效益，而與基期時總鹼性磷酸酶(ALP)數值、基期時雙磷酸鹽藥物的使用，以及先前使用docetaxel均無關。

生活品質

在第III期ALSYMPCA試驗中使用特定問卷評估健康相關生活品質(HRQOL)：EQ-5D（通用工具)以及FACT-P（前列腺癌特定工具)。EQ-5D分析得到相結果證實Xofigo治療在整個試驗期間的HRQOL效益高於安慰劑，測量方式為效用指數(-0.101相較於-0.161，p = 0.002)與自我通報視覺類比健康狀態分數(-5.225相較於-8.516，p = 0.008)。FACT-P分析證實在整個試驗期間，Xofigo治療相對於安慰劑的相關HRQOL顯著較高，測量方式為FACT-P總分(-4.828相較於-8.689，p = 0.004)。回答特定分析證實第16週時FACT-P總分(p=0.006)、試驗結果指數分數(p = 0.012)、FACT-G分數(p = 0.004)、情緒安適度(p < 0.001)，功能性安適度(p = 0012)以及前列腺癌子量表(p = 0.012)均得到改善。FACT-P前列腺癌疼痛相關子量表(以4個FACT-P項目為基礎)證實疼痛相對於安慰劑和相對於基期顯著減輕，測量方式為前列腺癌疼痛子量表分數(p = 0.001)。與Xofigo組相較，安慰劑組在任何時間點下的任何指標均未表現出顯著的效益。所有病人均接受最佳標準照護治療。

疼痛緩和

在第III期ALSYMPCA試驗中，從發生需以體外放射線治療(EBRT)緩和疼痛的時間結果，以及較少通報骨頭疼痛的不良事件佐證，顯示Xofigo組治療對骨頭疼痛有正面效果。

後續的細胞毒性骨質治療

表2：1隨機分配ALSYMPCA試驗進行期間，有93位(17%) Xofigo組病人及51位(16.8%)安慰劑組病人，在最後一次治療後的不同時間接受細胞毒性化學治療。兩組病人間的血液學實驗室數值並無明顯差異。

5.2 藥動學特性

概述

已從3項第I期試驗得到藥動學、生物分佈及劑量學資料。藥動學資料來自於使用劑量範圍介於51至276 kBq (0.00138至0.00746 mCi)/kg間的25位病人。藥動學、生物分佈及劑量學資料來自於6位接受間隔6週之2劑110 kBq (0.00297 mCi)/kg劑量的病人，以及10位接受55 (0.00149 mCi)、110 (0.00297 mCi)或221 kBq (0.00597 mCi)/kg劑量的病人。

吸收

Xofigo以靜脈注射的方式給藥，因此達100%生體可用率。

分佈與器官攝取

靜脈注射後，鐳-223從血液中迅速排除且主要分布進入骨頭及骨轉移病灶中，或排除到小腸中。

注射15分鐘後，約20%注射的放射活性存留於血液中。在4小時後，約有4%注射的放射活性留在血液中，而後，於注射24小時後即降至低於1%。分佈體積高於血液體積，顯示藥物分佈到周邊室中。注射10分鐘後，在骨頭中及小腸中觀察到放射活性。在注射4小時後，觀察到在骨頭和腸道中出現的放射性劑量平均百分比分別約為61%和49%。其他器官(例如心臟、肝臟、腎臟、膀胱和脾臟)在注射4小時後並未觀察到顯著的攝取量。

生物轉化

鐳-223是一種放射性同位素，會進行衰變而不會或代謝。

排除

藥品排出體外的主要路徑為糞便排除。約有5%排除到尿液中，且無肝膽排除的證據。注射7天後的全身測量(經衰變校正後)顯示中位數76%的投予放射活性已從體內排除。鐳-223二氯化物從胃腸道的排除速率，會受到不同族群的小腸傳輸速率高度變異性的影響，正常範圍從每天一次到每週一次的腸道排空。

線性/非線性

在研究的劑量活性範圍內(51至276 kBq/kg)，鐳-223二氯化物的藥動學為線性。

兒童族群

Xofigo於兒童和18歲以下青少年的安全性與有效性尚未研究。

肝功能受損病人

尚未在肝功能受損病人中進行過藥動學試驗。然而，由於鐳-223作為一種同位素並不會被代謝，因此並不預期肝功能受損會影響氯化鐳-223的藥動學。

腎功能受損病人

尚未在腎功能受損病人中進行過藥動學試驗。然而，由於原液排除極少而主要的清拉路徑是透過糞便，因此並不預期腎功能受損會影響氯化鐳-223的藥動學(請參閱「用量用法」一節)。

心臟電生理學/QT友長

在第III期試驗(ALSYMPCA)的一個29位病人的次組中(接受Xofigo治療的病人有21位，接受安慰劑治療的病人有8位)，靜脈注射Xofigo 6小時後並未觀察到相較於安慰劑的顯著(QTc延長效果(即，>20 ms)。

5.3 臨床前安全性資料

全身毒性

在大鼠中進行的單一及重複劑量毒性試驗中，主要發現為體重增加不足、血液學變化、血清鹼性磷酸酶減少以及於顎很總中發現骨髓(造血細胞耗竭、髓腔化)、脾臟(髓骨性髓質外造血)和骨頭(骨細胞、成骨細胞、做骨細胞耗竭、臟腺骨性病灶、生長板/成長腹腸/混亂)。這些發現與放射線清發的造血功能受損以及骨生成減少有關，且在最低放射活性劑量22 kBq/kg(臨床建議劑量的0.4倍)即開始出現。

在大鼠試驗中，給予最低放射活性55 kBq/kg (同臨床建議劑量)開始即觀察到血液學變化。在單次投予497 kBq/kg的鐳-223二氯化物/kg (臨床建議劑量的9倍)後，在大鼠觀察到劑量限制性骨髓毒性。

每4週重複投予同臨床建議之放射活性劑量55 kBq/kg試驗6個月後，2隻大類發生無任停性骨盆骨折。由於試驗動物在其他骨頭位置出現不同程度的骨小梁溶骨情形，無法排除是因溶骨造成自發性骨折。這些發現的臨床相關性目前未知。

單次在大類注射放射活性劑量166及8,497 kBq/kg (臨床建議劑量的3倍及9倍)，觀察到乳頭腺刺激，但於每4週重複投予同臨床建議之放射活性劑量55 kBq/kg試驗6個月後，則並未觀察到。誘發視網膜刺激的嗅切機轉目前未知，但文獻資料顯示鐳會專門被攝取到大類眼睛的照膜(tapetum lucidum)中。由於人類不具有照膜，因此無法判定這些發現對人體的臨床相關性。臨床試驗中並無視網膜刺激的案例通報。

並未在參與鐳-223二氯化物排除的器官中觀察到組織學變化。

在接受同臨床相關劑量的大鼠中，試驗開始後7至12個月時觀察到骨肉瘤，這是親骨性放射性核種(bone-seeking radionuclide)的已知不良反應。在大類試驗中並未觀察到骨肉瘤。Xofigo的臨床試驗中亦無骨肉瘤的案例通報。基露於鐳-223的病人產生骨肉瘤的風險目前未知。骨肉瘤以外的其他腫瘤變化，亦曾報導於大鼠的長期(12至15個月)毒性試驗中 (請參閱第4.8節)。

胚胎毒性/生殖毒性

尚未針對生殖和發育毒性進行試驗。一般而言，放射性核種認為會誘發生殖與發育缺不良反應。

單次投予大約2270 (Bq/kg (≥臨床建議劑量的41倍)的鐳-223二氯化物後，在雄性大鼠睾丸中的少數曲細精管中觀察到極少量異常的精母細胞，除此之外，睾丸功能產玄正常，且副睾中的精漳和細胞數量正常。單次或重複投予大約359 kBq/kg的鐳-225二氯化物(≥臨床建議劑量的6.5倍)後，在雌性大鼠中觀察到子宮息肉(子宮肉腫間質)。

由於鐳-223主要分佈在骨頭，故應有去勢抗性攝護腺癌的癌症病人，其發生男性性腸不良反應的潛在風險非常低，但無法排除(請參閱第4.6節)。

基因毒性/致癌性

尚未針對Xofigo的致突變性和致癌可能性進行試驗。一般而言，放射性核種都被視為具有基因毒性和致癌性。

安全藥理學

單次投予放射活性劑量介於497至1100 kBq/kg (臨床建議劑量的9倍[大類]至20倍[大鼠])的鐳-223二氯化物，並未觀察到重要器官系統(即亦心血管[犬類]、呼吸或中樞神經系統[大鼠])的重大不良反應。

6. 藥劑特性

6.1 賦形劑

氯化鈉

檸檬酸鈉

氫氯酸(稀釋)

注射用水

6.2 不相容性

由於缺乏相容性研究，本藥品不得與其他藥品混合。

6.3 保存期限

28天。

6.4 儲存特殊注意事項

本藥品請儲存於 40°C以下。

Xofigo應依照國內勇於放射活性物質的規定進行儲存。

6.5 容器性質與內容物

本藥品包裝為包覆了乙烯-四氟乙烯(ETFE)的灰色溴化丁基橡膠瓶塞及鋁箔封口的無色第I類玻璃藥瓶，含有6 mL的注射用溶液。

藥瓶放置於鋁罐中。

6.6 棄置與其他處理的特殊注意事項

一般警語

應只經由合格人員於專門指定的臨床場所收取、使用及給予放射性藥物。其收取、儲存、使用、移轉及棄置均應遵照政府主管機關的規定和/或取得適當許可。

Xofigo的使用方式為同時符合放射安全及藥物品質規定。應採取適當的無菌預防措施。

放射線防護

鐳-223及其子代(daughters)於衰變時產生的γ放射線，得以運用標準儀器來測量Xofigo的放射活性，以及偵測放射污染。

投予放射性藥物會目體外輻射或反流、糞便、嘔吐物漩溫等造成的放射污染，而對主病人員造成風險。因此，必須依照國家規定遵守放射線防護事項，處理接觸這類體液的物質(例如廢單)時應特別小心，聯然鐳-223主要為α粒子放射，但鐳-223及其共放射活性的衰變子代同位素於某變時亦會產生β及β射線。由於給予的放射活性通常低於8 MBq，目此處理病人劇量過程中的體外輻射線暴露會與其他作為治療目的的放射性藥物相比明顯較低。然而，應遵循ALARA (As Low As Reasonably Achievable)原則，為了將放射線暴露量減至最低，建議儘可能減少在病房區域停留的時間、與放射源保持最文距離，並使用適當的屏蔽物。

任何未使用的藥品或廢棄物質之棄置均應依照當地規定。

製備或給予Xofigo過程中使用的任何物質，均應視為放射性廢棄物。

7. 放射線劑量

吸收放射線的劑量為依據臨床生物分佈資料計算，其吸收劑量的計算為使用OLINDA/EXM (器官層級內部劑量評估/指數模型[Organ Level INternal DoseAssessment/EXponential Modding])，這是以醫用體內輻射劑量(MIRD)演算法為基礎的一個軟體，其廣泛用於管理使用的β及γ放射性核種中。針對鐳-223而言，由於其主要為α粒子放射體，因此針對小腸、紅骨髓及骨頭/成骨細胞作出額外假設，並考慮其觀察到的生物分佈與特殊性質，計算出Xofigo治療中最可能的吸收劑量(請參閱表6)。

表6：計算器官吸收的放射線劑量

Target Organ	Alpha[1] emission (Cy/MBq)	Beta emission (Gy/MBq)	Gamma emission (Gy/MBq)	Total dose (Gy/MBq)	Total dose (rad/mCi)	Coefficient of variation (%)
Adrenals	(.00000	0.00002	0.00009	0.00312	0.44	56
Brain	(.00000	0.00002	0.00008	0.00310	0.37	80
Breasts	(.00000	0.00002	0.00003	0.00305	0.18	120
Gallbladder wall	(.00000	0.00002	0.00021	0.00323	0.85	14
LLI[2] Wall	(.00000	0.04561	0.00085	0.04545	171.88	83
Small intestine wall	(.00319	0.00360	0.00047	0.00726	26.87	45
Stomach wall	(.00000	0.00002	0.00011	0.00314	0.51	22
ULI[3] wall	(.00000	0.03149	0.00082	0.03232	119.58	50
Heart wall	(.00161	0.00007	0.00005	0.00173	6.40	42
Kidneys	(.00299	0.00011	0.00011	0.00321	11.86	36
Liver	(.00279	0.00010	0.00008	0.00298	11.01	36
Lungs	(.00109	0.00007	0.00005	0.00121	4.47	--[4]
Muscle	(.00000	0.00002	0.00010	0.00312	0.44	41
Ovaries	(.00000	0.00002	0.00046	0.00349	1.80	40
Pancreas	(.00000	0.00002	0.00009	0.00311	0.41	43
Red marrow	(.13217	0.00642	0.00020	0.13879	513.51	41
Osteogenic cells	1.13689	0.01487	0.00030	1.15206	4262.60	41
Skin	(.00000	0.00002	0.00005	0.00307	0.27	79
Spleen	(.00000	0.00002	0.00007	0.00309	0.33	54
Testes	(.00000	0.00002	0.00006	0.00308	0.31	59
Thymus	(.00000	0.00002	0.00003	0.00306	0.21	109
Thyroid	(.00000	0.00002	0.00005	0.00307	0.27	96
Urinary bladder wall	(.00371	0.00016	0.00016	0.00403	14.90	63
Uterus	(.00000	0.00002	0.00023	0.00326	0.94	28
Whole body	0.02220	0.00081	0.00012	0.02312	85.56	16

[1] 由於並大部分的軟組織中都並未觀察到鐳-223吸收，因此設定這些器官中α射線佔總器官劑量的比例為0。
[2] LLI：下段大腸
[3] ULI：上段大腸
[4] 肺臟吸收劑量資料乃是使用所有受試者中合併血液時間-活性資料，以模型導出的計算為準

在Xofigo臨床試驗中觀察到的血液學不良反應頻率及嚴重度，這低於從計算出的紅骨髓吸收劑量下的預期情況。這可能與α粒子放射線的空間分佈造成紅骨髓接受到非均勻的放射線劑量有關。

8. 放射性藥物製備說明

使用本藥品前應目視檢查。Xofigo為澄清無色溶液，若變色，出現顆粒物質或色紫或揖即不應使用。

Xofigo為即用型溶液，不應稀釋或與任何溶液混合。

每個藥瓶僅供單次使用。

應使用以下資料計算特定病人的注射給藥體積：

- 病人體重(公斤)
- 劑量標準(55 kBq/公斤體重)
- 藥品希參照日期時的放射線活性濃度(1100 kBq/mL)。參照日期標於藥瓶及鋁罐標籤上。
- 鐳-223自然衰變之衰變校正(DK)因子。衰變校正表提供如下(請參閱表5)。

給藥體積中的放射活性含量應使用正確校準的活性測量儀嚴謹。

病人注射的給藥總體積計算方式如下：

$$\text{注射體積(mL)} = \frac{\text{體重(kg)} \times \text{放射活性(55 kBq/kg體重)}}{\text{DK因子} \times 1100\ \text{kBq/mL}}$$

任何未使用的藥品或廢棄物質之棄置均應依照當地規定。

表7：鐳223的衰變校正因子表

自參照日期起的天數	衰變因子	自參照日期起的天數	衰變因子
-14	2.38	0	1.02
-13	2.24	1	0.96
-12	2.11	2	0.90
-11	1.98	3	0.85
-10	1.87	4	0.80
-9	1.76	5	0.75
-8	1.65	6	0.71
-7	1.56	7	0.67
-6	1.46	8	0.63
-5	1.38	9	0.59
-4	1.30	10	0.56
-3	1.22	11	0.52
-2	1.15	12	0.49
-1	1.08	13	0.46
		14	0.44

衰變校正因子表為以香港/新加坡/台灣標準時間(HKT/SST/TST)中午12點來做校正。衰變校正因子的決定，依計算參照日期期之前或之後的天數。目光節約時制所產生的變化並未涵蓋於該表中，因為以半支期為11.4天的放射性核種而言，並不認為1個小時為有明顯變化。

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