Horizon Scanning in Oncology

Radium-223 dichloride (Xofigo®) for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease

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DSD: Horizon Scanning in Oncology No. 44
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Institute for Health Technology Assessment
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1 Drug description

Generic/Brand name/ATC code:

Radium-223 dichloride (formerly Alpharadin)/Xofigo®/V10XX03

Developer/Company:

Bayer HealthCare Pharmaceuticals Inc.

Description:

Radium-223 dichloride is a radiopharmaceutical composed of the dichloride salt of the alpha-emitting isotope radium-223, with antineoplastic activity. It targets bone tissue and accumulates in areas of high bone turnover by forming a complex with hydroxyapatite, the inorganic calcium-containing constituent of bone. Since bone metastases frequently demonstrate increased bone metabolism, radium-223 is taken up preferentially in areas of bone metastases. Radium-223 is an alpha emitter and has thus a higher energy and a shorter ionisation path than existing beta-emitting radiopharmaceuticals. The physical half-life of radium-223 is 11.4 days [1-4].

radium-223 dichloride is an alpha emitter with a half-life of 11.4 days

Xofigo® is available as a solution for injection (vials containing 6 ml of solution, each ml of solution contains 1,000 kBq radium Ra-223 dichloride). The dose regimen of Xofigo® is 50 kBq (1.35 microcurie) per kg body weight, given at four-week intervals for six injections [3, 5].

given intravenously at four-week intervals for six injections

2 Indication

Xofigo® is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.

indicated for CRPC, bone metastases, no known visceral metastatic disease

3 Current regulatory status

On 13 November 2013, the European Medicines Agency (EMA) licensed Xofigo® (radium-223 dichloride) for the treatment of adults with CRPC, symptomatic bone metastases and no known visceral metastases [6].

EMA licensed Xofigo® in November 2013

The U.S. Food and Drug Administration (FDA) approved Xofigo® (radium-223 dichloride) for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease on 15 May 2013 [5].

FDA licensed Xofigo® in May 2013

4 Burden of disease

prostate cancer most common cancer affecting men in Austria

417,000 new cases of prostate cancer were diagnosed in Europe in 2012 [7]. In Austria, about 4,700 men were newly diagnosed with prostate cancer and 1,146 died in 2011. Prostate cancer is therefore the most common type of cancer in Austrian men. Due to widespread prostate-specific antigen (PSA) testing, prostate cancer is mostly diagnosed at an early, asymptomatic stage of disease, resulting in 60% of patients being diagnosed before the tumour has spread [8]. From 2006 to 2010, the median age at diagnosis for cancer of the prostate was 66 years [9].

risk factors are age, ethnicity, family history, diet, genetic factors

Risk factors for developing prostate cancer include age, ethnicity, family history, diet and genetic factors such as mutations in BRCA1 and BRCA2 genes. Prognostic factors are age, extent of tumour, histologic grade of tumour and the PSA level [10, 11].

TNM staging and the Gleason score are used to establish prognosis

Staging is done by using the TNM system which provides information for choosing the initial therapy. Other factors which impact on the choice of initial therapy are life expectancy, comorbidities, therapeutic side effects and patients' preferences. Besides the TNM system, the Gleason score is used to establish prognosis. This score is a histopathologic grading system that distinguishes between well and poorly differentiated prostate tissue [11].

prognosis strongly depends on the stage at diagnosis

Prognosis strongly depends on the stage at diagnosis. If the tumour is confined to the prostate gland, a median survival of more than five years can be expected. Locally advanced forms of prostate cancer can rarely be cured, but median survival is still about five years. Patients with metastasised tumours have a median survival of one to three years [12].

bone metastases are prevalent with advanced disease

Osteoblastic metastases to the skeleton are prevalent in most men with mCRPC causing pain, debility, and/or functional impairment leading to reduced quality of life. Bone destruction is an important factor in the aetiology of pain and other complications due to bone metastases. Measurement of biochemical bone markers such as alkaline phosphatase (ALP) can be a reliable indicator for therapeutic response [13]. With disease progression visceral metastases may occur [14].

5 Current treatment

initial treatment for metastatic prostate cancer is androgen deprivation therapy

Androgen deprivation therapy (ADT) is generally the initial treatment for men with metastatic prostate cancer. Despite initial response rates of 80 to 90%, nearly all men eventually develop progressive disease following ADT [15].

further treatment options are: secondary hormone therapy, immunotherapy, docetaxel

If the PSA level rises despite castrate levels of testosterone (serum testosterone < 20 ng/dl) the cancer is called "castrate-resistant", "hormone-refractory" or "androgen-independent". Therapeutic options for CRPC are:

- Multiple and sequential secondary hormone therapies including withdrawal of ADT, antiandrogen therapy, oestrogens and corticosteroids [16].

- Immunotherapy with sipuleucel-T indicated for minimally symptomatic/asymptomatic and chemotherapy-naive patients [12, 17].
- Arbiraterone acetate usually administered with prednisone and not only given in hormone-refractory patients but also in patients after docetaxel.
- Docetaxel injection concentrate in combination with prednisone [12, 18] is seen as the standard first-line treatment for mCRPC who are suitable candidates for chemotherapy because of its survival benefit [12, 19].

therapy options after disease progression on docetaxel

However, many patients experience progression of disease after docetaxel or are not eligible for docetaxel therapy. Systemic therapeutic options then are:

- Abiraterone acetate: a CYP17 inhibitor usually administered with prednisone
- Cabazitaxel: a "second-generation" taxane in addition to prednisone
- Enzalutamide: an oral androgen-signaling inhibitor
- Mitoxantrone: an anthracenedione antineoplastic agent [12, 18, 20].

painful bone metastases can be treated with radiation therapy, beta emitters or focused ultrasound

Besides these systemic therapies, palliative therapies (like external beam radiation therapy) may be used for treating bone pain that is limited to one or a limited number of sites. In men with extensive painful bone metastases and those with persistent or recurrent pain despite receiving radiation therapy to maximal normal tissue tolerance, treatment with multiple beta-emitting radiopharmaceuticals or focused ultrasound is recommended [14, 18, 21].

two groups of bone-targeted therapies

Concerning specific bone-targeted therapies, i.e. therapies which are primarily active in the bones and show no influence on visceral metastases, two groups may be distinguished:

- Osteoclast-targeted therapies: azoledronic acid and denosumab
- Bone-seeking radioisotopes: strontium-89 (beta emitter) and samarium-153 (beta and gamma emitter).

These therapies can also be given in an earlier stage of disease or additionally to other agents and are administered to prevent skeletal events [20].

6 Evidence

literature search in four databases: 231 hits

included: one phase III, four phase II trials

A literature search was conducted on the 12th of December 2013 in four databases (Medline, Embase, CRD, Cochrane Central). Search terms were "prostate cancer", "radium-223", "xofigo" and "alpharadin". Overall, 231 references were identified through literature search. The manufacturer additionally submitted 14 posters, nine articles, four phase II and one phase III study. The phase II and III trials had already been identified through literature search. Eligible for inclusion were phase III trials (full text, abstracts) and phase II studies published as full text but also other study designs such as results from compassionate-use programmes or meta-analyses. After applying these inclusion criteria, one phase III trial [22] and four phase II trials [23-26] were included in this report.

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title Alpha emitter radium-223 and survival in metastatic prostate cancer [3, 20, 22, 27]			
Study identifier	NCT00699751, ALSYMPCA trial		
Design	Double-blind, placebo-controlled trial, phase III, randomisation in a 2:1 ratio, international, multicentre (136 study centres in 19 countries)		
	Duration	Enrolment: June 2008–February 2011 Follow-up: 3 years Cut-off dates for analyses: 14 Oct 2010 (interim analysis) and 15 July 2011 (updated analysis)	
Hypothesis	Superiority 90% to detect a hazard ratio of 0.76 for the risk of death in the radium-223 group compared with the placebo group, with a two-sided alpha significance level of 0.05.		
Funding	Bayer HealthCare Pharmaceuticals Inc.		
Treatment groups	Intervention (n=614)	Six intravenous injections of radium-223 (at a dose of 50 kBq per kilogram of body weight); one injection administered every 4 weeks plus best standard of care. Best standard of care includes e.g. local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens, oestrogens, estramustine or ketoconazole [3]	
	Control (n=307)	Matched placebo (saline injections) plus best standard of care (as above)	
Endpoints and definitions	Overall survival (primary outcome)	OS	Time from randomisation to the date of death, regardless of cause
	Time to first symptomatic skeletal event	-	First use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or nonvertebral bone fractures, spinal cord compression, or tumour-related orthopaedic surgical intervention
	Time to increase in total ALP level	-	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
	Total ALP response	-	Reduction of ≥30% from the baseline value, confirmed ≥4 weeks later
	Time to increase in PSA level	-	Relative increase of ≥25% from the baseline level and an absolute increase of ≥2 ng per millilitre 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 millilitre above the nadir, confirmed ≥3 weeks later, in patients with an initial decrease from baseline
	Normalisation of the total ALP level	-	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
	Quality of life	QOL	Increase in the score of ≥10 points on a scale of 0–156 on the Functional Assessment of Cancer Therapy-Prostate (FACT-P) instrument

Results and analysis		
Analysis description	ITT A formal interim analysis was planned after 50% of the deaths (320 deaths). A stratified log-rank test was used as the primary analysis for survival. Other endpoints were tested at a two-sided significance level of 0.05.	
Analysis population	Inclusion	✵ Progressive CRPC with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases ✵ Patients who received docetaxel, were not healthy enough or declined to receive it, or for whom it was not available ✵ Serum testosterone level of 50 ng per decilitre or lower ✵ 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 ✵ Baseline PSA level of 5 ng per millilitre or higher with evidence of progressively increasing PSA values ✵ ECOG performance-status score 0–2 ✵ Life expectancy of 6 months or longer ✵ Adequate haematological, renal and liver function
	Exclusion	✵ Chemotherapy within the previous 4 weeks or not recovered from Aes due to chemotherapy ✵ Previous hemibody external radiotherapy, systemic radiotherapy with radioisotopes within the previous 24 weeks ✵ Blood transfusion or use of erythropoietin-stimulating agents within the previous 4 weeks ✵ Malignant lymphadenopathy (>3 cm in the short-axis diameter) ✵ History of or presence of visceral metastases and imminent or established spinal cord compression
	Characteristics	✵ Age – median (range): I 71 (49-90) vs C 71 (44-94) ✵ ≥75 years, no of patients (%): I 171 (28) vs C 90 (29) ✵ Total ALP, no of patients (%) <220 U/litre: I 348 (57) vs C 169 (55) ≥220 U/litre: I 266 (43) vs C 138 (45) ✵ Current use of bisphosphonates, no of patients (%) Yes: I 250 (41) vs C 124 (40) No: I 364 (59) vs 183 (60) ✵ Any previous use of docetaxel, no of patients (%) Yes: I 352 (57) vs C 174 (57) No: I 262 (43) vs C 133 (43) ✵ ECOG performance-status score 0/1/≥2, no of patients (%) I 165 (27) vs C 78 (25)/I 371 (60) vs C 187 (61)/I 77 (13) vs C 41 (13) ✵ WHO ladder for cancer pain 1/2/3, no of patients (%) I 257 (42) vs C 137 (45)/I 151 (25) vs C 78 (25)/I 194 (32) vs C 90 (29) ✵ Extent of disease, %: <6/6-20/>20 metastases/Superscan: I 16 vs C 12/I 43 vs C 48/I 32 vs C 30/I 9 vs C 10 ✵ External-beam radiation therapy within 12 weeks after screening, no of patients (%) Yes: I 99 (16) vs C 48 (16) No: I 515 (84) vs C 259 (84) ✵ Median biochemical values (range) Haemoglobin – g/dl: I 12.2 (8.5–15.7) vs C 12.1 (8.5–16.4) Albumin – g/litre: I 40 (24–53) vs C 40 (23–50) Total ALP – U/litre: I 211 (32–6431) vs C 223 (29–4805) Lactate dehydrogenase – U/litre: I 315 (76–2171) vs C 336 (132–3856)

		PSA – µg/litre: I 146 (3.8–6026) vs C 173 (1.5–14500)	
Results (interim analysis)	Treatment group	*Intervention* Radium-223	*Control* Placebo
	Number of subjects	N=541	N=268
	Median OS, months 95% CI	14.0 12.1–15.8	11.2 9.0–13.2
Results (updated analysis) [3, 27] *p –value <0.001	Overall treatment group	*Intervention* Radium-223	*Control* Placebo
	Number of subjects	N=614	N=307
	Median OS, months 95% CI	14.9 13.9–16.1	11.3 10.4–12.8
	Median time to first symptomatic skeletal event, months 95% CI*	15.6 13.5–18.0	9.8 7.3–23.7
	Median time to increase in total ALP level, months 95% CI*	7.4 NR	3.8 NR
	Median time to increase in PSA level, months 95% CI*	3.6 NR	3.4 NR
	Median time to deterioration in FACT-P total score (QOL), months	6.3	5.6
Subgroups	Number of subjects	N=497	N=211
	Patients with ≥30% reduction in total ALP response, no (%)*	233 (47)	7 (3)
	Number of subjects	N=321	N=140
	Patients with normalisation of total ALP level, no (%)*	109 (34)	2 (1)
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	OS (interim analysis)	HR	0.70
		95% CI	0.55–0.88
		P value	<0.002
	OS (updated analysis)	HR	0.70
		95% CI	0.58–0.83
		P value	<0.001
	Median time to first symptomatic skeletal event	HR	0.66
		95% CI	0.52–0.83
		P value	<0.001
	Median time to increase in total ALP level	HR	0.17
		95% CI	0.13–0.22
		P value	<0.001
	Median time to increase in PSA level	HR	0.64
		95% CI	0.54–0.77
		P value	<0.001

	Median time to deterioration in FACT-P total score (QOL)	HR	0.75
		95% CI	0.59–0.94
		P value	0.015
Subgroup analysis	OS, patients with no/with previous docetaxel use	HR	0.71/0.74
		95% CI	0.56–0.89/0.56–0.99
		P value	NR
	OS, patients aged <65/65-75/>75	HR	0.49/0.73/0.82
		95% CI	0.29-0.81/0.51-1.03/0.53-1.27
		P value	0.005/0.072/0.381
	OS, patients with baseline ECOG PS 0 or 1/≥2	HR	0.68/0.82
		95% CI	0.56–0.82/0.50–1.35
		P value	NR
	OS, patients with <6/6–20 metastases	HR	0.95/0.71
		95% CI	0.46–1.95/0.54–0.92
		P value	NR
	OS, patients with >20 metastases/superscan	HR	0.64/0.71
		95% CI	0.47–0.88/0.40–1.27
		P value	NR

Abbreviations: AEs = adverse events, ALP = alkaline phosphatase, C = control, cm = centimetre, CI = confidence interval, CRPC = castration-resistant prostate cancer, ECOG PS = Eastern Cooperative Oncology Group performance status, FACT-P = Functional Assessment of Cancer Therapy-Prostate, g/dl = gram/decilitre, g/litre = gram/litre, HR = hazard ratio, I = intervention, ITT = intention to treat, kBq = kilobecquerel, no = number, ng = nanogram, nmol = nanomol, NR = not reported, OS = overall survival, PSA = prostate-specific antigen, QOL = quality of life, U/litre = units/litre, WHO = World Health Organization

Table 2: Most frequent AEs (All Grades: >15%, Grade 3: >3%, Grade 4: >2%, Grade 5: >1% are displayed)

NCT00699751 [20, 22]			
Grade (according to CTCAE version 3.0)	**Outcome, n** (%)	**Radium-223** (n=600)	**Placebo** (n=301)
All Grades	Anaemia	187 (31)	92 (31)
	Constipation	108 (18)	64 (21)
	Diarrhoea	151 (25)	45 (15)
	Nausea	213 (36)	104 (35)
	Vomiting	111 (18)	41 (14)
	Fatigue	154 (26)	77 (26)
	Weight loss	69 (12)	44 (15)
	Anorexia	102 (17)	55 (18)
	Bone pain	300 (50)	187 (62)
	Progression of malignant neoplasm	77 (13)	44 (15)
Grade 3	Anaemia	65 (11)	37 (12)
	Thrombocytopenia	20 (3)	5 (2)
	Fatigue	21 (4)	16 (5)
	Bone pain	120 (20)	74 (25)
	Pathologic fracture	13 (2)	8 (3)
	Spinal cord compression	14 (2)	16 (5)
Grade 4	Anaemia	11 (2)	2 (1)
	Thrombocytopenia	18 (3)	1 (<1)
Grade 5	Deterioration in general physical health	5 (1)	2 (1)
	Pneumonia	4 (1)	0
	Progression of malignant neoplasm	55 (9)	33 (11)
	Dyspnoea	1 (<1)	3 (1)
Others	Patients with serious AEs	281 (47)	181 (60)
	Patients with at least 1 AE leading to treatment discontinuation	93 (16)	57 (19)
	Therapy discontinuation because of AEs	99 (16)	62 (21)
	Aes with an outcome of death during treatment period + 30 days	16 (3)	14 (5)
	Aes with an outcome of death 3-year follow up	44 (7)	36 (12)

Abbreviations: AEs = adverse events, CTCAE = Common Terminology Criteria for Adverse Events, n = number of patients

In the ALSYMPCA trial (a randomised, double-blind, multicentre study) the efficacy and safety of radium-223 in patients with CRPC was investigated. Overall, 921 patients were randomly assigned in a 2:1 ratio to best supportive care plus radium-223 (one dose every four weeks for six cycles) or best supportive care plus placebo. Best standard of care included e.g. local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens, oestrogens, estramustine or ketoconazole [3]. Patients with confirmed CRCP were included who had either progressed on docetaxel chemotherapy or were not candidates for docetaxel chemotherapy. Additionally, patients were required to have two or more symptomatic bone metastases and no known visceral metastases. The median age of patients included was 71 years. 28% of the patients in the treatment group and 29% in the placebo group were ≥ 75 years old. 526 (57%) of the patients had received prior docetaxel (radium-223 group: n = 352; placebo group: n = 174). The majority of the study population had a good ECOG performance status (0 or 1) and had 6–20 or more than 20 metastases. Besides best standard of care, concomitant therapies were blood transfusions and erythropoietin-stimulating agents. Cytotoxic agents, systemic radioisotopes, hemibody, or other investigational drugs were prohibited and prompted treatment discontinuation [3].

the ALSYMPCA study enrolled 921 patients treated with radium-223 or placebo

included: patients who had progressed on docetaxel and having symptomatic bone metastases

median age: 71

good ECOG performance status

OS, the primary endpoint of the trial, was 14.9 months in the radium-223 group compared with 11.3 months in the placebo group (HR 0.70, 95% CI 0.58–0.83, $p<0.001$) in the updated analysis. The interim analysis on OS showed 14.0 months in the intervention group and 11.2 months in the control group (HR 0.70, 95% CI 0.55–0.88, $p<0.002$). The interim analysis was evaluated by an independent data and safety monitoring committee. Based on this evaluation which showed a survival advantage of radium-223 and an acceptable safety profile, the committee recommended early discontinuation of the trial and crossover from placebo to radium-223. The survival benefit was consistent across the patient subgroups (patients with previous/no previous docetaxel use, ECOG performance status, number of metastases). Secondary outcomes like the time to first symptomatic skeletal event was longer in the treatment group (HR 0.66, 95% CI 0.52–0.83, $p<0.001$). The time to increase in total ALP level was 7.4 months in the radium-223 group and 3.8 months in the placebo group (HR 0.17 95% CI 0.13–0.22) and the time to increase in PSA level was extended for patients treated with radium-223 by 0.2 months (HR 0.64, 95% CI 0.54–0.77, $p<0.001$). In terms of quality of life, the median time to deterioration in the FACT-P total score was 6.3 months for patients treated with radium-223 compared with 5.6 months in patients with placebo (HR 0.75, 95% CI 0.59–0.94, $p=0.015$) [27].

OS was extended by 3.6 months in the radium-223 group

data and safety monitoring committee recommended early discontinuation and crossover after interim analysis

secondary outcomes favoured treatment with radium-223

Bone pain (50%), nausea (36%) and anaemia (31%) were the most common treatment-related AEs of all grades with radium-223. In the control group, 62% of the patients experienced bone pain, 35% nausea and 31% anaemia as AEs of all grades. 281 patients (47%) treated with radium-223 and 181 patients (60%) of the control group had serious AEs. Therapy was discontinued because of AEs in 99 patients (16%) receiving radium-223 and in 62 patients (21%) in the control group respectively. Deaths were less common in the treatment group compared to the placebo group (55% vs. 63%) [20, 22].

bone pain, nausea, anaemia were most frequent AEs

6.2 Efficacy and safety – further studies

four phase II studies on efficacy and safety

Four phase II studies [23-26] in patients with CRPC and bone metastases were identified.

study on three different doses of radium-223

A multicentre, randomised, double-blind phase II trial [23] evaluated the efficacy and safety of three different doses of radium-223 chloride in 122 patients with CRPC and bone metastases. Patients received either three injections at six-week intervals at doses of 25 kBq/kg (n=41), 50 kBq/kg (n=39) or 80 kBq/kg (n=42). The primary endpoint was PSA response (≥50% decrease from baseline) to the three dose regimens. ≥ 50% PSA declines were shown for no patient (0%) in the 25 kBq/kg-dose group, two patients (6%) in the 50 kBq/kg-dose group, and five patients (13%) in the 80 kBq/kg-dose group (p=0.0297). Bone ALP differed between the 25 kBq/kg and the 50 kBq/kg-dose groups, favouring the 50 kBq/kg group. Differences in terms of bone ALP response were also evident between the 25 kBq/kg and the 80 kBq/kg-dose group (favouring the 80 kBq/kg-dose group) but not between the 50 kBq/kg and the 80 kBq/kg-dose groups. 122 (92%) patients reported one or more AEs. The most common treatment-related AEs (≥10%) across all dose groups were diarrhoea (21%), nausea (16%), and anaemia (14%). For all dose groups the safety profile showed no dose response (except an increase of gastrointestinal AEs). Dose-dependent improvements in confirmed 50% PSA declines between the 25 and 80-kBq/kg and the 25 and 50-kBq/kg cohorts were shown and no increase in toxicity occurred [20, 23].

trial on dose-response relationship and pain-relieving effect of radium-223

Another multicentre, randomised phase II study [24] evaluated the dose-response relationship and pain-relieving effect of radium-223 in 100 patients with CRPC and painful bone metastases. Patients received a single intravenous dose of 5, 25, 50 or 100 kBq/kg radium-223. The primary endpoint was pain index. A significant dose response for pain index was evident at week two (p=0.035). At week eight there were 40%, 63%, 56% and 71% pain responders (reduced pain and stable analgesic consumption) in the 5, 25, 50 and 100 kBq/kg groups respectively. At least one AE was reported by 97% of the patients. The most frequent haematological AEs were anaemia (11%) and haemoglobin decrease (15%), with no differences between dose groups.

study in patients with CPRC and bone pain needing external-beam radiotherapy

A multicentre, randomised, double-blind, placebo-controlled phase II trial [25] was conducted in 64 CPRC patients with bone pain requiring external-beam radiotherapy. Patients in the treatment group (n=33) were given 4 injections of radium-223 at 50 kBq/kg every four weeks or placebo (n=31). Primary endpoints were change in bone-ALP concentration and time to skeletal-related events. The median change in bone ALP was -65.6% (95% CI -69.5 to -57.7) compared to 9.3% (95% CI 3.8 to 60.9) in the placebo group (p<0.0001). Median time to first skeletal-related event was 14 weeks in the treatment group and 11 weeks in the placebo group (p=0.257). Median OS for patients treated with radium-223 was 65.3 weeks (95% CI 48.7 to ∞) and 46.4 weeks (95% CI 32.1 to 77.4) for the control group (p=0.066). 12 serious AEs were reported in 8 patients receiving radium-223 compared with 19 serious AEs in patients receiving placebo.

follow-up on two-year survival

At two-year survival follow-up (results of continuation of the previous study [25]), 10 patients (30%) of the radium-223 group were alive compared with four patients (13%) in the control group. The most frequent cause of death for both groups was progression of disease. Treatment-related AEs or long-term haematological toxicity during the follow-up were not reported [26].

7 Estimated costs

one vial of Xofigo® costs € 4,600 in Austria

Xofigo® is available as a solution for injection (vials containing 6 ml of solution, each ml of solution contains 1000 kBq radium Ra-223 dichloride). The six ml vial costs € 4,600 in Austria (price for social health insurance) [28].

in the US cost estimates vary

Cost information for Xofigo® in the US varies between around $69,000 [29] and $82,800 [30] for the complete course of therapy (six injections given at four-week intervals).

8 Ongoing research

two ongoing phase III trials in patients with CRPC

At http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ two ongoing phase III studies investigating radium-223 in patients with CRPC were found.

- NCT01618370: A prospective, interventional, open-label, multicentre trial for the use of radium-223 in CRPC patients diagnosed with bone metastasis, aiming to collect additional short-term and long-term safety data. The estimated study completion date is April 2015.
- NCT01810770: A single-arm, international, prospective, open-label, multicentre study of radium-223 dichloride in the treatment of patients with CRPC with bone metastasis, aiming to evaluate the safety and efficacy of multiple doses of Ra-223 dichloride in an Asian population. The estimated study completion date is April 2018.

radium-223 is also investigated in sarcoma and breast cancer patients

Several other phase I and phase II studies are currently conducted in patients with CRPC but also in patients with sarcoma (NCT01833520) and in breast-cancer patients with a bone-dominant disease (NCT01070485). No ongoing trials were identified examining radium-223 in combination or compared with enzalutamide, cabazitaxel, abiraterone acetate or mitoxantrone. A study investigating radium-223 in combination with docetaxel in patients with CRPC is currently recruiting participants (NCT01106352). The estimated study completion date is October 2014.

9 Commentary

approval in Europe and in the USA

In November 2013, the EMA licensed Xofigo® (radium-223 dichloride) for the treatment of adults with CRPC, symptomatic bone metastases and no known visceral metastases [6, 31]. The FDA had already licensed Xofigo® (radium-223 dichloride) for the same indication in May 2013 [5].

phase III study on efficacy and safety in patients with CRPC and symptomatic bone metastases

A phase III study [22] examined the efficacy and safety of radium-223 in patients with CRPC having two or more symptomatic bone metastases. 921 patients were randomly assigned to radium-223 (one dose every four weeks for six cycles) plus best supportive care or to placebo plus best supportive care. Best supportive care included e.g. local external beam radiotherapy, bisphosphonates, corticosteroids, antiandrogens, oestrogens, estramustine or ketoconazole. For patients treated with radium-223, OS was extended by 3.6 months (14.9 versus 11.3 months, HR 0.70, 95% CI 0.58–0.83). Subgroup analysis demonstrated that OS improvement was consistent across subgroups, but patients with increased age (>75 years) and prior docetaxel showed a less pronounced benefit [20]. The secondary endpoints time to skeletal event, time to alkaline phosphatase progression and time to PSA progression favoured treatment with radium-223. Quality of life (measured by EQ-5D, FACT-P) showed a decline in both arms, but to a lesser extent in the radium-223 arm. Mean differences in FACT-P scores were statistically significant in only one instance (at 16-week follow-up), but a higher proportion of patients had a response in this score (24.6% versus 16.1%) [20].

OS was extended by 3.6 months in the radium-223 group

secondary outcomes favoured treatment with radium-223

most frequent AEs were bone pain, anaemia, nausea and diarrhoea fewer deaths, treatment discontinuations,…

In terms of safety, the most frequent AEs of all grades were bone pain, nausea, anaemia and diarrhoea in both groups. However, in the radium-223 group fewer people died (55% vs. 63%), fewer deaths were due to AEs (19% vs. 28%), fewer non-fatal serious AEs (44% vs. 57%) occurred, less people discontinued due to AEs (16% versus 19%) and overall fewer grade 3 and 4 AEs (59% versus 65%) were observed [20].

radium-223 expands the treatment scope for CRPC
lower radiation toxicity, less negative impact on surrounding tissue than beta/gamma emitters

Even though other radioisotopes are available for the palliation of bone pain, radium-223 is the first alpha emitter. Differences concerning radium-223 are, first of all, that already available therapies such as strontium-89 or samarium-153 were licensed due to their effect on bone pain and not, like radium-223, based on their effect on OS. Secondly, since alpha emitters have a shorter ionisation path than beta and gamma emitters, radiation-related toxicities to adjacent tissue are expected to be rarer [4].

implementation in the therapeutic pathway is not clear

Despite radium-223's impact on OS [22], questions of where to precisely incorporate the radioisotope in the therapeutic pathway cannot be fully answered yet. Lack of significant toxicity and its gains in OS [20, 32] may qualify this compound for combination therapy even for patients with visceral disease [32]. No ultimate statement can be made because in the phase III study, radium-223 was not examined in combination with other systemic therapies, including enzalutamide, arbiraterone acetate or docetaxel [32, 33], but radium-223 is currently investigated in combination with docetaxel (NCT01106352). The results are eagerly awaited, also due to the potential for additive myelosuppression [12]. Moreover, when selecting appropriate therapies, different modes of administration of available treatment regimens have to be taken into account and may determine patients' preferences. Enzalutamide and abiraterone acetate are taken orally, while cabazitaxel and radium-223 are administered intravenously.

trials are needed to examine the best combination of radium-223 with other already licensed agents such as enzalutamide, arbiraterone acetate, cabazitaxel or docetaxel

Furthermore, the radiopharmaceutical may also be used for earlier stages of disease, for example, instead of sipuleucel-T indicated for minimally symptomatic/asymptomatic and chemotherapy-naive patients, but administration of chemotherapy after radium-223 and its influence on safety have not been evaluated yet either [32]. Earlier use raises the question of long-term safety primarily concerning the risk of secondary malignancies. Epidemiology studies have demonstrated an increased risk of bone sarcoma and possible association with other secondary malignancies and hereditary defects. The expected latency period for bone sarcomas and other secondary malignancies exceeds the duration of follow-up in the ALSYMPCA trial (which was three years) [20]. The risk for secondary malignancies needs to be examined in post-marketing observations. With Radium-223 there is also a potential risk due to radiation or contamination from body fluids for medical staff and family members [20, 34-36].

use at earlier stages of disease?

risk of secondary malignancies needs to be observed

potential risks for staff and family

Also, the optimal dose of radium-223 is still a topic under discussion. As the improved level of efficacy with a comparable level of safety shows, the results of the phase II trial [22] suggest that the optimal dose of radium-223 could be higher than the 50 kBq/kg used in the phase III study [20]. Changes in dosage directly affect costs, and cost comparisons can only be made conditionally because of varying lengths of therapy cycles. When radium-223 is administered as an alternative treatment path to enzalutamide, cost estimates differ. Costs for enzalutamide are estimated at $59,600 (assuming a median of eight cycles) [35] and for radium-223 between $69,000 [28] and $82,800 [29] in a six-month course of treatment. Cabazitaxel (six cycles) costs about $50,000, and the costs for abiraterone acetate are about $47,000 (eight-month course of treatment) [36]. However, when radium-223 will be administered in addition to other treatment regimens, either concurrently or sequentially, the costs for treating patients with prostate cancer will increase even further.

dosage of radium-223 is unclear and may have to be higher than examined in phase III study

cost estimates differ and depend on cycle lengths

As bone metastases occur in many solid tumours, radium-223 may also be used in the future for other patient populations and in new areas of application [37]. Currently, radium-223 is investigated in patients with sarcoma and in breast-cancer patients with a bone-dominant disease [37].

may be used for other cancers

To summarise, radium-223 leads to increased OS in patients with CPRC and symptomatic bone metastases compared with patients getting best standard of care. A topic under discussion is whether placebo is a valid comparator considering the need to compare radium-223 with other already licensed agents. Moreover, optimal dosing of radium-223 and its implementation in the therapeutic pathway have yet to be examined.

radium-223 increases OS in patients with CRPC and symptomatic bone metastases, but questions on dosage and best combination remain

References

[1] National Cancer Institute. NCI thesaurus: Radium Ra 223 Dichloride (Code C62535). 2013 [19.12.2013]; Available from: http://ncit.nci.nih.gov/ncitbrowser/pages/concept_details.jsf;jsessionid=89EB12E5778E065DDC7CC3CC242C2C32.
[2] National Library of Medicine. Drug Information Portal: Xofigo. 2013 [19.12.2013]; Available from: http://druginfo.nlm.nih.gov/drugportal/ProxyServlet?mergeData=true&objectHandle=DBMaint&APPLICATION_NAME=drugportal&actionHandle=default&nextPage=jsp/drugportal/ResultScreen.jsp&TXTSUPERLISTID=0444811409&QV1=XOFIGO.
[3] European Medicines Agency (EMA). Summary of product characteristics. 2013 [13.01.2014]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002653/WC500156172.pdf.
[4] Acar O, Esen T, Lack NA. New therapeutics to treat castrate-resistant prostate cancer. ScientificWorldJournal. 2013;2013:379641.
[5] U.S. Food and Drug Administration (FDA). Prescribing information: Xofigo. 2013 [19.12.2013]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf.
[6] European Medicines Agency (EMA). Authorisation details: Xofigo. 2013 [19.12.2013]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002653/human_med_001692.jsp&mid=WC0b01ac058001d124.
[7] Ferlay J, Steliarover-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh J, Comberg H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
[8] Statistik Austria. Krebserkrankungen - Prostata. 2013 [19.12.2013]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/prostata/index.html.
[9] National Cancer Institute. Incidence and mortality of prostate cancer. 2013 [19.12.2013]; Available from: http://seer.cancer.gov/statfacts/html/prost.html#incidence-mortality.
[10] Sartor O. Up to Date - risk factors for prostate cancer. 2013 [19.12.2013]; Available from: http://www.uptodate.com/contents/risk-factors-for-prostate-cancer?source=search_result&search=prostate+cancer&selectedTitle=9~150.
[11] National Cancer Institute. Prostate cancer treatment. 2013 [19.12.2013]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional.
[12] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines for Prostate Cancer. 2013 [19.12.2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
[13] Sartor O. Up to Date - bone metastases in advanced prostate cancer: clinical manifestations and diagnosis. 2014 [22.01.2014]; Available from: http://www.uptodate.com/contents/bone-metastases-in-advanced-prostate-cancer-clinical-manifestations-and-diagnosis?source=search_result&search=alkaline+phosphatase+CRPC&selectedTitle=1~150.
[14] Dawson N. Up to Date - Overview of the treatment of disseminated prostate cancer. 2013 [20.12.2013]; Available from: http://www.uptodate.com/contents/overview-of-the-treatment-of-disseminated-prostate-cancer?source=see_link#H31.
[15] Lee RJ, Smith, M.,. Up to Date - Initial hormone therapy for metastatic prostate cancer. 2014 [20.02.2014]; Available from: http://www.uptodate.com/contents/initial-hormone-therapy-for-metastatic-prostate-cancer?source=search_result&search=Androgen+deprivation+therapy&selectedTitle=2~70.
[16] Dawson N, Ryan, C.,. Up to Date - Castrate resistant prostate cancer. 2013 [20.12.2013]; Available from: http://www.uptodate.com/contents/castrate-resistant-prostate-cancer-treatments-targeting-the-androgen-pathway?source=search_result&search=prostate+cancer&selectedTitle=29~150.
[17] El-Amm J, Aragon-Ching JB. The changing landscape in the treatment of metastatic castration-resistant prostate cancer. Ther Adv Med Oncol. 2013;5(1):25-40.
[18] European Association of Urology. Guidelines on Prostate Cancer. 2013 [20.12.2013]; Available from: http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf.

[19] Bahl A, Masson S, Birtle A, Chowdhury S, de Bono J. Second-line treatment options in metastatic castration-resistant prostate cancer: A comparison of key trials with recently approved agents. Cancer Treat Rev. 2014;40(1):170-7.
[20] U.S. Food and Drug Administration (FDA). Medical Review. 2013 [14.01.2014]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203971Orig1s000MedR.pdf.
[21] Sartor O, Di Biase, S. Up to date - management of bone metastases in advanced prostate cancer. 2013 [20.12.2013]; Available from: http://www.uptodate.com/contents/management-of-bone-metastases-in-advanced-prostate-cancer?source=see_link&anchor=H19250956#H261306184.
[22] Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23.
[23] Parker CC, Pascoe S, Chodacki A, O'Sullivan JM, Germa JR, O'Bryan-Tear CG, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol. 2013;63(2):189-97.
[24] Nilsson S, Strang P, Aksnes AK, Franzen L, Olivier P, Pecking A, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer. 2012;48(5):678-86.
[25] Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol. 2007;8(7):587-94.
[26] Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. Clin Genitourin Cancer. 2013;11(1):20-6.
[27] Parker C, Heinrich, D., Bottomley,D., Hoskin, P., Franzén, A., Solberg, A, Cislo, P.,. Effects of Radium-223 Dichloride (Radium-223) on Health-Related Quality of Life (QOL) Outcomes in the Phase 3 ALSYMPCA Study in Patients With Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases (Poster). 2013.
[28] Apothekerverlag Online. Warenverzeichnis. 2014 [21.01.2014]; Available from: http://warenverzeichnis.apoverlag.at/artikelstamm/view/dg/%7B%22filter%22%3A+%7B%22KTXT%22%3A+%22xofigo%22%7D%2C+%22page%22%3A+1%2C+%22ipP%22%3A+10%7D/ARNR/1807874000/archiv/ar_public__2014_01.
[29] Bayer Healthcare Pharmaceuticals and Algeta ASA. Reimbursement Information and Support. 2013 [20.12.2013]; Available from: http://www.xofigo-us.com/hcp/licensing-ordering/reimbursement/.
[30] Up to date. Radium-223: Drug information. 2014 [09.01.2014]; Available from: http://www.uptodate.com/contents/radium-223-drug-information?source=search_result&search=prostate+cancer+visceral+metastases&selectedTitle=49~150.
[31] European Medicines Agency (EMA). EPAR: Xofigo. 2013 [19.12.2013]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002653/WC500156172.pdf.
[32] Hafeez S, Parker C. Radium-223 for the treatment of prostate cancer. Expert Opin Investig Drugs. 2013;22(3):379-87.
[33] Wissing MD, van Leeuwen FWB, van der Pluijm G, Gelderblom H. Radium-223 chloride: extending life in prostate cancer patients by treating bone metastases. Clin Cancer Res. 2013;19(21):5822-7.
[34] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97.
[35] Ferraldeschi R, Pezaro C, Karavasilis V, de Bono J. Abiraterone and novel antiandrogens: overcoming castration resistance in prostate cancer. Annu Rev Med. 2013;64:1-13.
[36] De Bono JS OS, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147 - 54.
[37] Seal BS, Asche CV, Puto K, Allen PD. Efficacy, patient-reported outcomes (PROs), and tolerability of the changing therapeutic landscape in patients with metastatic prostate cancer (MPC): a systematic literature review. Value Health. 2013;16(5):872-90.