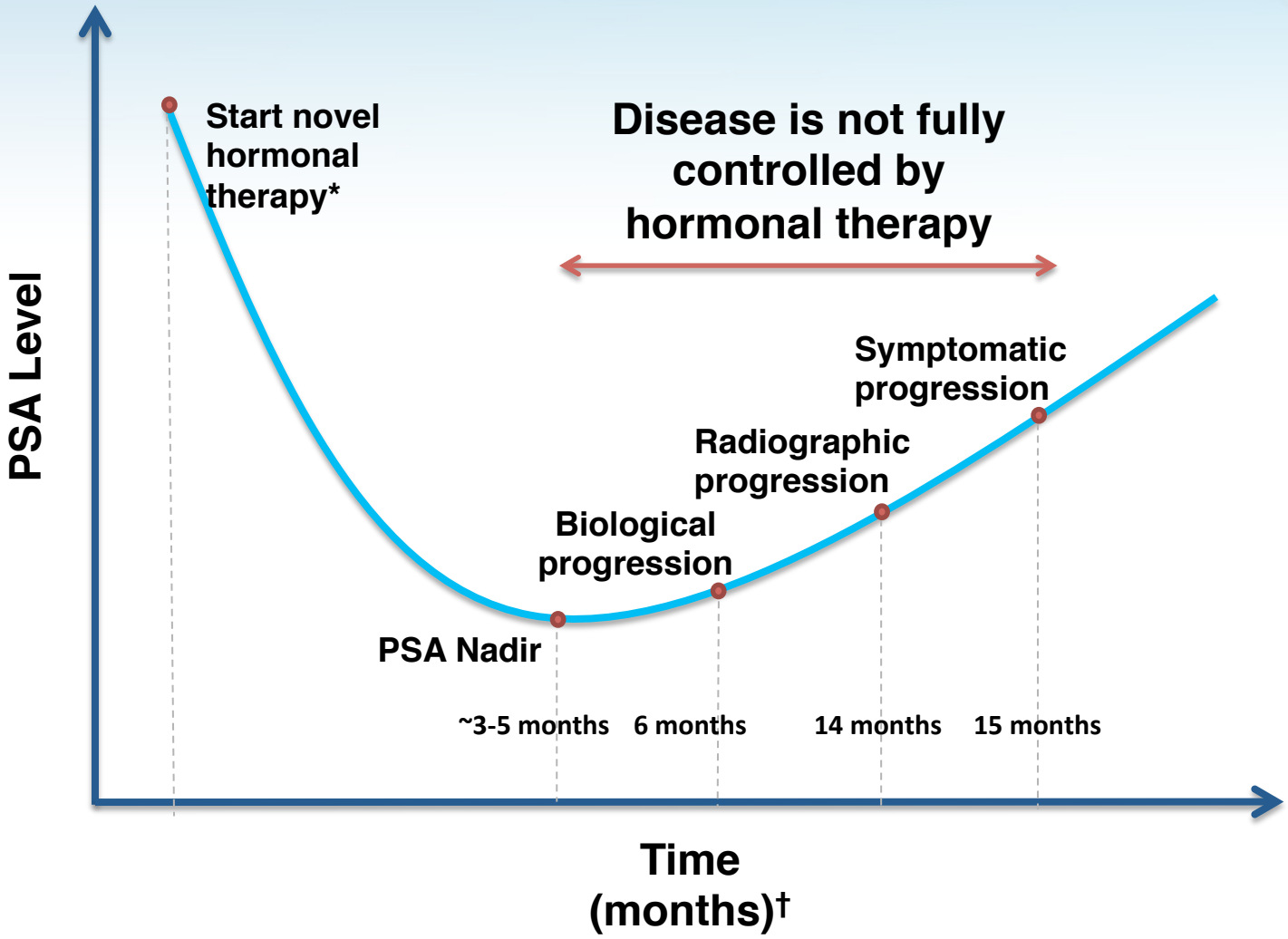
Radiopharmaceuticals : Has There been progress?

Neal D. Shore, MD

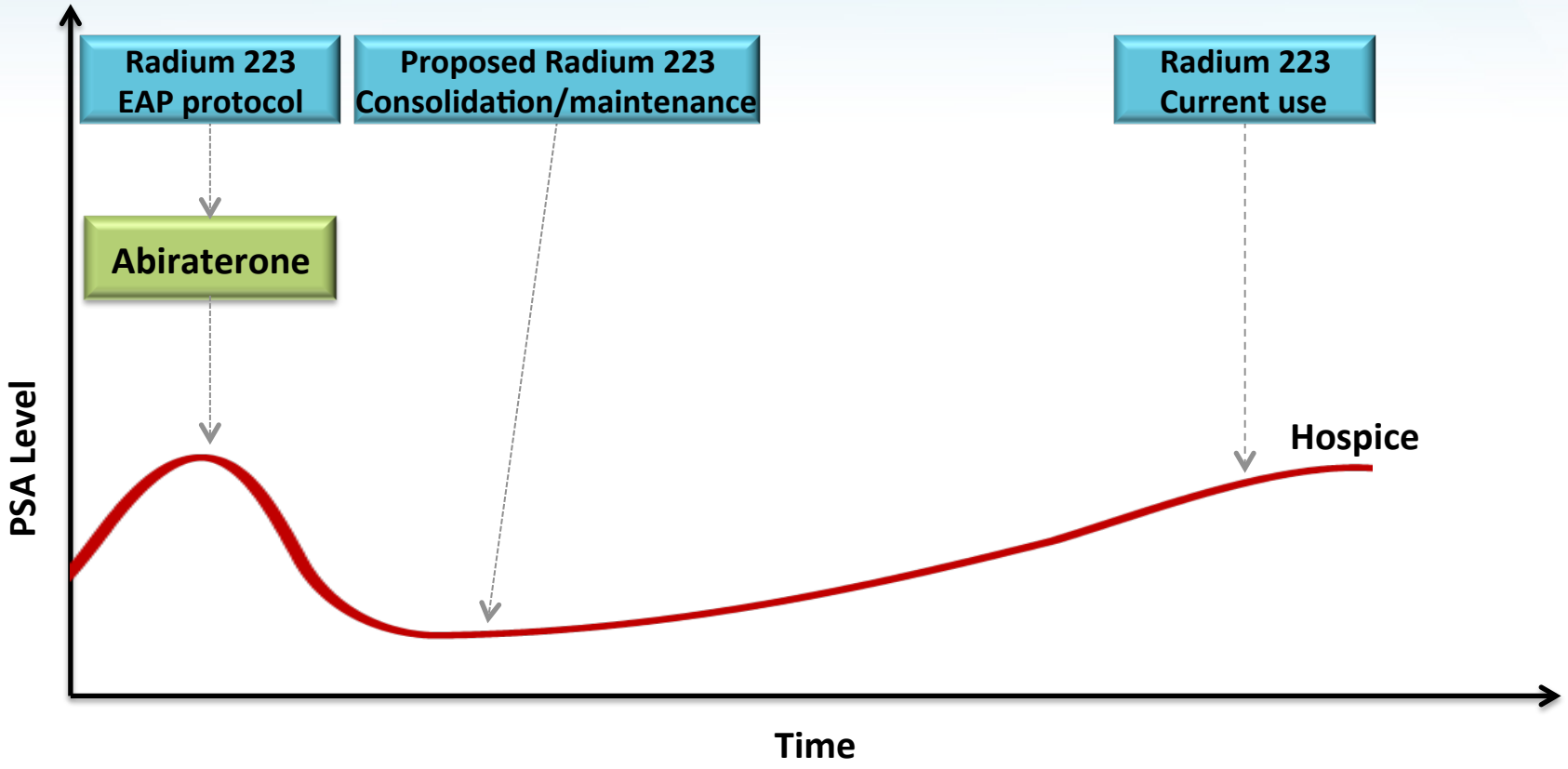
IPCU 2016

Place in therapy: Radium 223



*Such as abiraterone acetate or enzalutamide
†Not drawn to scale

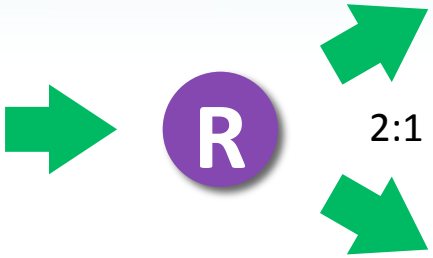
Proposed Location of Radium 223: Trough Transition



ALSYMPCA: Study Design

PATIENTS (N=921)
- Confirmed symptomatic CRPC
- ≥2 bone metastases
- No known visceral metastases
- Post-docetaxel, unfit for docetaxel, or refused docetaxel[a]

STRATIFICATION
- Total ALP: <220 U/L vs ≥220 U/L
- Bisphosphonate use: Yes vs No
- Prior docetaxel: Yes vs No



Radium-223 (50 kBq/kg IV) 6 injections at 4-week intervals + best standard of care[b]

Placebo (saline) 6 injections at 4-week intervals + best standard of care[b]

- 136 centers in 19 countries
- Planned follow-up is 3 years

ALSYMPCA was halted early after the positive efficacy results reported from a planned interim analysis of 809 patients with 314 deaths occurred. An updated analysis of efficacy and safety was performed from all 921 enrolled patients when 528 deaths had occurred.

ALP, alkaline phosphatase; ALSYMPCA, ALpharadin in SYMptomatic Prostate CAncer; CRPC, castration-resistant prostate cancer.

a. Unfit for docetaxel includes patients who were ineligible for docetaxel, refused docetaxel, or lived where docetaxel was unavailable.
b. Best standard of care defined as a routine standard of care at each center, e.g., local external beam radiation therapy, corticosteroids, antiandrogens, estrogens (e.g., stilbestrol), estramustine, or ketoconazole.

SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213–223.

ALSYMPCA summary

- In the ALSYMPCA trial, Xofigo® compared with placebo in patients with CRPC and symptomatic bone metastases[1,2]
  - Established efficacy with an overall survival (OS) benefit of 3.6 months ($P<0.001$)
  - Significantly prolonged the time to first SSE* (15.6 vs 9.8 months, $P<0.001$)
  - Had a favorable safety profile with low rates of myelosuppression

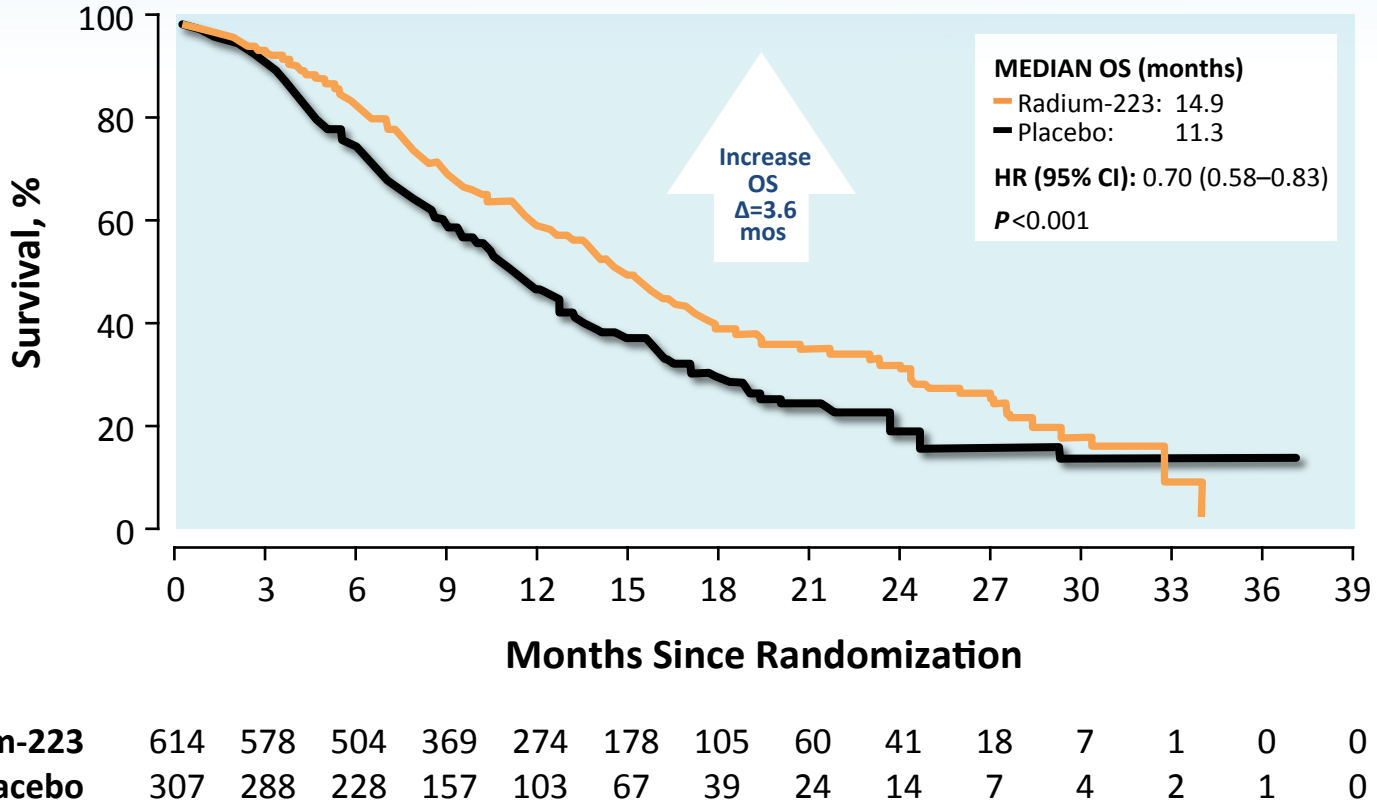
* Secondary endpoint

ALSYMPCA: ALpharadin in SYMptomatic Prostate CAncer; CRPC: castration resistant prostate cancer, OS: overall survival, SSE: symptomatic skeletal event.

1. Parker et al. N Engl J Med. 2013;369:213-223.
2. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; May 2013.

ALSYMPCA Updated Analysis: Radium-223 Significantly Improved Overall Survival

The updated analysis confirmed the 30% reduction in risk of death (HR=0.70) for patients in the radium-223 group compared with placebo.



CI, confidence interval; HR, hazard ratio; OS, overall survival.

SOURCE: Parker C, et al. *N Engl J Med.* 2013;369(3):213–223.

A Urologist's Perspective

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Review Article

Radium-223 Dichloride for Metastatic Castration-resistant Prostate Cancer: The Urologist's Perspective

Neal D. Shore

Radium-223 dichloride (radium-223) is an important therapeutic option for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no visceral disease. The unique mechanism of action of this first-in-class alpha-emitting radiopharmaceutical underlies its favorable safety profile and low incidence of myelosuppression. In the pivotal phase 3 ALpharadin in SYMptomatic Prostate CAncer Patients study, radium-223 reduced the risk of death by 30% and prolonged time to first symptomatic skeletal event by 5.8 months. This article summarizes current guidelines and clinical studies that led to the approval of radium-223 as an overall survival therapy, and discusses the urologist's perspective on using radium-223 in clinical practice. UROLOGY ■: ■—■, 2015. © 2015 Elsevier Inc.

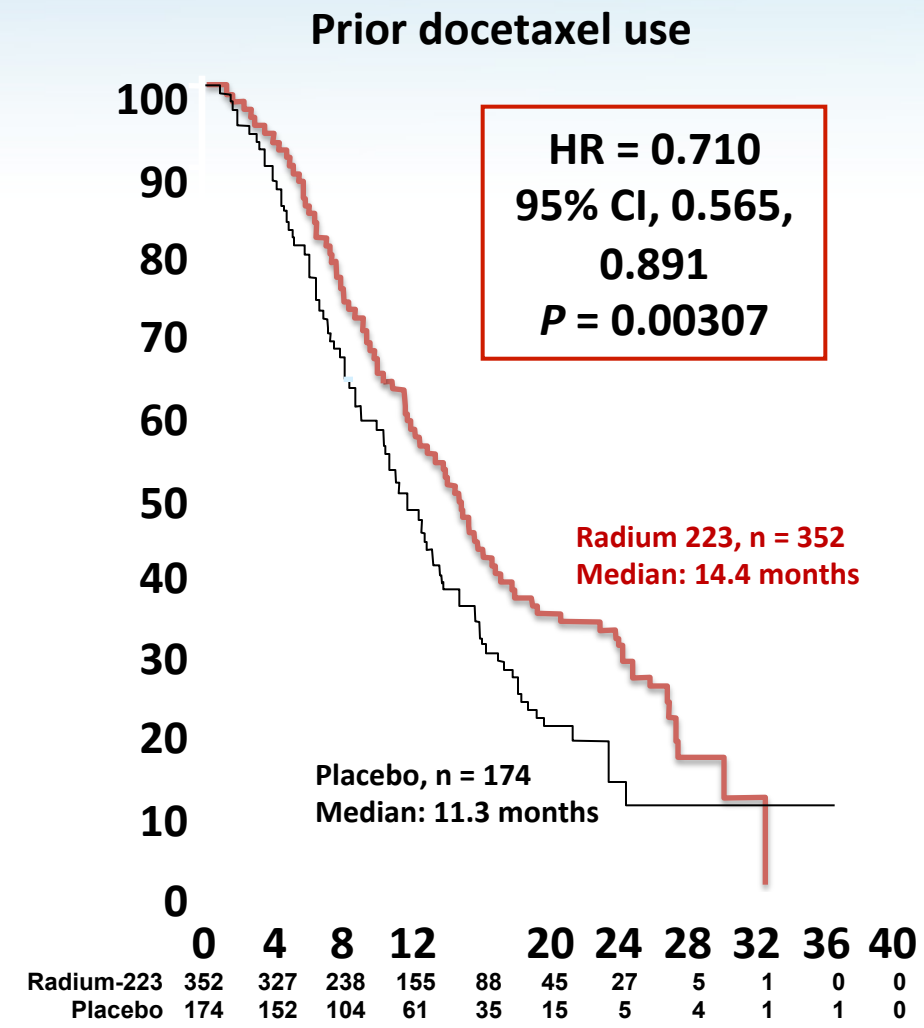
Prostate cancer is the fourth leading cause of US cancer deaths and the most common cancer managed by urologists, with >233,000 new cases estimated for 2014.[1] On diagnosis, approximately 12% of patients will have locally advanced disease, and 4% of newly diagnosed patients will present with metastatic disease.[1] Although newly diagnosed localized disease may be cured with interventional therapies, approximately 30% of patients develop recurrent disease and may progress to castration-resistant prostate cancer (CRPC).[1,2] As the clinicians chiefly responsible for diagnosing, treating, and monitoring prostate cancer patients, urologists are uniquely positioned to provide a detailed discussion of therapeutic options and promote shared decision making with patients regarding approved CRPC treatment options.

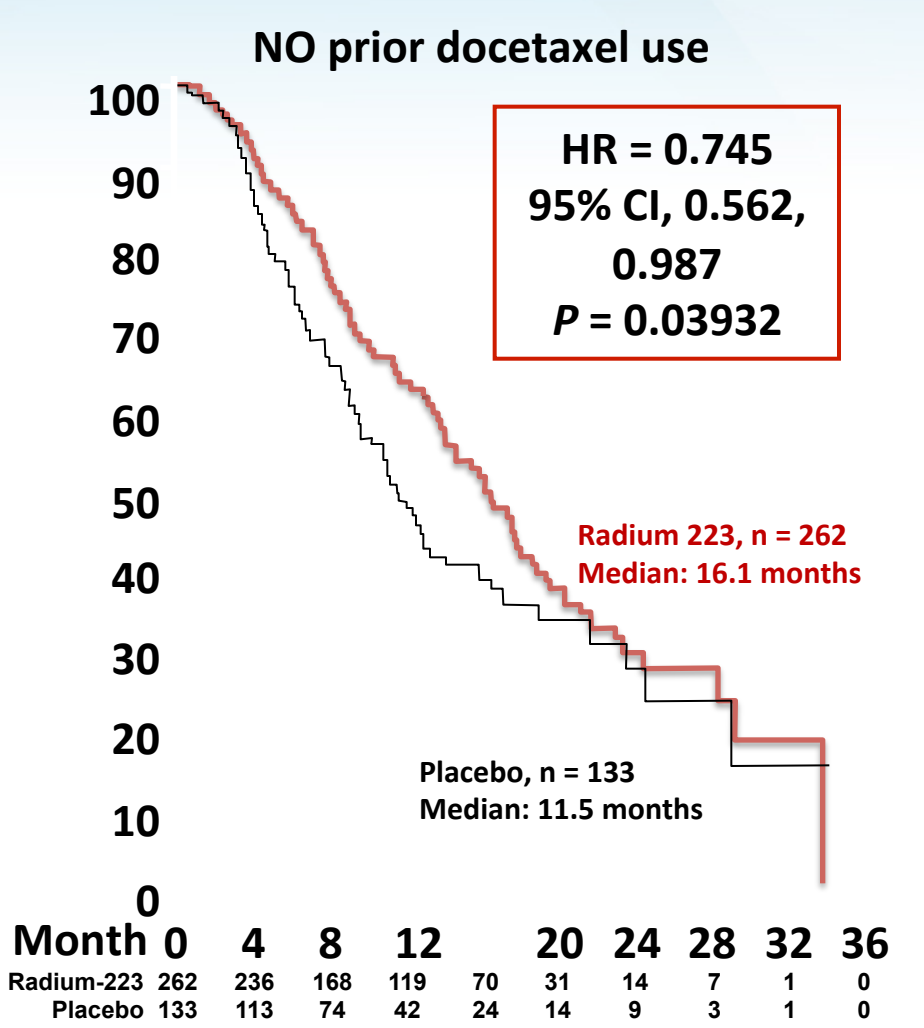
Although CRPC treatment options with unique mechanisms of action (MOAs) have burgeoned since 2010, the disease eventually evolves via selective pres-

or surgical intervention.[4,5] Bone-metastatic CRPC (mCRPC)—associated events can cause functional disability, reduced quality of life (QOL), further complications that may impact survival, and ultimately health care cost escalations.[4-6] Urologists dedicated to evaluating and managing therapeutic options for patients with progressive CRPC must be knowledgeable of approved therapies that can delay disease progression and prolong survival, and they must proactively manage the relatively ubiquitous metastatic skeletal disease and the associated potential complications.

Radium-223 dichloride (radium-223) is a first-in-class alpha-emitting radiopharmaceutical approved for treating CRPC patients with symptomatic bone metastases with no known visceral metastatic disease.[7] Clinicians caring for patients with progressive CRPC should understand the radium-223 MOA, its role in the treatment plan for appropriate CRPC patients, and its administration, efficacy, and safety profile. This review summarizes

ALSYMPCA: OS by Prior Docetaxel Use





Urology, May 2015

US EXPANDED ACCESS PROGRAM (EAP)
SAFETY AND EXPLORATORY EFFICACY ANALYSIS

Rationale and objectives for EAP studies

- Building off of the findings of the ALSYMPCA trial, the EAP for Xofigo® was designed to:[1-3]
  - Provide earlier access of Xofigo® to CRPC patients with bone metastases prior to regulatory approval
  - Monitor long-term safety and efficacy data of Xofigo®

ALSYMPCA: ALpharadin in SYMptomatic Prostate CAncer; CRPC: castration resistant prostate cancer; EAP: expanded access program .
1. Shore N, et al. ASCO 2015, Abs 15-6266.; 2. Sartor O, et al, ASCO GU 2015 Abs 253.; 3. Saad F,et al. ASCO 2015, Abs 5034.

Shore N, et al. Radium-223 Dichloride in Expanded-Access Setting in the US: Overall and Concurrent Experience with Abiraterone or Enzalutamide (AUA 2015, Abstract 15-6266)

Abstract 15-6266

Radium-223 Dichloride in Expanded-Access Setting in the United States: Overall and Concurrent Experience With Abiraterone or Enzalutamide

Neal Shore,[1] Nicholas J. Vogelzang,[2] Daniel C. Fernandez,[3] Michael J. Morris,[4] Andrei Iagaru,[5] Alan Brown, Jr,[6] Christopher Sweeney,[7] Matthew R. Smith,[8] Adam P. Dicker,[9] Yu-Ning Wong,[10] Keith Bangerter,[11] Jeremy Gratt,[11] Oana Petrenciuc,[11] Oliver Sartor[12]

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BACKGROUND

Radium-223 Dichloride (Radium-223)

- First approved alpha-emitting radiopharmaceutical with a potent and highly targeted cytotoxic effect on bone metastases[1]
- In phase 3 ALSYMPCA, radium-223 + best standard of care (BSoC) compared with placebo + BSoC in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases[2]
  - Established efficacy with overall survival (OS) benefit; improved OS by 3.6 months (HR = 0.70; 95% CI, 0.58-0.83; *P* < 0.001)
  - Had a favorable safety profile with low rates of myelosuppression

US Expanded Access Program (EAP) (15995)

- A phase 2, prospective, interventional, open-label, multicenter study conducted in the United States and designed to
  - Provide early access of radium-223 to patients with CRPC and symptomatic bone metastases prior to regulatory approval
  - Monitor acute and long-term safety of radium-223

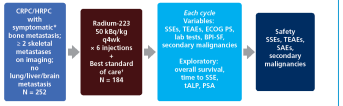
RATIONALE AND OBJECTIVE

- At the time of this study, the new hormonal agents abiraterone and enzalutamide were available and administered prior to start of, during, and following the US EAP treatment period
- The objective of this study is to present safety and OS in US patients from EAP who received prior and concurrent abiraterone or enzalutamide
  - Data presented here are updated since the abstract submission

METHODS

- US EAP study design and end points are shown in **Figure 1**
  - Eligibility criteria were similar to those of ALSYMPCA[1]

Figure 1. US EAP Study Design



End Points

Primary: safety (assessed during treatment and up to 30 days post-treatment [acute] and ≥ 30 days post-treatment through follow-up [q 6 mo until death or study termination]) and quality of life

Exploratory efficacy: overall survival, time to first SSE, time to disease progression, changes in tALP and PSA, confirmed tALP and PSA response, tALP normalization, and time to tALP and PSA progression

*Regular use of opioid or nonopioid analgesics for cancer-related bone pain or external beam radiation therapy within 12 weeks prior to treatment.
†According to local clinical practice, if chemoradiotherapy is considered best standard of care, radium-223 must be discontinued.
BPI-SF = Brief Pain Inventory-Short Form; CRPC = castration-resistant prostate cancer; EAP = Expanded Access Program; ECOG PS = Eastern Cooperative Oncology Group performance status; HRPC = hormone-refractory prostate cancer; PSA = prostate-specific antigen; SAEs = serious adverse events; SSE = symptomatic skeletal event; tALP = total alkaline phosphatase; TEAEs = treatment-emergent adverse events.

- Treatment period is defined as the time from first dose of study treatment through last dose + 30 days
- Follow-up was short (~3-9 mo) because of study termination by the sponsor due to commercial availability of radium-223
- Prior therapies were defined as those taken prior to and stopped at study entry
- Concurrent therapies were defined as those started and received with radium-223 or received prior to and with radium-223 up to 30 days after last radium-223 dose
- All variables were analyzed primarily by descriptive statistics

RESULTS

Prior and Concurrent Systemic Anticancer Therapy

- Prior anticancer therapy was common to what one would see in this patient population (**Table 1**)

Table 1. Select Prior and Concurrent Systemic Anticancer Therapy

Anticancer Therapy, n (%)	EAP N = 184*	
	Prior	Concurrent
Bicalutamide	147 (80)	9 (5)
Abiraterone	120 (65)	25 (14)
Docetaxel†	110 (60)	4 (2)
Enzalutamide	59 (32)	15 (8)
Ketoconazole	48 (26)	3 (2)
Nilutamide	39 (21)	3 (2)
Cabazitaxel‡	33 (18)	4 (2)
Flutamide	19 (10)	2 (1)
Denosumab	10 (5)	31 (17)
Zoledronic acid	0 (0)	17 (9)

*A patient could have > 1 medication; therefore, the sum of medication counts and percentages may not equal the total counts.
†Agents were not given with radium-223, but were started within a 30-day period following the last radium-223 injection.
EAP = Expanded Access Program.

Prior Abiraterone or Enzalutamide

- 120/184 (65%) patients received prior abiraterone and 59/184 (32%) patients received prior enzalutamide
- Baseline characteristics of patients who received prior abiraterone or enzalutamide were generally similar to those of patients who had not received these agents (**Table 2**)
- 72% and 81% of patients with prior abiraterone or enzalutamide, respectively, had prior use of docetaxel (**Table 2**)
- Patients who had prior abiraterone or enzalutamide had higher baseline alkaline phosphatase and prostate-specific antigen (PSA) than patients with no prior abiraterone or enzalutamide (**Table 2**)

Table 2. Demographics and Baseline Characteristics of Patients Who Received Prior Abiraterone or Enzalutamide

	Abiraterone		Enzalutamide	
	Yes n = 120	No n = 64	Yes n = 59	No n = 125
Age, median (range), y	71 (47-97)	69 (47-89)	69 (47-85)	71 (47-97)
Weight, median (range), kg	84 (49-134)	89 (59-138)	84 (62-133)	86 (49-138)
ECOG PS 0-1, n (%)	107 (89)	58 (91)	53 (90)	112 (90)
ALP, median (range), U/L	157 (34-1190)	135 (38-795)	209 (39-1190)	135 (34-857)
PSA, median (range), µg/L	187 (1-5150)	108 (< 1-1660)	222 (2-5150)	117 (< 1-3000)
Albumin, median (range), g/dL	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
Hemoglobin, median (range), g/dL	12 (8-15)	12 (10-15)	12 (9-15)	12 (8-15)
Current use of bisphosphonates, n (%)*	11 (9)	6 (9)	3 (5)	14 (11)
Current use of denosumab, n (%)*	17 (14)	14 (22)	12 (20)	19 (15)
Prior use of docetaxel, n (%)	86 (72)	24 (38)	48 (81)	62 (50)

*Current use defined as use during the treatment period.
ALP = alkaline phosphatase; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

- Safety profiles of radium-223 were similar regardless of prior exposure to abiraterone or enzalutamide (**Table 3**)
  - Most common grade 3-4 events were anemia and thrombocytopenia

Table 3. Summary of AE Categories of Patients Who Received Prior Abiraterone or Enzalutamide During Treatment Period

	Abiraterone		Enzalutamide	
AE Category, n (%)	Yes n = 120	No n = 64	Yes n = 59	No n = 125
Grade 3-4 TEAE	45 (38)	22 (34)	23 (39)	44 (35)
Treatment-related TEAE	64 (53)	29 (45)	31 (53)	62 (50)
Serious AE	31 (26)	14 (22)	18 (31)	27 (22)
Discontinuation due to TEAE	21 (18)	9 (14)	12 (20)	18 (14)

AE = adverse event; TEAE = treatment-emergent adverse event.

Concurrent Abiraterone or Enzalutamide

- The number of patients who received concurrent abiraterone or enzalutamide was small; results should be interpreted with caution
- 25/184 (14%) patients received concurrent abiraterone, and 15/184 (8%) patients received concurrent enzalutamide (**Table 4**)
  - Among patients with concurrent abiraterone, 8/25 (32%) had received prior enzalutamide
  - Among patients with concurrent enzalutamide, 14/15 (93%) had received prior abiraterone

Table 4. Summary of Patients Who Received Medication Sequences Including Abiraterone, Enzalutamide, and Docetaxel

	Patients, n/N (%)
Concurrent abiraterone and Prior enzalutamide No prior enzalutamide	25 8/25 (32) 17/25 (68)*
Concurrent enzalutamide and Prior abiraterone No prior abiraterone	15 14/15 (93) 1/15 (7)*
Concurrent abiraterone and prior docetaxel	11/25 (44)
Concurrent enzalutamide and prior docetaxel	11/15 (73)

*One patient received both abiraterone and enzalutamide concurrently with radium-223 and had no prior abiraterone or enzalutamide; this patient is counted in both groups.

- Baseline characteristics of patients who received concurrent abiraterone or enzalutamide were generally similar to those in the overall population (**Table 5**), with some exceptions
  - PSA and prior use of docetaxel were higher in patients with concurrent enzalutamide than in patients with concurrent abiraterone or the overall population

Table 5. Demographics and Baseline Characteristics of Patients Who Received Concurrent Abiraterone or Enzalutamide

	Abiraterone n = 25	Enzalutamide n = 15	EAP Overall N = 184
Age, median (range), y	66 (47-81)	70 (54-84)	70 (47-97)
Weight, median (range), kg	86 (58-109)	89 (65-110)	86 (49-138)
ECOG PS 0-1, n (%)	25 (100)	14 (93)	165 (90)
ALP, median (range), U/L	168 (51-575)	168 (86-513)	154 (34-1190)
PSA, median (range), µg/L	94 (1-1236)	322 (21-2320)	129 (< 1-5150)
Albumin, median (range), g/dL	4 (3-5)	4 (3-4)	4 (3-5)
Hemoglobin, median (range), g/dL	12 (10-15)	11 (9-15)	12 (8-15)
Current use of bisphosphonates, n (%)*	5 (20)	3 (20)	17 (9)
Current use of denosumab, n (%)*	5 (20)	4 (27)	31 (17)
Prior use of docetaxel, n (%)	11 (44)	11 (73)	110 (60)

*Current use defined as use during the treatment period.
ALP = alkaline phosphatase; EAP = Expanded Access Program; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

- Safety profiles of radium-223 were generally similar regardless of whether patients received concurrent abiraterone or enzalutamide (**Table 6**)
  - Most frequently occurring grade 3-4 treatment-emergent adverse events were anemia (abiraterone 16%, enzalutamide 13%), thrombocytopenia (abiraterone 4%, enzalutamide 0%), and back pain (abiraterone 0%, enzalutamide 13%)

Table 6. Summary of AE Categories of Patients Who Received Concurrent Abiraterone or Enzalutamide During Treatment Period

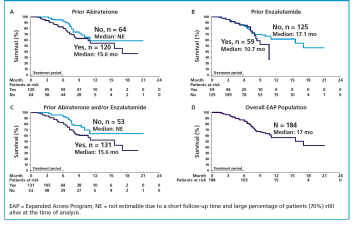
AE Category, n (%)	Abiraterone n = 25	Enzalutamide n = 15	EAP Overall N = 184
Grade 3-4 TEAE	10 (40)	6 (40)	67 (36)
Treatment-related TEAE	15 (60)	12 (80)	93 (51)
Serious AE	6 (24)	4 (27)	45 (24)
Discontinuation due to TEAE	6 (24)	4 (27)	30 (16)

AE = adverse event; EAP = Expanded Access Program; TEAE = treatment-emergent adverse event.

Overall Survival: Prior Abiraterone or Enzalutamide

- Median OS of patients with prior abiraterone (15.6 mo, n = 120) and prior abiraterone and/or enzalutamide (15.6 mo, n = 131) was similar to that of the overall EAP population (17 mo, n = 184) (**Figure 2 A, C, and D**)

Figure 2. Overall Survival of Patients Who Received Prior Abiraterone (A), Enzalutamide (B), Abiraterone and/or Enzalutamide (C), and Overall EAP Population (D)

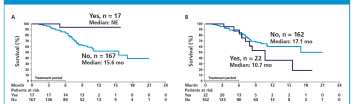


EAP = Expanded Access Program; NE = not estimable due to a short follow-up time and large percentage of patients (70%) still alive at the time of analysis.

Overall Survival: Concurrent Abiraterone or Enzalutamide

- Median OS for patients with (n = 25) and without (n =159) concurrent abiraterone were not estimable and 15.6 months, respectively
- Median OS for patients with (n = 15) and without (n = 169) concurrent enzalutamide were 10.7 and 17.1 months, respectively
- Patients who received concurrent abiraterone and/or enzalutamide with no prior abiraterone or enzalutamide (n = 17) appeared to have longer OS than those who did not (**Figure 3A**)
- The effect of concurrent abiraterone and/or enzalutamide was not as pronounced in patients who had received prior abiraterone or enzalutamide (**Figure 3B**)

Figure 3. Overall Survival of Patients Who Received Concurrent Abiraterone and/or Enzalutamide (With No Prior Abiraterone or Enzalutamide [A]* and With Prior Abiraterone or Enzalutamide [B]†)



*Concurrent abiraterone with no prior enzalutamide or concurrent enzalutamide with no prior abiraterone.
†Concurrent abiraterone with prior enzalutamide or concurrent enzalutamide with prior abiraterone.
NE = not estimable due to a short follow-up time and large percentage of censored patients (70%) ie, alive at the time of analysis).

CONCLUSIONS

- In this is EAP, radium-223 was safe and well tolerated regardless of prior or concurrent exposure to abiraterone and/or enzalutamide
- OS was comparable in radium-223–treated patients who received prior abiraterone and/or enzalutamide versus the overall EAP population
- Initial findings of OS in the small numbers of patients receiving concurrent abiraterone or enzalutamide are indeterminate. Current trials are under way to assess radium-223 combinations

REFERENCES

1. Xofigo (radium Ra 223 dichloride) injection, for intravenous use [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; May 2013.
2. Parker et al. *N Engl J Med.* 2013;369:213-223.

Acknowledgments

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Abstract 15-6266

Radium-223 Dichloride in Expanded-Access Setting in the United States: Overall and Concurrent Experience With Abiraterone or Enzalutamide

Neal Shore,[1] Nicholas J. Vogelzang,[2] Daniel C. Fernandez,[3] Michael J. Morris,[4] Andrei Iagaru,[5] Alan Brown, Jr,[6] Christopher Sweeney,[7] Matthew R. Smith,[8] Adam P. Dicker,[9] Yu-Ning Wong,[10] Keith Bangerter,[11] Jeremy Gratt,[11] Oana Petrenciuc,[11] Oliver Sartor[12]

[1]*Carolina Urologic Research Center, Myrtle Beach, SC, USA;* [2]*Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA;* [3]*H. Lee Moffitt Cancer Center, Tampa, FL, USA;* [4]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [5]*Stanford University, Stanford, CA, USA;* [6]*21st Century Oncology, Fort Myers, FL, USA;* [7]*Dana-Farber Cancer Institute, Boston, MA, USA;* [8]*Massachusetts General Hospital, Boston, MA, USA;* [9]*Thomas Jefferson University, Philadelphia, PA, USA;* [10]*Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA, USA;* [11]*Bayer HealthCare Pharmaceuticals, Inc, Whippany, NJ, USA;* [12]*Tulane Cancer Center, New Orleans, LA, USA*

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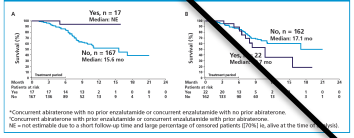
Figure 3. Overall Survival of Patients Who Received Concurrent Abiraterone and/or Enzalutamide (With No Prior Abiraterone or Enzalutamide [A]* and With Prior Abiraterone or Enzalutamide [B]†)



*Concurrent abiraterone with no prior enzalutamide or concurrent enzalutamide with no prior abiraterone.
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REFERENCES

1. Xofigo (radium Ra 223 dichloride) injection, for intravenous use [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; May 2013.
2. Parker et al. *N Engl J Med.* 2013;369:213-23.

Acknowledgments

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The authors wish to thank SciStrategy Communications for editorial and creative assistance in the preparation of this poster.

Sartor O, et al. Radium-223 Dichloride Experience in Pretreated Patients: Early Access Program Setting (ASCO 2015, Abstract 5063)

Abstract 5063

Radium-223 Dichloride Experience in Pretreated Patients: Early Access Program Setting

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BACKGROUND AND OBJECTIVE

Radium-223 Dichloride (Radium-223)

- First approved alpha-emitting radiopharmaceutical with a potent and highly targeted cytotoxic effect on bone metastases[1]
- In the phase 3 ALSYMPCA trial, radium-223 compared with placebo in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases[2]
  - Established efficacy with an overall survival (OS) benefit of 3.6 months ($P < 0.001$)
  - Had a favorable safety profile with low rates of myelosuppression

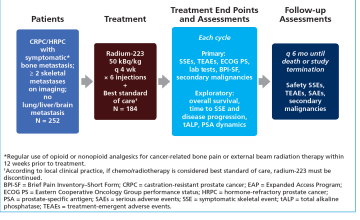
US Early Access Program (EAP)

- A phase 2, prospective, interventional, open-label, multicenter study was conducted in the United States to
  - Provide early access of radium-223 to patients with CRPC and symptomatic bone metastases prior to regulatory approval
  - Monitor acute and long-term safety of radium-223
- Radium-223 concurrently administered with abiraterone (Abi) or enzalutamide (Enza) was safe and well tolerated[3]
- The objective of this analysis is to explore the impact of prior Abi and/or Enza treatment on patient demographics, safety, and OS

METHODS

- US EAP eligibility criteria were similar to those of ALSYMPCA[2] (**Figure 1**)

Figure 1. US EAP Study Design



*Regular use of opioid or nonopioid analgesics for cancer-related bone pain or external beam radiation therapy within 12 weeks prior to treatment.
†According to local clinical practice, if chemo/radiotherapy is considered best standard of care, radium-223 must be discontinued.
BPI-SF = Brief Pain Inventory–Short Form; CRPC = castration-resistant prostate cancer; EAP = Expanded Access Program; ECOG PS = Eastern Cooperative Oncology Group performance status; HRPC = hormone-refractory prostate cancer; PSA = prostate-specific antigen; SAEs = serious adverse events; SSE = symptomatic skeletal event; tALP = total alkaline phosphatase; TEAEs = treatment-emergent adverse events.

- Treatment period: time from first dose of study treatment through last dose + 30 days
- Follow-up was short (~3-9 mo) because of study termination due to commercial availability of radium-223
- Prior therapies: taken prior to and stopped at study entry; patient numbers were updated from the abstract
- Chi-square tests were done to assess differences in patient demographics and number of injections between prior-treatment subgroups
- Stepwise logistic regression analysis identified baseline covariates predictive of receiving 1-4 versus 5-6 injections of radium-223
  - Parameters examined: prior Abi and Enza, baseline albumin, baseline hemoglobin below normal, baseline log prostate-specific antigen (PSA), baseline log alkaline phosphatase (ALP), 3 or more prior anticancer medications, baseline Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2, and prior docetaxel
- All variables were analyzed primarily by descriptive statistics

RESULTS

Patients

- Of the 184 patients in EAP, 48 (26%) had prior Abi and Enza, 83 (45%) had prior Abi or Enza, and 53 (29%) were Abi and Enza naïve
- Patients with prior Abi and Enza had the greatest extent of disease based on ALP and PSA (**Table 1**)
- 83% of patients with prior Abi and Enza also had prior docetaxel treatment, compared with 30% of Abi- and Enza-naïve patients (**Table 1**)

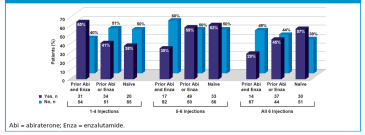
Table 1. Demographics and Baseline Characteristics, by Prior Abiraterone and/or Enzalutamide

	Prior Abiraterone and Enzalutamide		Prior Abiraterone or Enzalutamide		Naïve (No Prior Abiraterone or Enzalutamide)	
	Yes n = 48	No n = 136	Yes n = 83	No n = 101	Yes n = 53	No n = 131
Age, median, y	70	70	71	69	69	71
Weight, median, kg	83	87	87	86	88	84
ECOG PS ≤ 1, n (%)	43 (90)	122 (90)	74 (89)	91 (90)	48 (91)	117 (89)
PSA, median, µg/L	230	119	146	129	107	172
ALP, median, U/L	215	137	147	162	130	159
Total ALP ≥ 220 U/L, n (%)	23 (48)	33 (24)	23 (28)	33 (33)	10 (19)	46 (35)
Prior docetaxel, n (%)	40 (83)	70 (52)	54 (65)	56 (55)	16 (30)	94 (72)

ALP = alkaline phosphatase; ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen.

- Patients with prior Abi and Enza had a lower median number of injections (4) compared with those with prior Abi or Enza, and Abi- and Enza-naïve patients (5 and 6, respectively)
- Patients with prior Abi and Enza had a significantly lower percentage of patients completing 5-6 injections, compared with those without prior Abi and Enza (35% vs 60%; $P = 0.003$) (**Figure 2**)
- A significantly greater percentage of Abi- and Enza-naïve patients received all 6 injections, compared with patients who had prior Abi and Enza (57% vs 29%; $P = 0.006$) (**Figure 2**)

Figure 2. Number of Injections Received, by Prior Abiraterone and/or Enzalutamide

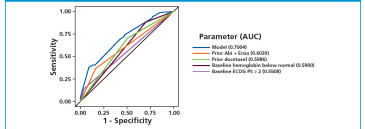


Abi = abiraterone; Enza = enzalutamide.

Logistic Regression Analysis

- Baseline covariates predicting receipt of 1-4 versus 5-6 radium-223 injections were prior Abi and Enza ($P = 0.0141$), baseline ECOG PS ≥ 2 ($P = 0.0202$), and baseline hemoglobin below normal ($P = 0.0042$); prior docetaxel was nearly significant ($P = 0.0501$) (**Figure 3**)

Figure 3. Logistic Regression ROC Curves



Abi = abiraterone; AUC = area under the curve; ECOG PS = Eastern Cooperative Oncology Group performance status; Enza = enzalutamide; ROC = receiver operating characteristic.

Safety

- Safety profiles were comparable across prior-treatment subgroups (**Table 2**)

Table 2. Summary of AE Categories, by Prior Abiraterone and/or Enzalutamide

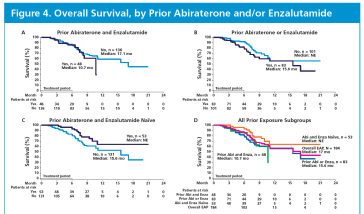
	Prior Abiraterone and Enzalutamide		Prior Abiraterone or Enzalutamide		Naïve (No Prior Abiraterone or Enzalutamide)	
	Yes n = 48	No n = 136	Yes n = 83	No n = 101	Yes n = 53	No n = 131
Grade 3-4 TEAE	18 (38)	49 (36)	32 (39)	35 (35)	17 (32)	50 (38)
Treatment-related TEAE	25 (52)	68 (50)	45 (54)	48 (48)	23 (43)	70 (53)
Serious AE	15 (31)	30 (22)	19 (23)	26 (26)	11 (21)	34 (26)
Discontinuation due to TEAE	9 (19)	21 (15)	15 (18)	15 (15)	6 (11)	24 (18)

AE = adverse event; TEAE = treatment-emergent AE.

OS: Prior Abiraterone and/or Enzalutamide

- Median OS of patients with either prior Abi or Enza was similar to that of the overall EAP population, 15.6 versus 17 months, respectively (**Figure 4 B and D**), and
  - Patients with prior Abi and Enza had a shorter median OS (10.7 mo) (**Figure 4 A and D**)
- Median OS of Abi- and Enza-naïve patients was not estimable due to short follow-up time and patient censoring, appearing longer than that of patients with prior treatment (**Figure 4 C and D**)

Figure 4. Overall Survival, by Prior Abiraterone and/or Enzalutamide

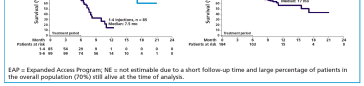


Abi = abiraterone; EAP = Expanded Access Program; Enza = enzalutamide; NE = not estimable due to a short follow-up time and large percentage of patients in the overall population (70%) still alive at time of analysis.

OS: Number of Radium-223 Injections

- Because a greater percentage of Abi- and Enza-naïve patients received all 6 injections (57%) and appeared to have longer OS, survival was analyzed by number of radium-223 injections received
  - Median OS of patients receiving 5-6 radium-223 injections (54%) trended longer than that of patients receiving 1-4 injections (46%) (**Figure 5A**)
  - In the overall EAP population, median OS was 17 months (**Figure 5B**) and 44% of patients received all 6 radium-223 injections (median, 5 injections)

Figure 5. Overall Survival, by Number of Radium-223 Injections



EAP = Expanded Access Program; NE = not estimable due to a short follow-up time and large percentage of patients in the overall population (70%) still alive at the time of analysis.

CONCLUSIONS

- In this EAP, radium-223 was safe and well tolerated regardless of prior Abi and/or Enza treatment
- A trend was observed: patients with less prior treatment were more likely to complete 5-6 radium-223 injections
- Baseline covariates predictive of receiving only 1-4 versus 5-6 injections were prior Abi and Enza, ECOG PS ≥ 2, and decreased baseline hemoglobin
- Prolonged OS was associated with receiving 5-6 versus 1-4 radium-223 injections, a finding that requires further validation
- Using radium-223 later in the current sequencing paradigm may limit the number of patients able to receive 6 cycles of treatment, as recommended in the radium-223 label

REFERENCES

1. Xofigo (radium Ra 223 dichloride) injection, for intravenous use [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; May 2013.
2. Parker et al. *N Engl J Med*. 2013;369:213-223.
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Acknowledgments

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Abstract 5063

s Program Setting

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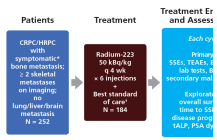

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Abi- and Enza-naïve patients (5 and 6, respectively)

- Patients with prior Abi and Enza had a significantly lower percentage of patients completing 5-6 injections, compared with those without prior Abi and Enza (35% vs 60%; $P = 0.003$) **(Figure 2)**

Treatment-related TEAE	25 (52)	68 (50)	45 (54)	48 (48)	23 (43)	70 (53)
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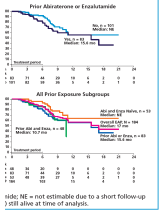

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ium-223 injections (median,

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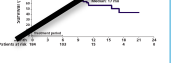

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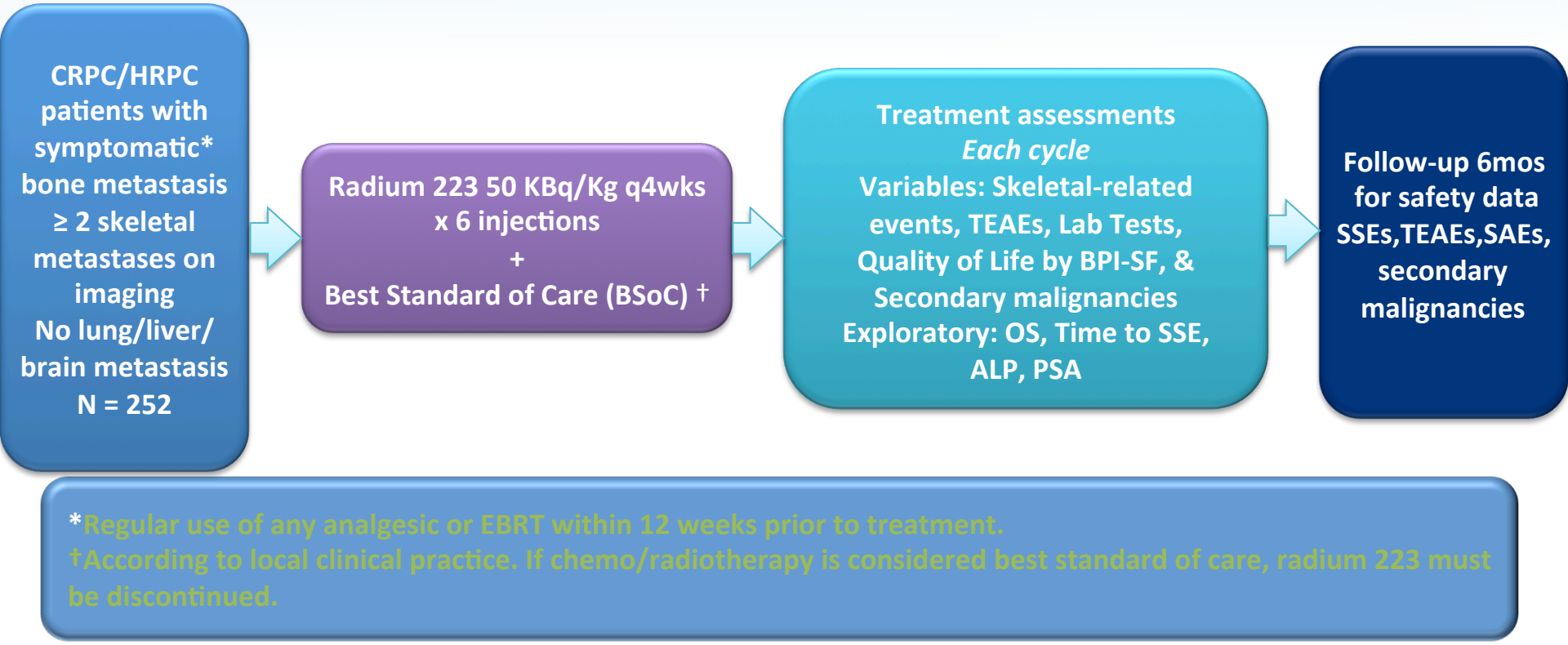
Study Design

Phase 2, prospective, interventional, open-label, multicenter study

EAP (15995)



*Regular use of any analgesic or EBRT within 12 weeks prior to treatment.
†According to local clinical practice. If chemo/radiotherapy is considered best standard of care, radium 223 must be discontinued.

Select Prior Systemic Anticancer Therapy (≥5 Patients)[a]

Hormone and Hormone-Related Agents (N=184)	n
Bicalutamide	147
Leuprolide acetate	111
Abiraterone	120 (65%)
Enzalutamide	59 (32%)
Prednisone	47
Diethylstilbestrol	24
Nilutamide	21
Goserelin	21
Flutamide	21
Nilandron	18
Triptorelin pamoate	17
Luteinizing hormone–releasing hormone	14
Degarelix acetate	13
Dutasteride	12
Estrogen	7

[a]A patient could have had >1 medication.

Source: New Table 14.4.

Summary of TEAEs

	US EAP[a] (N=184)	
	n	(%)
Number of patients with at ≥1 TEAE	**133**	**(72)**
Grade 3	58	(32)
Grade 4	9	(5)
Grade 5 (death)	8	(4)
Any serious TEAE	45	(25)
TEAEs leading to dose modifications,[a] delay[b]	18	(10)
TEAEs leading to permanent discontinuation	30	(16)
Number of patients with any related TEAE	**93**	**(51)**
Grade 3	23	(13)
Grade 4	6	(3)
Grade 5 (death)	0	
Any serious related TEAEs	11	(6)
Related leading to dose modifications	13	(7)
Related leading to permanent discontinuation	16	(9)

TEAE: Treatment Emergent Adverse Events.

Total Number of Injections Received by Patients

Number of Patients Receiving Injections	US EAP[a] (N=184)	
	n	(%)
1 injection	6	(3)
2 injections	26	(14)
3 injections	27	(15)
4 injections	26	(14)
5 injections	18	(10)
6 injections	81	(44)
Mean number of injections	4.5	

[a]Safety analysis set.

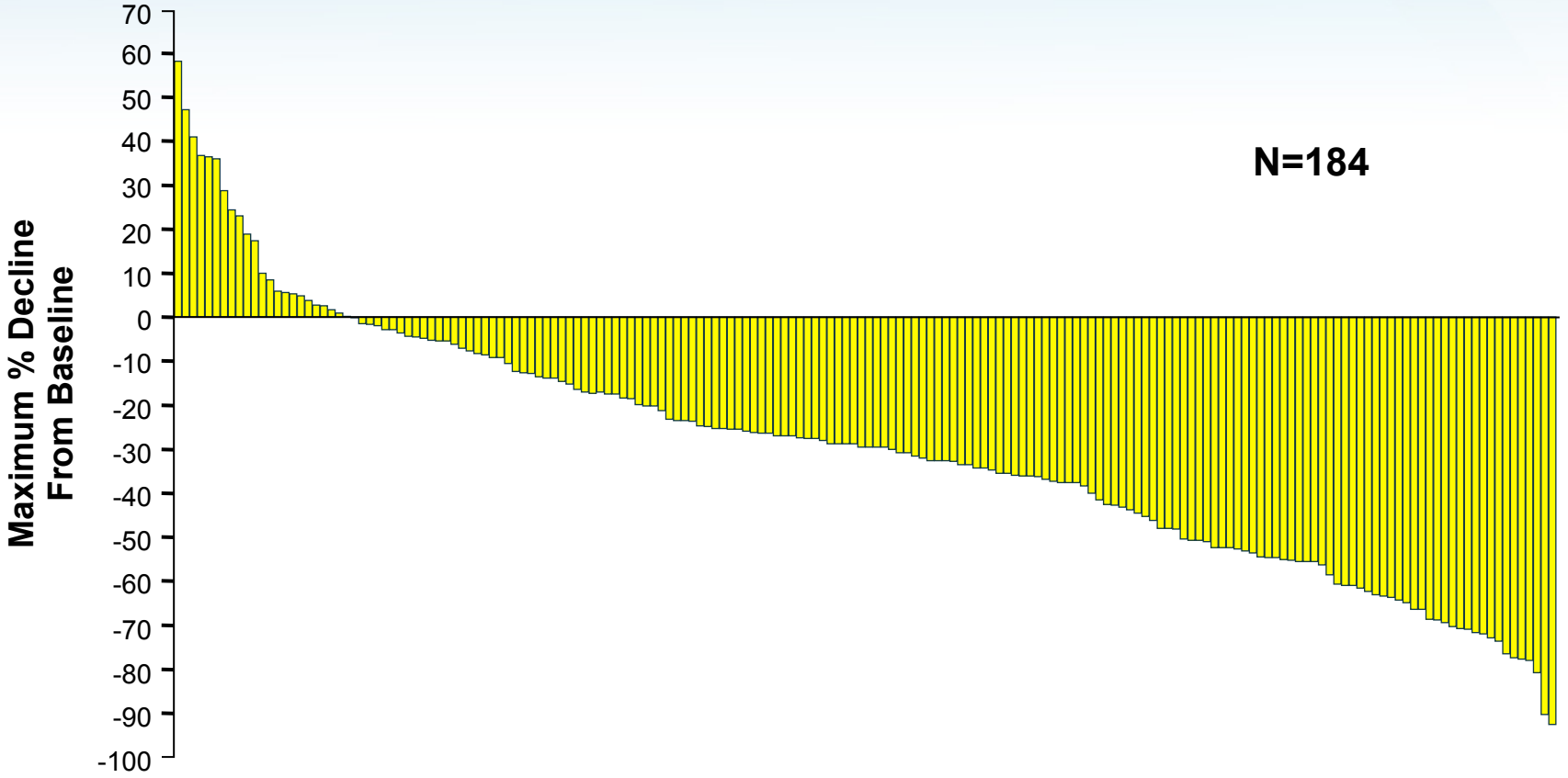
TEAEs of Interest

Event Term	US EAP[a] (N=184)							
	Any Grade		Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)
Blood and lymphatic system	32	(17)	11	(6)	3	(2)	0	
Anemia	29	(16)	10	(5)	1	(1)	0	
Thrombocytopenia	9	(5)	2	(1)	2	(1)	0	
Leukopenia	1	(1)	1	(1)	0		0	
Neutropenia	3	(2)	2	(1)	0		0	
Gastrointestinal disorders	42	(23)	2	(1)	1	(1)	0	
Diarrhea	23	(13)	1	(1)	0		0	
Gastric ulcer	1	(1)	1	(1)	0		0	
Rectal hemorrhage	1	(1)	1	(1)	0		0	
Upper GI hemorrhage	1	(1)	0		1	(1)	0	

[a]Safety analysis set

US EAP EXPLORATORY EFFICACY ANALYSES

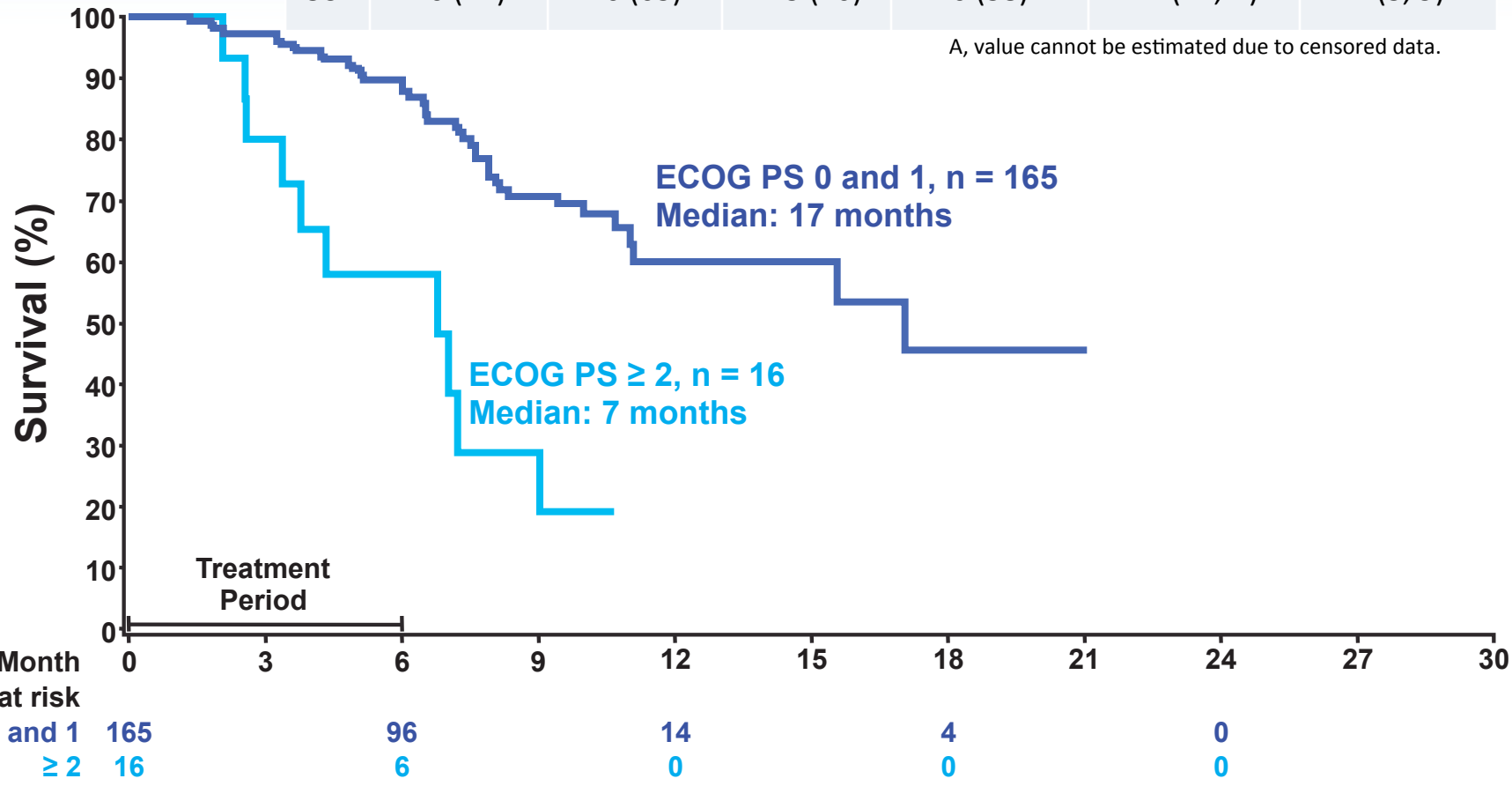
Exploratory Analyses: Maximum Percentage Decline in ALP by Patient



Exploratory Analyses: OS by ECOG Performance Status

	n (%) of Patients With Event		n (%) of Patients Censored		Median Time to First Event, mo (95% CI)	
	0 and 1	≥ 2	0 and 1	≥ 2	0 and 1	≥ 2
OS	40 (24)	10 (63)	125 (76)	6 (38)	17 (11, A)	7 (3, 9)

A, value cannot be estimated due to censored data.



SUBGROUP ANALYSES OF EFFICACY: CONCOMITANT BLOCKADE OF ANDROGEN SIGNALING AXIS AND RADIUM 223 IN US EAP

Subgroup Analysis: Concurrent Abiraterone Use

	Not Concurrent With Abiraterone (n=159)	Concurrent With Abiraterone (n=25)
Age, median (y)	72	66
Race n (%)		
White	147 (93)	22 (88)
African American	6 (4)	1 (4)
Asian	2 (1.3)	2 (8)
Not reported	4 (3)	0
Weight, median (kg)	86	86
ECOG PS ≤1, n (%)	140 (88)	25 (100)
Total ALP ≥220 U/L, n (%)	48 (30)	8 (32)
Current use of bisphosphonates (yes), n (%)	12 (8)	5 (20)
Prior use of docetaxel, n (%)	99 (62)	11 (44)
Pain at baseline, n (%)		
No pain	5 (3)	1 (4)
Mild to moderate	79 (50)	8 (32)
Severe	30 (19)	5 (20)
Missing	45 (28)	11 (44)

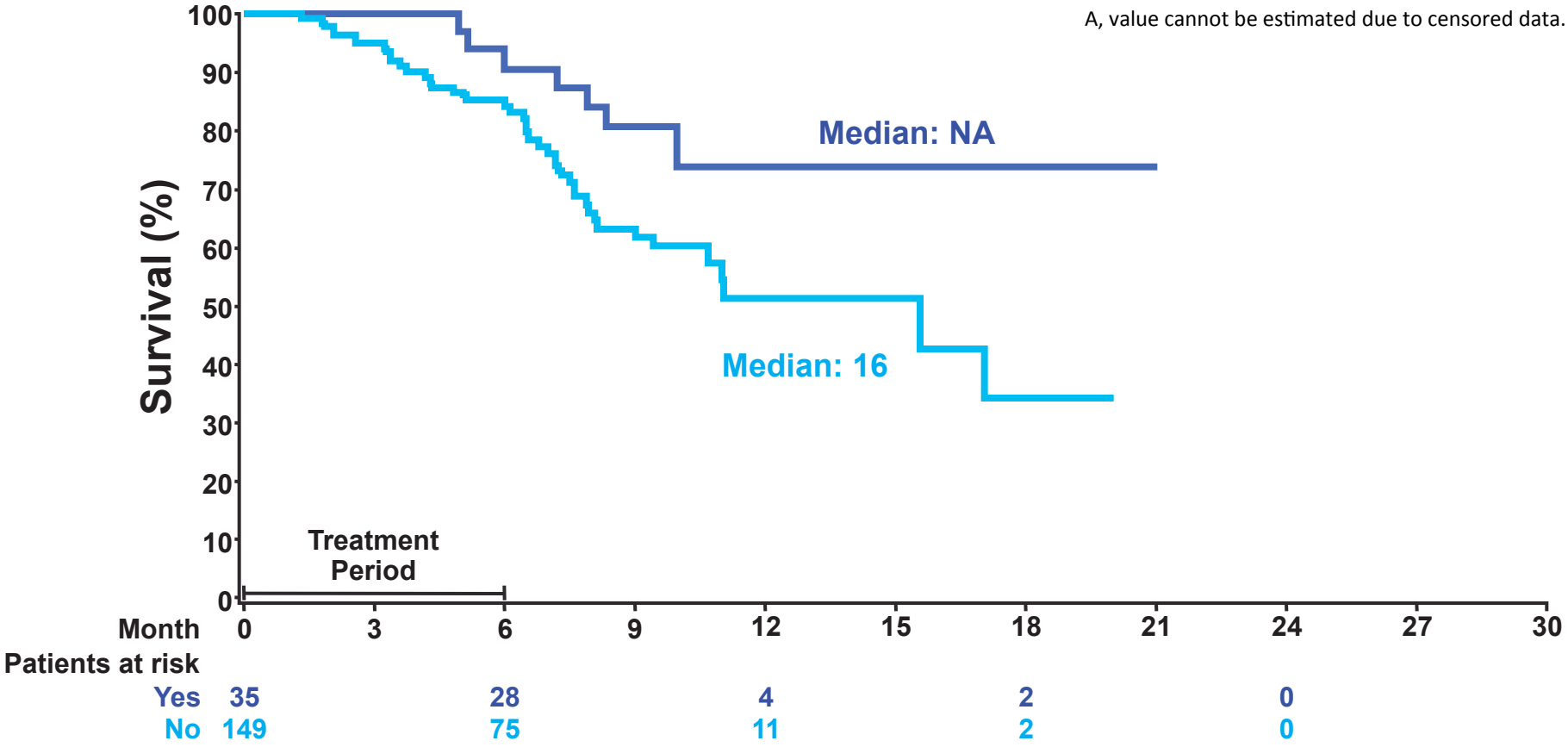
Grade 3 to 5 TEAEs of Interest: Concurrent Abiraterone Use

	During Treatment Period	
	Not Concurrent With Abiraterone (n=159)	Concurrent With Abiraterone (n=25)
TEAEs		
Hematologic, n (%)		
Anemia	17 (11)	4 (16) (12 vs 13% in ROW)
Neutropenia	2 (1)	0 (0) (1% in each)
Thrombocytopenia	4 (3)	1 (4) (3 vs 1% in ROW)
Nonhematologic, n (%)		
Diarrhea	0 (0)	1 (4) (<1% each in ROW)
Fatigue	4 (3)	0 (0)
Bone pain	4 (3)	0 (0)

Exploratory Analyses: OS by Current Use of Abiraterone

	n (%) of Patients With Event		n (%) of Patients Censored		Median Time to First Event, mo (95% CI)	
	Yes	No	Yes	No	Yes	No
OS	7 (20)	43 (29)	28 (80)	106 (71)	NA (A, A)	16 (9, A)

A, value cannot be estimated due to censored data.



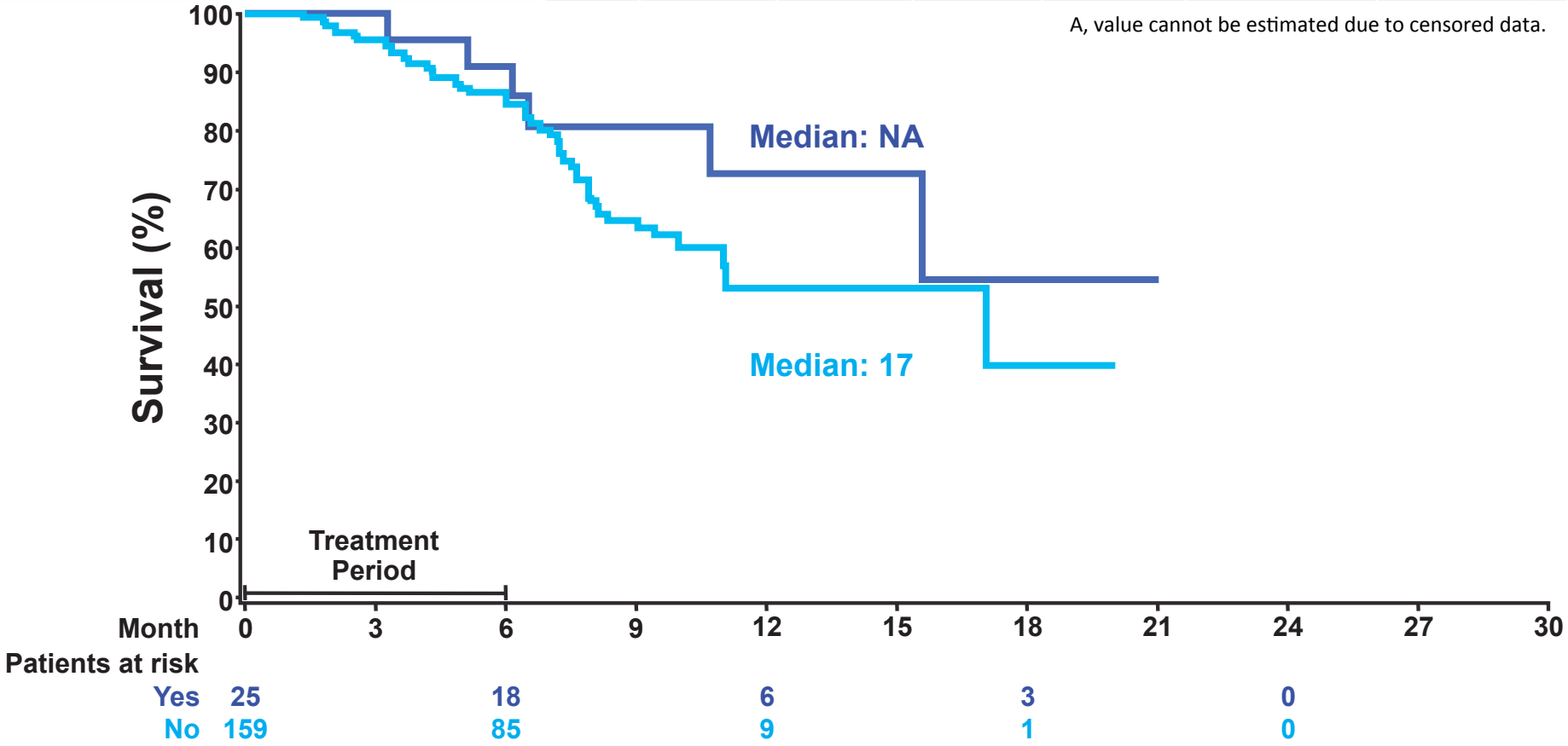
Grade 3 to 5 TEAEs of Interest: Concurrent Enzalutamide Use

	During Treatment Period	
	Not Concurrent With Enzalutamide (n=169)	Concurrent With Enzalutamide (n=15)
TEAEs		
Hematologic, n (%)		
Anemia	19 (11)	2 (13)
Neutropenia	2 (1)	0 (0)
Thrombocytopenia	5 (3)	0 (0)
Nonhematologic, n (%)		
Diarrhea	1 (1)	0 (0)
Fatigue	4 (2)	0 (0)
Bone pain	4 (2)	0 (0)

Exploratory Analyses: OS by Current Use of Enzalutamide

	n (%) of Patients With Event		n (%) of Patients Censored		Median Time to First Event, mo (95% CI)	
	Yes	No	Yes	No	Yes	No
OS	6 (24)	44 (27)	19 (76)	115 (72)	NA (11, A)	17 (10, A)

A, value cannot be estimated due to censored data.



Saad F, et al. Radium-223 in an International Early Access Program (EAP): Effects of Concomitant Medication on Overall Survival in mCRPC (ASCO 2015, Abstract 5063)

Radium-223 in an international early access program (EAP): Effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients

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Abstract 5034

BACKGROUND

- Radium-223 dichloride (Ra-223) is the first α-particle emitting bone-targeting agent approved for use in mCRPC patients with bone metastases and no known visceral metastases.
- In the pivotal ALSYMPCA study,[1] treating mCRPC patients with symptomatic bone metastases with Ra-223 and best standard of care (BSoC) compared with placebo and BSoC:
  - Improved overall survival (OS, median 14.9 vs 11.3 months, hazard ratio=0.70; p<0.001)[1]
  - Delayed time to first symptomatic skeletal event (SSE)[2]
  - Was generally well tolerated with minimal hematological toxicity reported.
- Safety and efficacy data of Ra-223 are presented from an EAP in which Ra-223 was administered to patients enrolled from sites in Canada, Europe, and Israel.

STUDY OBJECTIVES

- Primary outcome measures were safety and OS.
- Planned exploratory analyses included:
  - Time to first skeletal related event (SRE)
  - Changes in total alkaline phosphatase (ALP) activity and prostate specific antigen (PSA) levels from baseline
  - Time to ALP/PSA progression.
- Post hoc analyses included OS in subgroups based on:
  - Concomitant medication at baseline (abiraterone, enzalutamide, docetaxel, denosumab and bisphosphonates)
  - Baseline tota ALP values
  - Baseline Eastern Cooperative Oncology Group performance status (ECOG PS)
  - Baseline pain.

PATIENTS AND METHODS

- This was a phase 3b, international, prospective, interventional, open-label, multicenter EAP (Figure 1).
- Eligibility criteria were generally similar to those in the ALSYMPCA study with the exception that asymptomatic patients were allowed in the EAP.
- Analysis of variables was by descriptive statistics.
- The study was terminated on regulatory approval of Ra-223. Follow-up was 30 days from the last patient treated.

Figure 1. Study design

*BSoC according to local clinical practice. If chemotherapy/radiotherapy is considered BSoC, Ra-223 must be discontinued. †Adverse events were coded according to MedDRA version 17.1 and graded by NCI CTCAE version 4.03.

ALP=alkaline phosphatase; CRCHRPC=castration-resistant prostate cancer/hormone-resistant prostate cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; MedDRA=medical dictionary for regulatory activities; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PSA=prostate specific antigen; OS=overall survival; q4w=every 4 weeks; QoL (EPI-SF)=quality of life (by brief pain inventory short form); SRE=skeletal related events; SAEs=serious adverse events; TEAEs=treatment emergent adverse events.

RESULTS

Patients

- 839 patients were enrolled from 113 sites in 14 countries, of which 696 were treated with ≥1 dose of Ra-223 (safety population, Figure 2).
- Patient baseline characteristics in the EAP were generally similar to those for patients treated in the ALSYMPCA study except for pain at baseline and prior and concurrent treatment (Table 1).

Figure 2. Patient disposition in the Ra-223 EAP

AEs=adverse events; PD=progressive disease.

Table 1. Patient baseline characteristics

Characteristic	EAP N=696	ALSYMPCA N=614*
Age, years		
Median (range)	72 (45-94)	71 (49-90)
≥65	565 (81)	456 (74)
Median weight, kg (range)	81 (49-155)	82 (40-139)
ECOG PS ≤1	609 (88)	536 (87)
Gleason score at diagnosis		
2–4	16 (2)	7 (1)
5–7	288 (38)	274 (45)
8–10	350 (50)	261 (43)
Missing	62 (9)	72 (12)
Median time since PC diagnosis, mos (range)	(n=552) 64.5 (2-287)	(n=543) 59 (8-312)
Median time since BM diagnosis, mos (range)	(n=524) 26.1 (0-303)	(n=538) 24.8 (0-254.2)
Median PSA, µg/L (range)	141 (0-12150)	146 (3.8-6026)
ALP		
<220 U/L	431 (62)	348 (57)
≥220 U/L	263 (38)	266 (43)
Missing	2 (<1)	0
Pain at baseline†		
None	146 (21)	12 (2)
Mild-moderate	360 (52)	406 (66)
Severe	163 (23)	194 (32)
Missing	27 (4)	0
Prior use of docetaxel	418 (60)	352 (57)
Concomitant use of		
Bisphosphonates	122 (18)	250 (41)
Denosumab	138 (20)	NA
Abiraterone	156 (22)	NA
Enzalutamide	30 (4)	NA
Prior radiotherapy	490 (70)	306 (50)
Prior systemic anticancer therapy	677 (97)	NA

Data are n (%) unless otherwise stated.
*ALSYMPCA intention to treat population randomly assigned to Ra-223. †Measured by the Brief Pain Inventory Short Form (BPI-SF question 3 "Worst pain in the last 24 hours." Scores: no pain=0, mild-moderate pain=1 to 6, and severe pain=7 to 10).
ALP=total alkaline phosphatase; BM=bone metastases; ECOG PS=Eastern Cooperative Oncology Group performance status; mos=months; NA=not available; PC=prostate cancer; PSA=prostate specific antigen

- In the EAP and ALSYMPCA study the median number of Ra-223 injections was 6, 58% and 63% of patients received all 6 injections respectively.

Safety

- Safety profiles in the EAP and ALSYMPCA study were generally comparable (Tables 2 & 3).

Table 2. Summary of safety data

TEAEs, n (%)	EAP N=696	ALSYMPCA N=600*
At least one	522 (75)	556 (93)
Grade 3 or 4	263 (38)	339 (57)
Grade 5†	47 (7)‡	97 (16)
Any serious TEAEs	243 (35)	261 (47)
TEAEs leading to dose modifications	53 (8)	65 (11)
TEAEs leading to permanent discontinuation	144 (21)	99 (17)

*ALSYMPCA safety population. †Deaths reported as TEAEs during the treatment period.
TEAEs=treatment emergent adverse events.

Table 3. Summary of most common TEAEs*

TEAEs, n (%)	EAP N=696		ALSYMPCA N=600†	
	All grades	Grade 3/4	All grades	Grade 3/4
Anemia	140 (20)	74 (11)	187 (31)	76 (13)
Bone pain	108 (16)	29 (4)	300 (50)	125 (21)
Nausea	91 (13)	2 (<1)	213 (36)	10 (2)
Diarrhea	79 (11)	4 (<1)	151 (25)	9 (2)
Fatigue	67 (10)	13 (2)	154 (26)	24 (4)
Decreased appetite	50 (7)	3 (<1)	35 (6)	2 (<1)
Back pain	50 (7)	20 (3)	9 (2)	3 (<1)
Weight decreased	49 (7)	5 (<1)	69 (12)	4 (<1)
Vomiting	42 (6)	8 (1)	110 (18)	10 (2)
GPHD	33 (5)	14 (2)	27 (5)	11 (2)

*Occurring in ≥5% of patients in the EAP. †ALSYMPCA safety population.
GPHD=general physical health deterioration; TEAEs=treatment emergent adverse events

Efficacy

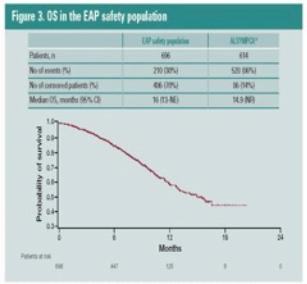
- Efficacy data from the EAP and the ALSYMPCA study are summarized in Table 4.
- Due to a shorter follow-up more patients were censored in the EAP than the ALSYMPCA study.
- In the EAP median OS was 16 months and was comparable with that reported in the ALSYMPCA study (Figure 3).
- In post hoc analyses of EAP patients grouped by baseline characteristics:
  - OS was statistically significantly longer in patients with an ALP level of <220 U/L (vs ≥220 U/L), no pain (vs any pain) or who had an ECOG PS 0–1 (vs ≥2), (Figures 4–6)
  - OS was statistically significantly longer for patients treated with concomitant abiraterone (vs no abiraterone, Figure 7) or denosumab (vs no denosumab, Figure 8).

Table 4. Summary of efficacy data

Parameter	EAP N=696	ALSYMPCA N=614*
Median OS, mos (95% CI)	16 (13-NE)	14.9 (NR)
Median time to first SRE, mos (95% CI)	19 (17-NE)	15.6 (13.5-18.0)
Median time, mos (95% CI),		
To disease progression†	6 (6-6)	NA
To ALP progression	8 (NE-NE)	7.4 (NR)
To PSA progression	4 (3-4)	3.6 (NR)
≥50% confirmed ALP decrease from BL, n (%)	165 (24)	135 (27)‡
≥50% confirmed PSA decrease from BL, n (%)	57 (8)	36 (8)‡

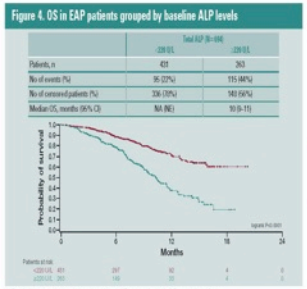
*ALSYMPCA ITT population randomly assigned to Ra-223. †Assessed according to methods of best standard of care at each study site. ‡Based on number of patients with complete data.
ALP=total alkaline phosphatase; BL=baseline; ITT=intention to treat; mos=months; OS=overall survival; SRE=skeletal-related events; NA=not available; NE=not estimated; NR=not reported.

Figure 3. OS in the EAP safety population



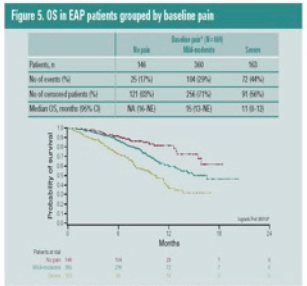
*Presented for comparison, the ALSYMPCA intention to treat population randomly assigned to Ra-223.
NE=not estimated; NR=not reported; OS=overall survival.

Figure 4. OS in EAP patients grouped by baseline ALP levels



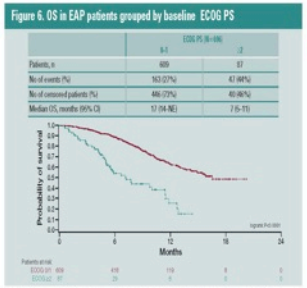
ALP=alkaline phosphatase; NA=not achieved; NE=not estimated; OS=overall survival.

Figure 5. OS in EAP patients grouped by baseline pain



*Measured by the Brief Pain Inventory Short Form (BPI-SF question 3 "Worst pain in the last 24 hours." Scores: no pain=0, mild-moderate pain=1 to 6, and severe pain=7 to 10). †No vs all pain.
NA=not achieved; NE=not estimated; OS=overall survival.

Figure 6. OS in EAP patients grouped by baseline ECOG PS

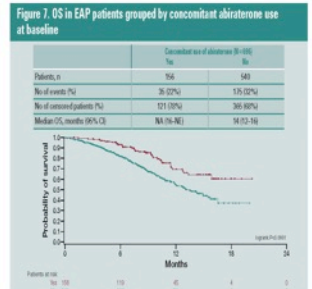


ECOG PS=Eastern Cooperative Oncology Group performance status; NE=not estimated; OS=overall survival.

CONCLUSIONS

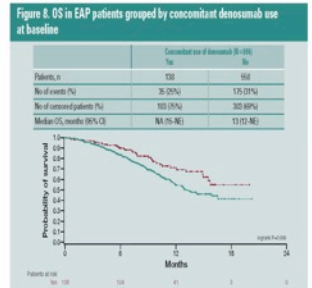
- In an EAP setting in mCRPC patients with bone metastases, Ra-223 was generally well tolerated with no new safety concerns compared with those treated in a randomized placebo controlled clinical trial.
- In post hoc analyses OS was longer in patients who were asymptomatic or had ECOG PS of 0–1 or ALP levels <220 U/L.
- Data from post hoc analyses revealing improved OS in patients treated with Ra-223 and concomitant denosumab or abiraterone are preliminary. These findings warrant further investigation of these treatment combinations in clinical trials.

Figure 7. OS in EAP patients grouped by concomitant abiraterone use at baseline



NA=not achieved; NE=not estimated; OS=overall survival.

Figure 8. OS in EAP patients grouped by concomitant denosumab use at baseline



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REFERENCES

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ACKNOWLEDGMENTS

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RADIUM 223 International EAP
International Expanded Access Program

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*BSoC according to local clinical practice. If chemotherapy/radiotherapy is considered BSoC, Ra-223 must be discontinued. †Adverse events were coded according to MedDRA version 17.1 and graded by NCI CTCAE version 4.03.

ALP=alkaline phosphatase; CRCHRPC=castration-resistant prostate cancer; hormone-resistant prostate cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; MedDRA=medical dictionary for regulatory activities; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PSA=prostate specific antigen; OS=overall survival; q4w=every 4 weeks; QoL (EPI-SF)=quality of life (by brief pain inventory short form); SREs=skeletal related events; SAEs=serious adverse events; TEAEs=treatment emergent adverse events.

Bisphosphonates	122 (18)	250 (41)
Denosumab	138 (20)	NA
Abiraterone	156 (22)	NA
Enzalutamide	1	NA
Prior radiotherapy	490 (70)	306 (50)
Prior systemic anticancer therapy	677 (97)	NA

Data are n (%) unless otherwise stated.
‡ALSYMPCA intention to treat population randomly assigned to Ra-223. §Measured by the Brief Pain Inventory Short Form (BPI-SF question 3 "Worst pain in the last 24 hours." Scores: no pain=0, mild-moderate pain=1 to 6, and severe pain=7 to 10).
ALP=total alkaline phosphatase; BM=bone metastases; ECOG PS=Eastern Cooperative Oncology Group performance status; mos=months; NA=not available; PC=prostate cancer; PSA=prostate specific antigen

- In post hoc analyses of EAP patients grouped by baseline characteristics:
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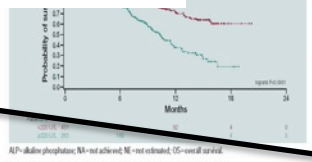

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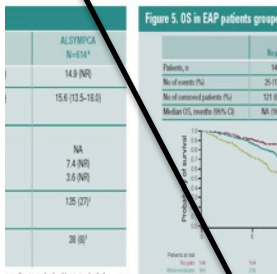

Figure 5. OS in EAP patients grouped by baseline pain

	No pain	Mild-moderate	Severe
Patients, n	146	360	163
No of events (%)	25 (17%)	104 (29%)	72 (44%)
No of censored patients (%)	121 (83%)	256 (71%)	91 (56%)
Median OS, months (95% CI)	NA (16–NE)	15 (13–NE)	11 (8–13)

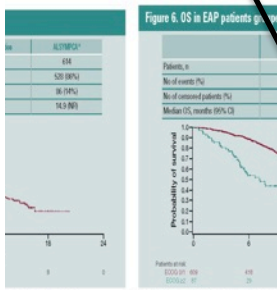

Figure 6. OS in EAP patients grouped by baseline ECOG PS

	ECOG PS 0–1	ECOG PS ≥2
Patients, n	459	87
No of events (%)	412 (90%)	41 (47%)
No of censored patients (%)	46 (10%)	46 (53%)
Median OS, months (95% CI)	17 (14–NE)	7 (5–11)

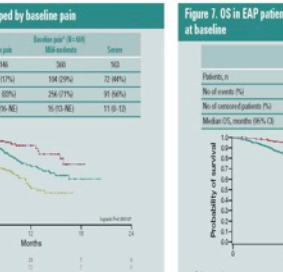

Figure 7. OS in EAP patients grouped by concomitant abiraterone use at baseline

	Concomitant use of abiraterone: Yes	No
Patients, n	156	569
No of events (%)	35 (22%)	135 (24%)
No of censored patients (%)	121 (78%)	365 (64%)
Median OS, months (95% CI)	NA (16–NE)	14 (12–16)

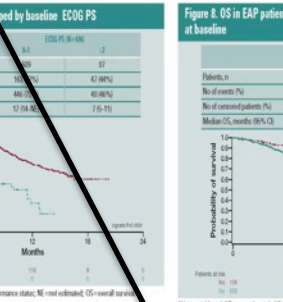

Figure 8. OS in EAP patients grouped by concomitant denosumab use at baseline

	Concomitant use of denosumab: Yes	No
Patients, n	138	160
No of events (%)	35 (25%)	135 (31%)
No of censored patients (%)	103 (75%)	365 (69%)
Median OS, months (95% CI)	NA (16–NE)	13 (12–NE)

NA=not achieved; NE=not estimated; OS=overall survival.

CONCLUSIONS

- In an EAP setting in mCRPC patients with bone metastases, Ra-223 was generally well tolerated with no new safety concerns compared with those treated in a randomized placebo controlled clinical trial.
- In post hoc analyses OS was longer in patients who were asymptomatic or had ECOG PS of 0–1 or ALP levels <220 U/L.
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RADIUM 223 International EAP
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Summary of patient enrollment*

Countries	Number of sites	Number of patients enrolled	Number of patients treated
Germany	20	155	124
United Kingdom	8	44	31
Poland	2	11	10
Italy	13	56	48
Spain	19	117	90
Canada	5	29	21
Belgium	5	12	11
Netherlands	2	18	16
Sweden	10	110	95
Norway	5	55	54
Israel	8	101	84
Switzerland	8	52	48
Finland	5	44	38
Ireland	3	35	26
Totals n=14	**113**	**839**	**696**

*Listed in order of ascending site number

Overview of EAP program

	US EAP	International EAP
Clinical study phase	2	3b
No. of patients (screened)	252	839
No. of patients (treated)	184	696
Patient diagnosis	**Symptomatic,** progressive, bone-predominant, metastatic CRPC/HRPC with ≥2 skeletal metastases on imaging with no lung, liver, and/or brain metastases (lymph node only metastasis allowed)	Progressive, bone-predominant, metastatic CRPC/HRPC with ≥2 skeletal metastases on imaging with no lung, liver, and/or brain metastases (lymph node only metastasis allowed)
Definition of symptomatic	Regular use of analgesics for cancer-related bone pain Treatment with EBRT for bone pain within last 12 weeks before treatment	Not applicable **Symptomatic disease is not a requirement of the study**
Primary variables	Acute (during treatment period up to 30 days post-treatment) and long-term (30 days post-treatment and onward) safety	Acute (during treatment period up to 30 days post-treatment) and long-term (30 days post-treatment and onward) safety **Overall survival**

CRPC, castration-resistant prostate cancer; EBRT, external beam radiation therapy; HRPC, hormone-resistant prostate cancer

SAFETY DATA

Summary of TEAEs

Adverse events*	Int EAP† N=696		ALSYMPCA N=901			
			Radium 223‡ (n=600)		Placebo (n=301)	
Patients with at least one TEAE	523	75%	558	93%	290	96%
Grade 3	232	33%	207	35%	121	40%
Grade 4	31	4%	53	9%	16	5%
Grade 5 (death)	34	5%	97	16%	66	22%
Any serious TEAE	243	35%	281	47%	181	60%
TEAEs leading to dose modifications§	53	8%	65	11%	35	11%
TEAEs leading to permanent discontinuation	144	21%	99	17%	62	21%
Patients with any treatment-related TEAE	281	40%	380	63%	171	57%
Grade 3	78	11%	82	14%	32	11%
Grade 4	8	1%	15	3%	2	1%
Grade 5 (AE that resulted in death)	1	<1%	7	1%	0	
Any serious related TEAEs	34	5%	72	12%	30	10%
Related leading to dose modifications§	18	3%	NA		NA	
Related leading to permanent discontinuation	38	5%	NA		NA	

Data are n, %; NA, not available

*Treatment emergent adverse events (TEAEs) were coded by System Organ Class and preferred term by MedDRA version 17.1, and graded by CTCAE version 4.03 in the EAP study and graded by CTCAE version 3 in the ALSYMPCA study; †Safety analysis set; ‡Safety population; §Including interruptions

Treatment-related AEs of interest

SOC/preferred term	Int-EAP* N=696								ALSYMPCA† (Radium 223 arm) N=600							
	Any grade		Grade 3		Grade 4		Grade 5		Any grade		Grade 3		Grade 4		Grade 5	
Blood and lymphatic system	82	12%	38	5%	6	<1%	0		139	23%	52	9%	17	3%	1	<1%
Anemia	65	9%	30	4%	0		0		109	18%	45	8%	3	1%	0	
Thrombocytopenia	20	3%	7	1%	4	<1%	0		43	7%	12	2%	13	2%	1	<1%
Leukopenia	11	2%	3	<1%	0		0		18	3%	6	1%	1	<1%	NA	NA
Neutropenia	8	1%	4	<1%	1	<1%	0		23	4%	6	1%	2	<1%	NA	NA
Gastrointestinal disorders‡	136	20%	10	1%	0		1	<1%	233	38%	16	3%	0		1	<1%
Diarrhea	62	9%	3	<1%	0		0		97	16%	6	1%	0		NA	NA
Constipation	9	1%	1	<1%	0		0									

Data presented are n, %
*Safety analysis set; †Safety population; ‡All other preferred terms under this category were <1%
AE, adverse event; NA, not available; SOC, System Organ Class

TEAEs leading to discontinuation in ≥1% patients

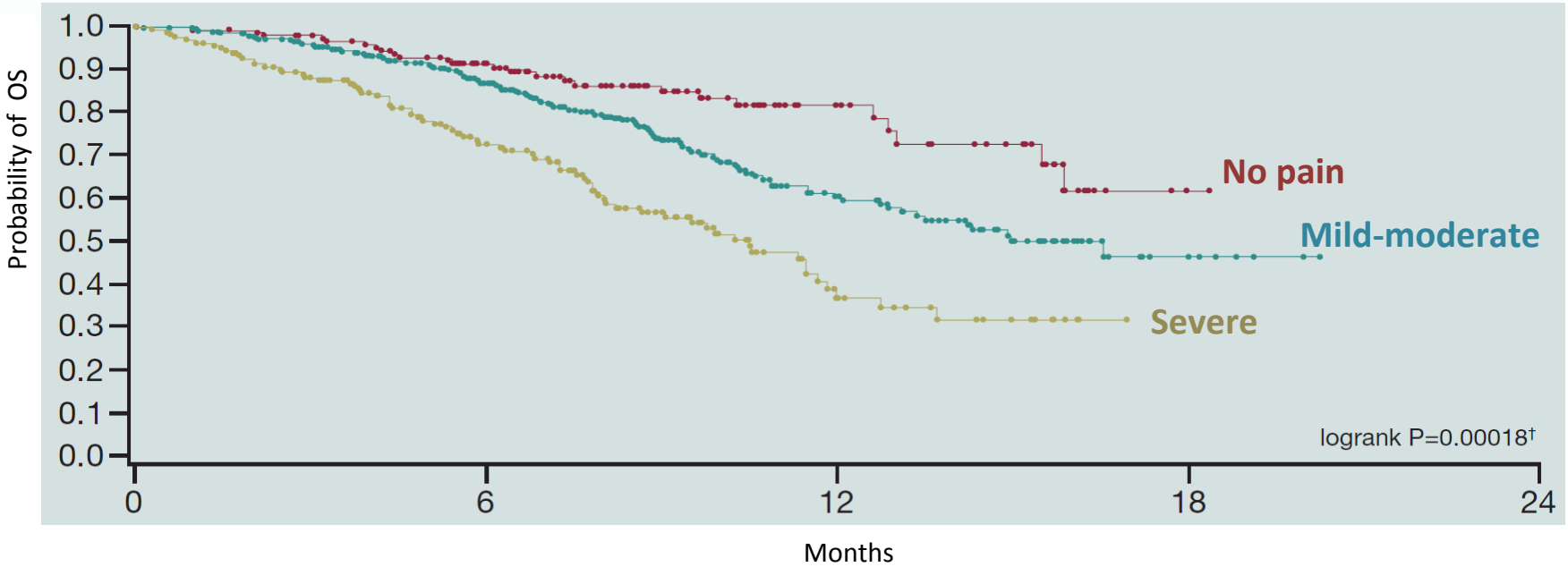
Preferred term	Int EAP* N=696		ALSYMPCA (Radium 223 arm)† N=600	
Any event	144	21%	99	17%
Anemia	15	2%	14	2%
Thrombocytopenia	11	2%	10	2%
Neutropenia	3	<1%	3	1%
Fatigue	1	<1%	5	1%
Bone pain	5	<1%	5	1%
Spinal cord compression	6	<1%	8	1%
Metastasis to the liver	NA		3	1%

Data presented are n, %
*Safety analysis set; †ITT population, data reported in Parker et al NEJM 2013; 369:213-22
NA, not available

EFFICACY ANALYSIS

In the INT EAP, overall survival was significantly longer for patients asymptomatic for pain

	Baseline pain (N=669)		
	No pain	Mild-moderate	Severe
Patients, n	146	360	163
No of events (%)	25 (17%)	104 (29%)	72 (44%)
No of censored patients (%)	121 (83%)	256 (71%)	91 (56%)
Median OS, months (95% CI)	NA (16–NE)	15 (13–NE)	11 (8–12)



No pain	146	104	29	1	0
Mild-moderate	360	236	72	7	0
Severe	163	90	19	0	0

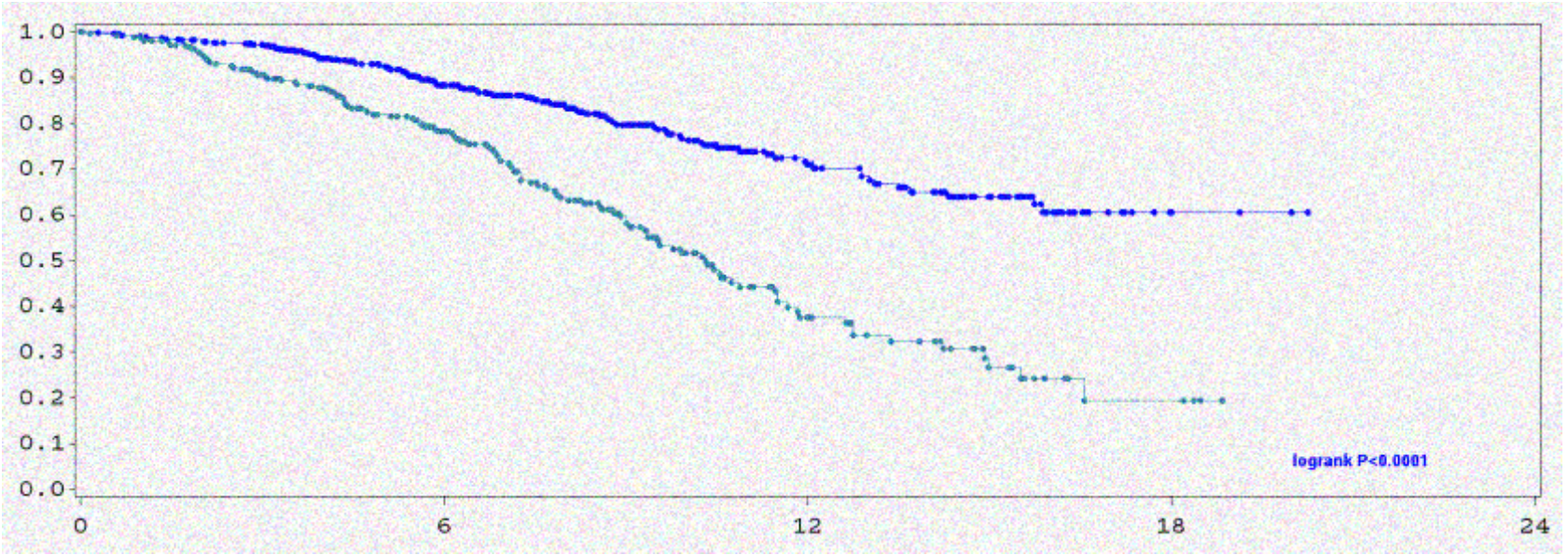
*Measured by the Brief Pain Inventory Short Form (BPI-SF question 3 "Worst pain in the last 24 hours." Scores: no pain=0, mild–moderate pain=1 to 6, and severe pain=7 to 10). †No vs all pain.

NA: not achieved; NE: not estimated; OS: overall survival.

1. Saad F,et al. ASCO 2015, Abs 5034.

Overall survival by total ALP*

	Total ALP (N=694)	
	<220 U/L	≥220 U/L
Patients, n	431	263
No of events (%)	95 (22%)	115 (44%)
No of censored patients (%)	336 (78%)	148 (56%)
Median OS, months (95% CI)	NA (NE)	10 (9–11)



Patients at risk

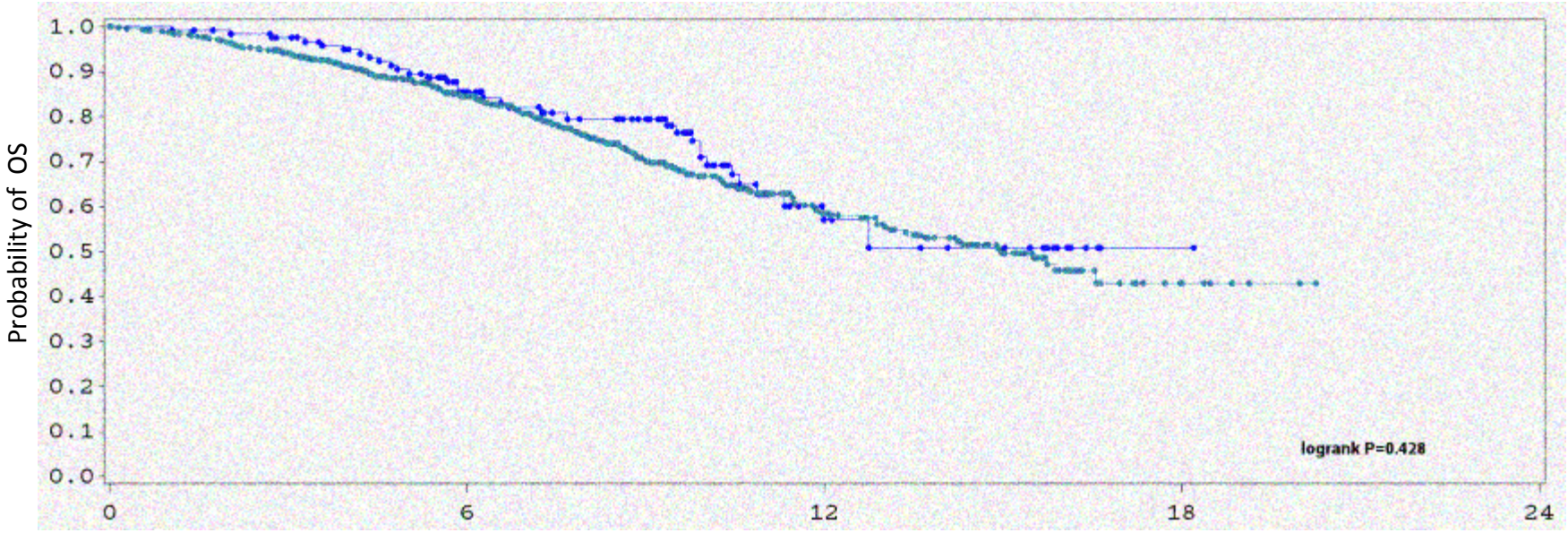
<220 U/L	431	297	92	4	0
≥220 U/L	263	149	33	4	0

*Post hoc analysis

ALP, alkaline phosphatase; NA, not available; NE, not estimated (due to censored data); OS, overall survival

Overall survival by current use of bisphosphonates*

	Current use of bisphosphonates (N=696)	
	Yes	No
Patients, n	122	574
No of events (%)	34 (28%)	176 (31%)
No of censored patients (%)	88 (72%)	398 (69%)
Median OS, months (95% CI)	NA (11–NE)	15 (13–NE)



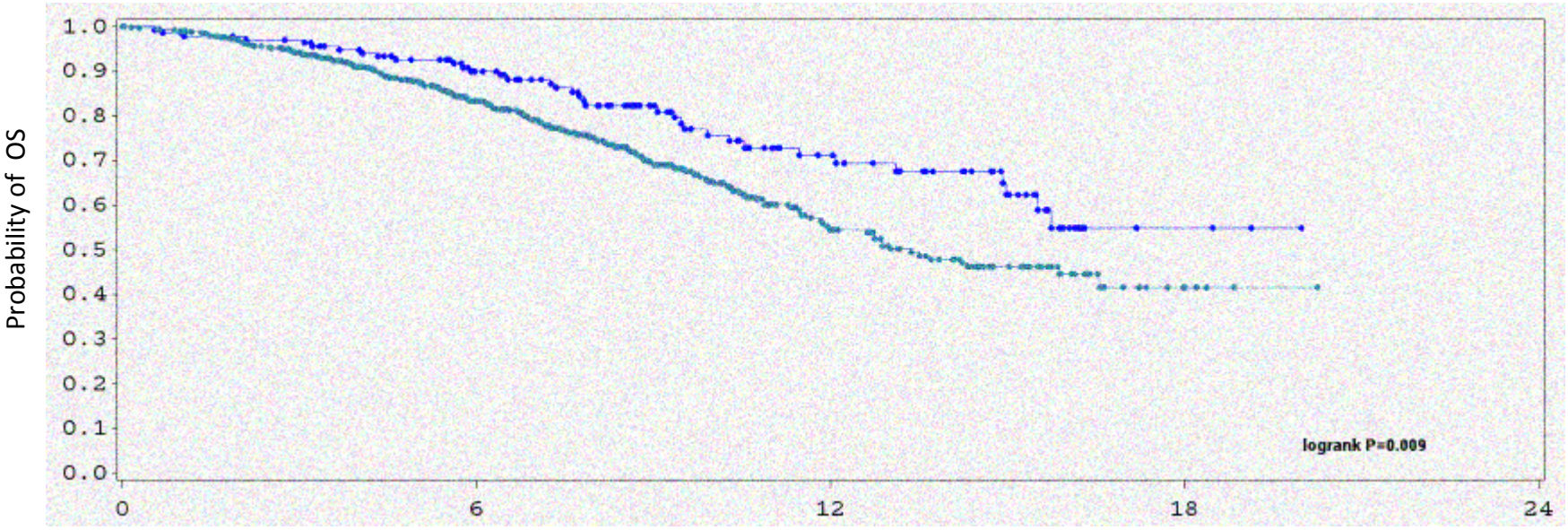
Patients at risk					
Yes	122	78	19	1	0
No	574	369	106	7	0

*Post hoc analysis

NA, not available; NE, not estimated (due to censored data); OS, overall survival

Overall survival by current use of denosumab*

	Current use of denosumab (N=696)	
	Yes	No
Patients, n	138	558
No of events (%)	35 (25%)	175 (31%)
No of censored patients (%)	103 (75%)	383 (69%)
Median OS, months (95% CI)	NA (15–NE)	13 (12–NE)



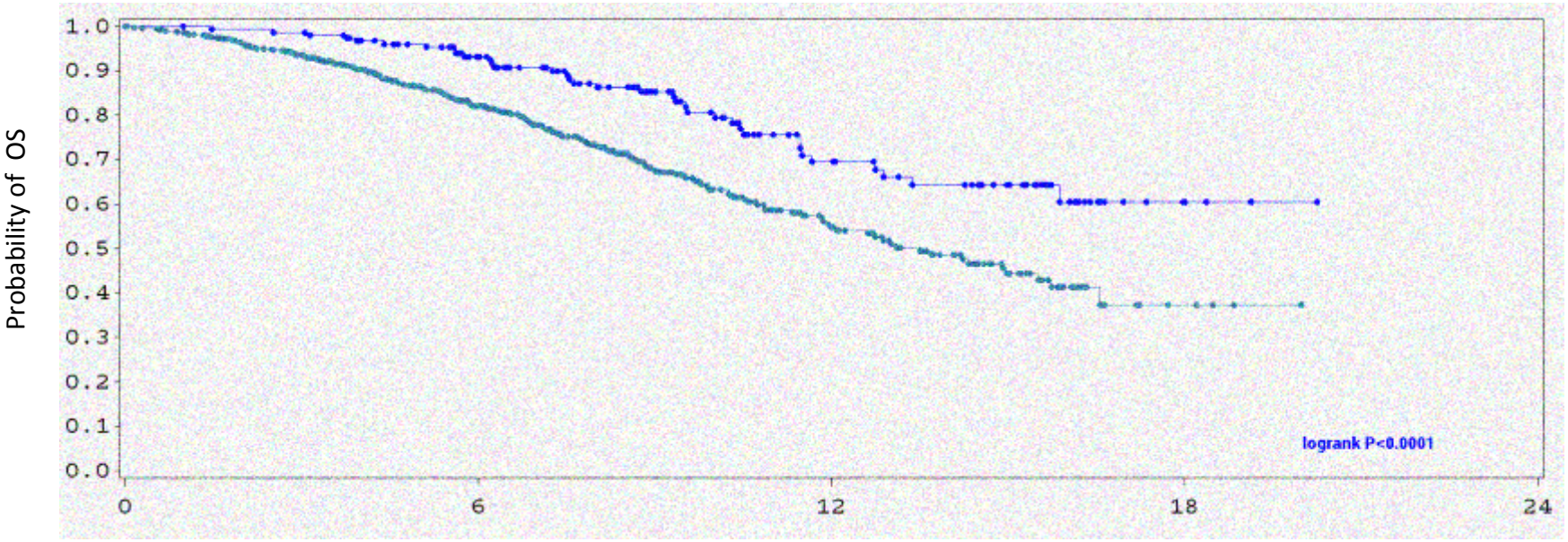
Patients at risk					
Yes	138	104	41	3	0
No	558	343	84	5	0

*Post hoc analysis

NA, not available; NE, not estimated (due to censored data); OS, overall survival

Overall survival by current use of abiraterone*

	Current use of abiraterone (N=696)	
	Yes	No
Patients, n	156	540
No of events (%)	35 (22%)	175 (32%)
No of censored patients (%)	121 (78%)	365 (68%)
Median OS, months (95% CI)	NA (16–NE)	14 (12–16)



Patients at risk

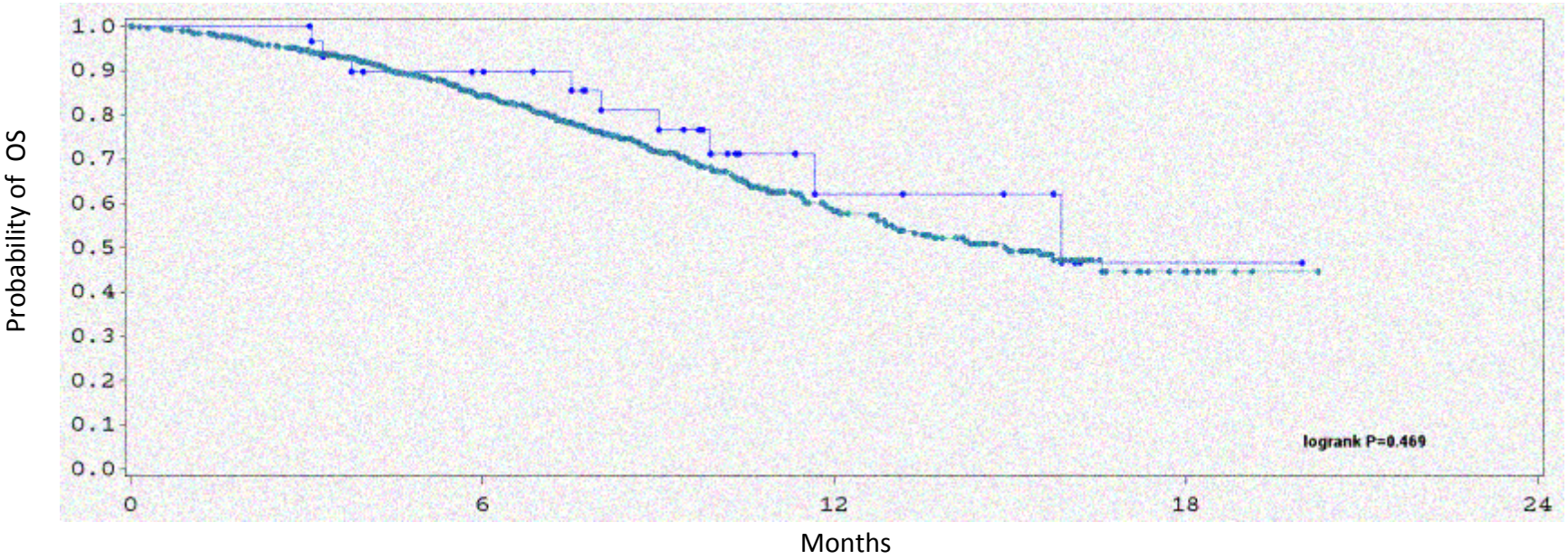
Yes	156	119	45	4	0
No	540	328	80	4	0

*Post hoc analysis

NA, not available; NE, not estimated (due to censored data); OS, overall survival

Overall survival by current use of enzalutamide*

	Current use of enzalutamide (N=696)	
	Yes	No
Patients, n	30	666
No of events (%)	9 (30%)	201 (30%)
No of censored patients (%)	21 (70%)	465 (70%)
Median OS, months (95% CI)	16 (10–NE)	15 (13–NE)



Patients at risk

Yes	30	24	7	1	0
No	666	423	118	7	0

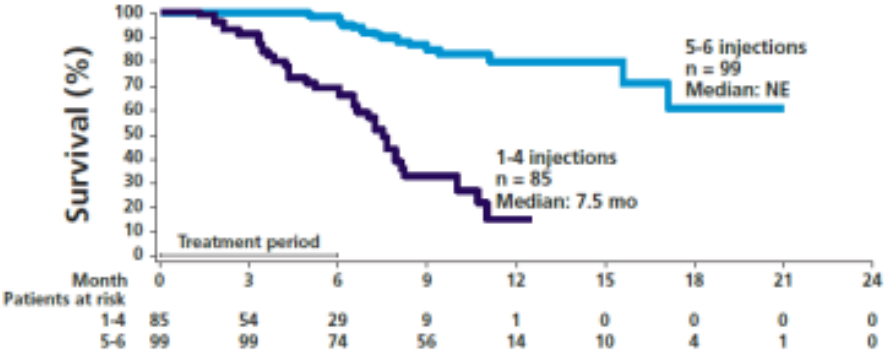
*Post hoc analysis

NA, not available; NE, not estimated (due to censored data); OS, overall survival

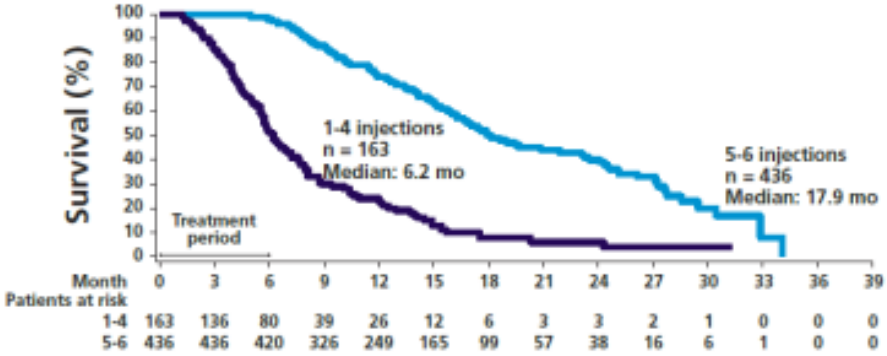
US EAP and ALSYMPSA Update: Median OS appeared to correlate with number of radium-223 injections received

- In both US EAP and ALSYMPCA, median OS appeared to be prolonged in patients receiving 5-6 vs 1-4 injections of radium-223

US EAP: Radium-223 Patients Who Received 1-4 vs 5-6 Injections



ALSYMPCA: Radium-223 Patients Who Received 1-4 vs 5-6 Injections



US, United States; EAP, expanded access program; ALSYMPCA: ALpharadin in SYMptomatic Prostate Cancer; OS, overall survival; NE, not estimable.

Sartor O, et al. Baseline characteristics, number of radium-223 injections, and overall survival in US Expanded Access Program and ALSYMPCA. In: Proceedings of the 18th European Cancer Congress; Sept 25-29, 2015; Vienna, Austria. Abstract 2530.

Summary

- This post hoc subgroup analysis in US EAP and ALSYMPCA patients receiving 1-4 vs 5-6 injections of radium-223 suggests
  - Patients with more advanced CRPC and symptomatic bone metastases are less likely to receive the recommended 6 injections of radium-223, the regimen associated with longer OS
    - US EAP: ≥3 prior anticancer therapies, baseline ECOG PS ≥2, lower baseline hemoglobin
    - ALSYMPCA: higher log LDH, lower albumin, baseline ECOG PS ≥2, and higher log PSA

US, United States; EAP, expanded access program; ALSYMPCA: ALpharadin in SYMptomatic Prostate Cancer; CRPC, castration resistant prostate cancer; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

Sartor O, et al. Baseline characteristics, number of radium-223 injections, and overall survival in US Expanded Access Program and ALSYMPCA. In: Proceedings of the 18th European Cancer Congress; Sept 25-29, 2015; Vienna, Austria. Abstract 2530.

Interim Results from eRADicAte: an Open-Label Phase 2 Study of Radium Ra 223 dichloride with Concurrent Administration of Abiraterone Acetate Plus Prednisone in Castration-Resistant Prostate Cancer Subjects with Symptomatic Bone Metastases

Neal D. Shore,[1] Ronald F. Tutrone,[2] Neil F. Mariados,[3] Luke T. Nordquist,[4] Bryan A. Mehlhaff,[5] Stacey S. Harrelson,[1]

[1]Carolina Urologic Research Center, Myrtle Beach, SC, [2]Chesapeake Urology Research Associates, Towson, MD, [3]GU Research Network, Omaha, NE, [4]Associated Medical Professionals of NY, Syracuse, NY, [5]Oregon Urology Institute, Springfield, OR

INTRODUCTION AND OBJECTIVES

Radium Ra 223 dichloride (Ra-223), an intravenous α-emitting radioisotope, is a calcium mimetic, forming complexes with hydroxyapatite at sites of bone metastases (mets) for castration-resistant prostate cancer (CRPC) patients.

Abiraterone Acetate (AA), an oral androgen receptor inhibitor, decreases serum testosterone for CRPC patients.

Potential synergy of their respective mechanisms of action exists in combining Ra-223 and AA plus prednisone. In addition to this study, an evidence-based approach to assess the consequences of the combined treatment is ongoing in a large phase 3 study. The combination potentially optimizes the benefits of these agents within the therapeutic paradigm for patients with symptomatic metastatic castrate resistant prostate cancer (mCRPC).

This prospective study evaluates the combinatorial use of concurrent Ra-223 and AA plus prednisone in CRPC patients with symptomatic bone metastases in both the pre- and post- chemotherapy settings. Both survival prolonging therapeutics are approved by the US Food and Drug Administration for this indication.

BACKGROUND

Abiraterone Acetate

Abiraterone Acetate (an androgen receptor inhibitor) plus prednisone delays patient-reported pain progression and [health-related quality-of-life] deterioration in patients with metastatic castration-resistant prostate cancer, as well as demonstrates a survival benefit. [1,2]

Radium Ra 223 Dichloride

Radium-223 dichloride (radium-223), a targeted α-emitter, improves overall survival and is well tolerated in patients with symptomatic castration-resistant prostate cancer with bone metastases.[3]

Statistical analysis provided by :
Department of Data Management & Statistical Analysis, American Urological Association, Linthicum, MD, USA.

METHODS

eRADicAte is an open-label, phase 2 prospective study (NCT02097303) of subjects with symptomatic bone mCRPC without visceral metastases conducted over approximately 8 months. All subjects are treated with Rad-223 every 4 weeks x 6 doses and concurrent AA plus prednisone BID.

The protocol defined primary efficacy outcome is QOL and bone pain assessments tracked using BPI-SF and FACT-P questionnaires.

Secondary endpoints include:

- Safety
- Time to measurable disease progression and SREs
- PSA and ALP progression
- Progression to further antineoplastic therapy
- Performance status (ECOG) changes

All adverse events and safety analysis are reported and performed from the first Rad-223 infusion through the End of Treatment visit for subjects who have received at least one infusion of Ra-223 . Subjects are assessed at screening, weeks 1, 5, 9, 13, 17, 21 and 25. Time to event variables are summarized using the Kaplan-Meier methodology to estimate the median, 25th and 75th percentiles and the minimum and maximum times to events.

RESULTS

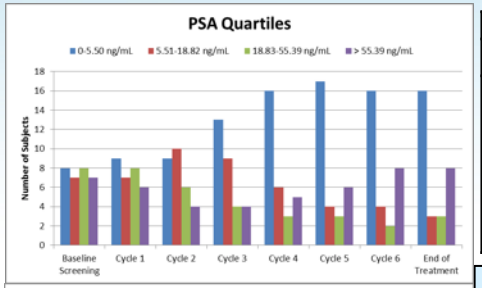
Of the 36 subjects enrolled, 30 have received all 6 cycles of Rad-223 with concurrent AA and completed the end of treatment visit, and are thus evaluable at this time.

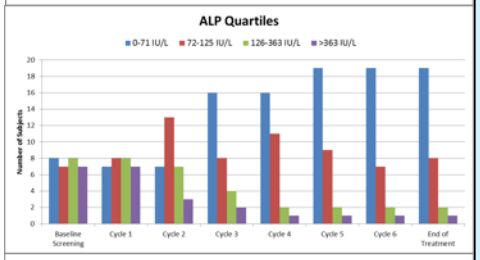
Bone pain assessments:

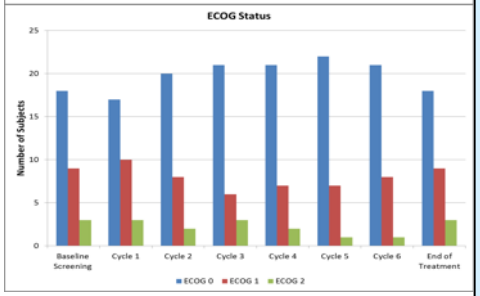
- **Subjects have reported an overall decrease in reported bone pain from the screening visit through the end of the study visit.**
- **Significant decreases are also seen in the amount of bone pain that interferes with: Work, General activity, and Mood.**
- **Per the BPI-SF scores, subjects have experienced No significant increases in how pain interferes with daily their lives.**
- **The Brief Pain Inventory table shows a significant decrease (p = 0.014) in self assessed average bone pain during this period.**

Quality of life assessments:

- **There have been significant increases in quality of life measures from the screening visit through the end of study visit**
- **Subjects have reported less pain, less life interferences and increased sleep quality**







Brief Pain Inventory (Short form) Results

Variable	Screening Rating	End of Treatment Rating	Change	p-value
BPI Worst	3.4	2.5	-0.9	0.134
BPI Least	2.1	1.6	-0.5	0.234
BPI Average	3.0	1.9	-1.0	**0.014**
BPI Now	1.8	1.3	-0.5	0.267
BPI Active	2.7	1.5	-1.3	**0.013**
BPI Mood	2.3	1.4	-0.9	**0.045**
BPI Walk	2.5	2.2	-0.3	0.343
BPI Work	2.9	2.1	-0.8	**0.019**
BPI Relate	1.7	1.3	-0.4	0.263
BPI Sleep	2.4	1.5	-0.8	0.128

BPI Values range from 0 to 10

Clinically Significant Abnormalities

Cycle	ALP	Potassium	AST	ALT	Hgb	WBC	PLT
Screening	0	0	0	0	0	0	0
Cycle 1/Week 1	0	0	1	1	0	0	0
Cycle 2/Week 5	1	0	0	0	0	0	0
Cycle 3/Week 9	0	0	0	0	1	1	0
Cycle 4/Week 13	0	0	0	0	0	0	0
Cycle 5/Week 17	0	0	1	0	1	0	0
Cycle 6/Week 21	0	0	0	0	0	1	0
End of Treatment	0	0	0	0	1	1	0

CONCLUSIONS

The primary purpose of the **eRADicAte** study is to evaluate the combined treatment regimen: Rad-223 with concurrent AA plus prednisone. 30 of the 36 subjects enrolled have received all 6 cycles of Rad-223 and completed the EOT visit, and are thus evaluable. This is an interim report.

eRADicAte subjects experienced improvements in both of the chosen efficacy end points:

- **Decreased bone pain**
- **Improved quality of life**

eRADicAte subjects also demonstrated:

- **Stability in ECOG scores**
- **A paucity of clinically significant serological parameters associated with these 2 therapeutics**

References

1. Ryan AJ et al. N Engl J Med 2013; 368: 138-148.
2. Basch E et al. Lancet Oncol 2013; 14: 1193-1199.
3. Nilsson S et al. Clin Adv Hematol Oncol 2014; 14: 12(4 Suppl 11):9-10.

Poster presented at the 2016 American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO-GU) in San Francisco, CA, USA, January 7–9, 2016

This Investigator Initiated Study was funded by Bayer HealthCare Pharmaceuticals

Randomized open label phase II trial of radium-223 with concurrent administration of abiraterone acetate plus prednisone in symptomatic CRPC patients with bone metastasis (eRADicAte)

Principal Investigator: Neal Shore
Sponsor: Carolina Research Professionals, Myrtle Beach, SC
NCT02097303

17355 – Shore

Randomized open label phase II trial of radium-223 with concurrent administration of abiraterone acetate plus prednisone in symptomatic CRPC patients with bone metastasis (N=30 - Actual=36)

Study objectives	**Primary endpoints:** To investigate the efficacy of concurrent treatment with Radium Ra 223 dichloride and Abiraterone Acetate (AA) plus Prednisone. Efficacy will be assessed by tracking bone pain assessments and quality of life questionnaires. **Secondary endpoints:** To measure safety, time to measurable disease progression, SREs, PSA progression, Changes and time to total ALP progression, progression to additional neoplastic therapy

First Author: Neal Shore
ASCO GU Abstract #: 177, Poster Board: G12, Jan 7th, poster session A

17355 – Shore
Methods

In this open-label, phase 2 study, 36 patients with symptomatic bone mCRPC with no visceral mets were enrolled. All evaluable patients are treated with Rad-223 every 4 weeks x6 doses, and concomitant AA 1000mg + prednisone 5 mg BID.

The primary endpoint is efficacy, assessed by tracking bone pain assessments and quality of life (QoL) using BPI-SF and FACT-P questionnaires.

Secondary endpoints include:

- Safety
- Time to measurable disease progression and SREs
- PSA and ALP progression
- Progression to further antineoplastic therapy
- Performance status (ECOG) changes

First Author: Neal Shore
ASCO GU Abstract #: 177, Poster Board: G12, Jan 7th, poster session A

At interim analysis, subjects in this study experienced improvements in both of the chosen efficacy assessments:

- a decrease in bone pain
- an improvement in their quality of life

Treatment of symptomatic bone mCRPC subjects with concurrent Rad-223 and AA plus prednisone has also demonstrated:

- a stability in ECOG scores
- A paucity of clinically significant serological parameters associated with these 2 therapeutics

17355 – Shore
Safety results

- The combined treatment has not produced significant adverse events that can be directly linked to the combined treatment regimen. Thus far, any observed adverse events occurred after 2 months of treatment, on average.

- None of the evaluable subjects have progressed nor require further treatment during the trial

- Subjects did not experience any SREs

3-Year Follow-up of Chemotherapy Following Radium-223 Dichloride in Castration-Resistant Prostate Cancer Patients With Symptomatic Bone Metastases From ALSYMPCA

Presented by: Neal Shore, MD
Carolina Urologic Research Center, Myrtle Beach, SC, USA

Overall Survival

- Similar proportions of radium-223 (41/142 [29%]) and placebo (21/64 [33%]) patients died during and within 30 days of completing chemotherapy
- Median OS from start of chemotherapy was 16.0 months post–radium-223 and 15.8 months post-placebo (HR = 1.23; 95% CI, 0.86-1.75)

Conclusions

- Safety of chemotherapy post–radium-223 assessed in post hoc analysis showed no detrimental effects on hematology or OS
- Findings indicate that chemotherapy can be administered safely after radium-223

Thank You