Caso Clinico

Giugno 2015

55 anni
Intensa lombo-sciatalgia dx - VAS 7-8
PSA 11.8 ng/dl **Testosterone** 4.1

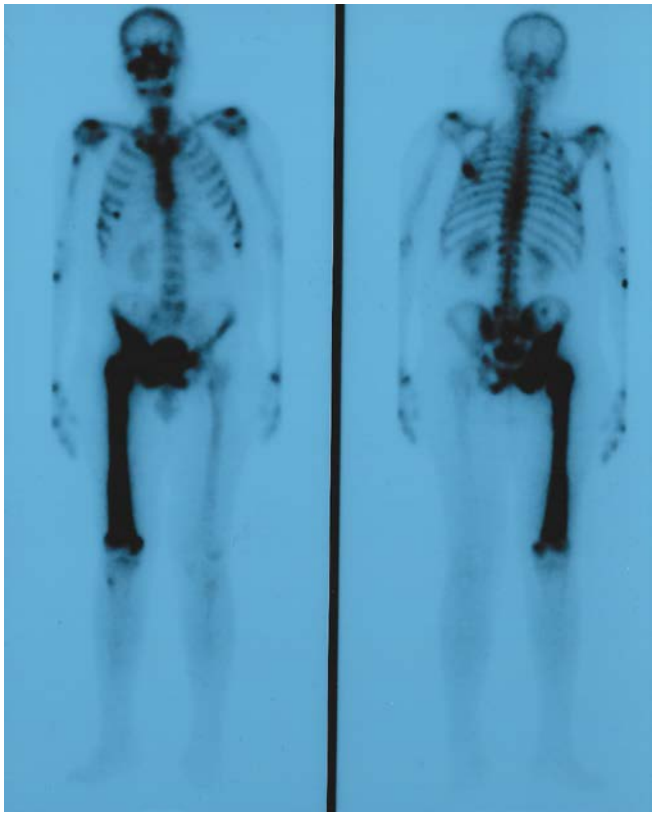
Biopsia prostatica**: adenocarcinoma Gleason 9 (5+4)**

TC: alterazioni ossee strutturali di tipo addensante a sede **iliaca dx, testa femorale e diafisi prossimale omolaterale**. Sclerosi delle limitanti articolari con aspetto cotonoso della spongiosa ai segmenti esaminati del **bacino**.

Scintigrafia ossea: iperaccumulo del radiofarmaco a livello dell'**emibacino dx** e **femore omolaterale**. Lieve iperaccumulo a livello dell'omero dx.

Urologo: ➔ avvia BAT e chiede visita radioterapica
Radioterapista ➔ NO RT e chiede visita oncologica
Oncologo ➔ sospende AA e chiede visita ortopedica
Ortopedico ➔ sospetto di Paget osseo

Biopsia femore dx → metastasi da adenocarcinoma prostatico



Cosa fare ?

ALGORITMO 2016

Treatment group			Standard recommendation	Level of evidence
	HSPC	M0	Orchiectomy LHRH agonist ± AA LH RH antagonist	IA IA IA
		M1	Continuous ADT ± Docetaxel x 6 cy	IA
	CRPC	M0	Clinical Trial Observation (PSADT > 10 m) Secondary OT (PSADT < 10 m)	 II A II A
First-line	mCRPC	asymptomatic mildly symptomatic	Abiraterone Enzalutamide Docetaxel *Sipuleucel T* Denosumab – ZA	IA IA IA IA
		symptomatic	Docetaxel **Radio 223** Denosumab – ZA	IA IA IA
Second – line	mCRPC	Post-ABI/ENZ	Docetaxel Enzalutamide/Abiraterone *Sipuleucel T* **Radio 223** Denosumab – ZA	IA IA IA IA
		Post-Docetaxel	Abiraterone/Enzalutamide Cabazitaxel *Sipuleucel T* **Radio 223** Denosumab – ZA	IA IA IA IA

Facchini et al., Curr Cancer Drug Targets. 2017 Feb 8.

E3805 – CHAARTED Treatment

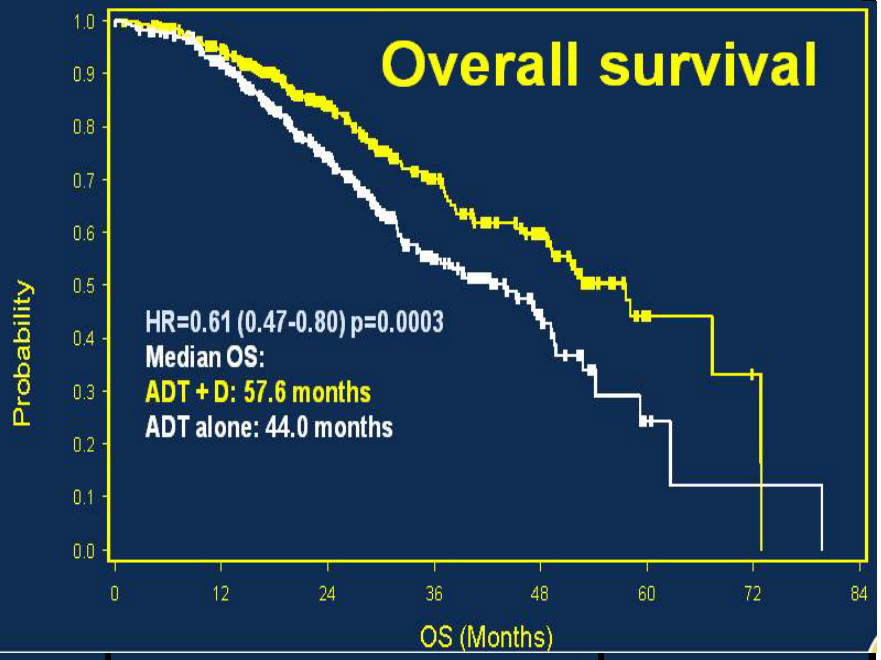
STRATIFICATION

Extent of Mets
-High vs Low
Age
≥70 vs < 70yo
ECOG PS
- 0-1 vs 2
CAB> 30 days
-Yes vs No
SRE Prevention
-Yes vs No
Prior Adjuvant ADT
≤12 vs > 12 months

→ RANDOMIZE

ARM A:
ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles

ARM B:
ADT (androgen deprivation therapy alone)



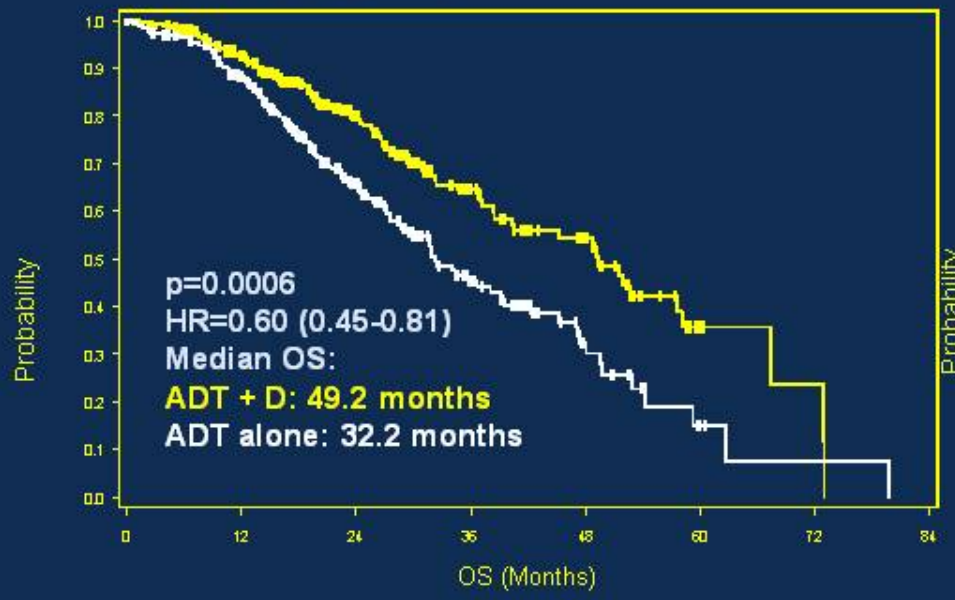
Presented by: Christopher J. Sweeney, MBBS

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

OS by extent of metastatic disease at start of ADT

High volume



Low volume

In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months

We projected 33 months in ADT alone arm with collaboration of SWOG9346 team

Presented by: Christopher J. Sweeney, MBBS

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented By Christopher Sweeney at 2014 ASCO Annual Meeting

Caso Clinico

mHSPC

Luglio 2015

Inizia trattamento combinato sec. schema CHAARTED

- taxotere 75 mg/mq g1 ogni 21 giorni
- analogo LH-RH.

Dicembre 2015

- Termina Chemioterapia
- Prosegue analogo LH-RH
- **PSA *2.5 ng/dl*** *vs* **11.8 ng/dl**
- **Testosterone** <0.05 vs **4.1**
- **VAS 2**
- Viene inviato a follow up clinico strumentale

Caso Clinico

mCRPC

Aprile 2016

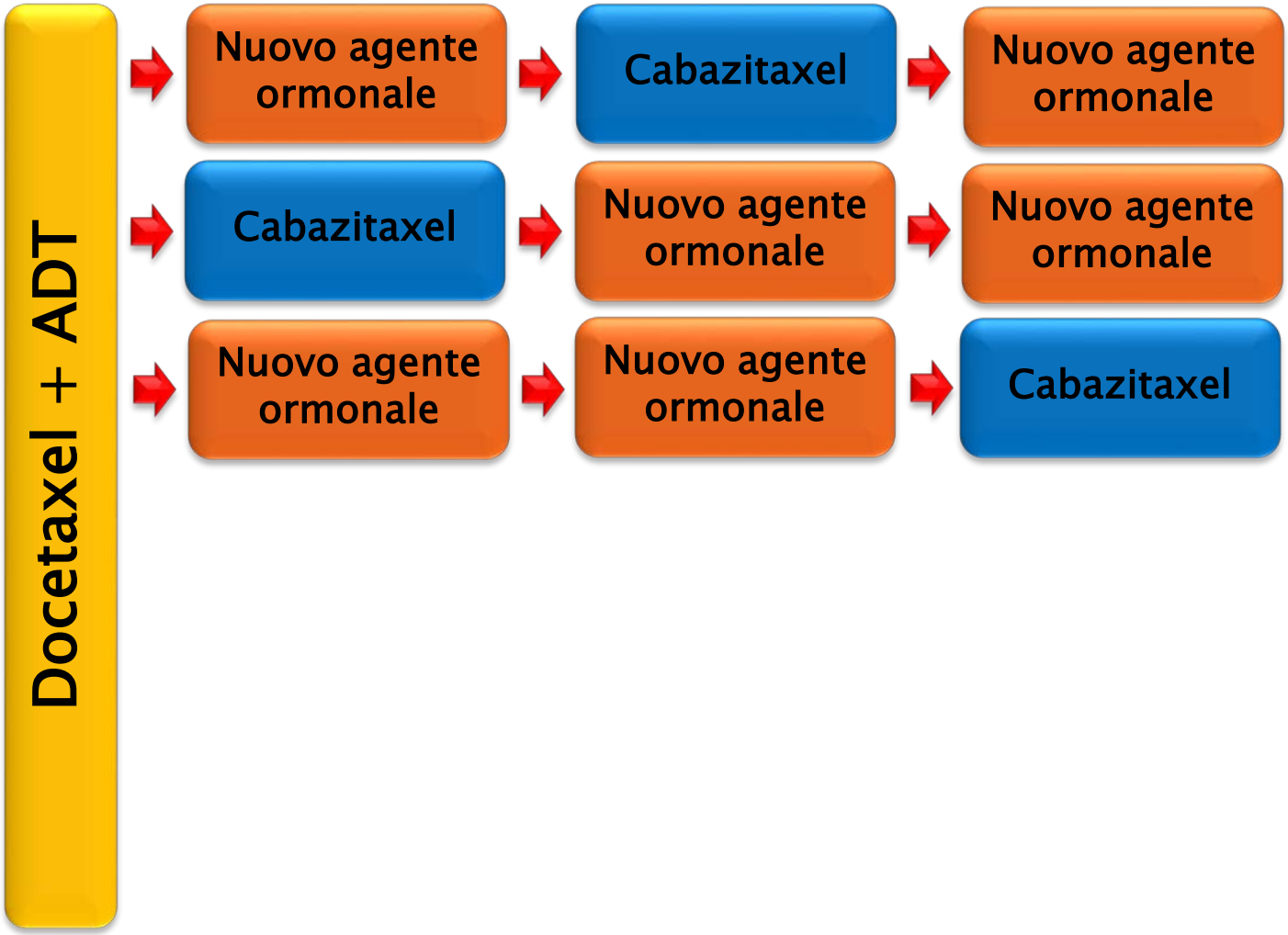
Dolore lombo-sciatalgico a destra VAS 9
PSA 6 ng/dl vs ***2.5 ng/dl*** *vs* **11.8 ng/dl**
Testosterone <0.04

PET con 18-FDG: iperaccumulo femore destro (SUV max 6 versus 4) + ala iliaca destra (SUV max 5 versus 3.8) + ala iliaca sinistra (SUV max 6 versus 3.4) + L3-L4-L5 (SUV max 3.2). Evidenza di area di iperaccumulo in corrispondenza di L1 (SUV max 5.0) e femore sx (SUV max 6)

PD sierica (PSA in incremento) e strumentale (comparsa di 2 nuove lesioni ossee)

Cosa fare ?

- SCENARIO -



RADIUM 223

- SCENARIO -

Facchini G.

ALGORITMO 2016

	Treatment group		Standard recommendation	Level of evidence
	HSPC	M0	Orchiectomy LHRH agonist ± AA LH RH antagonist	IA IA IA
		M1	Continuous ADT ± Docetaxel x 6 cy	IA
	CRPC	M0	Clinical Trial Observation (PSADT > 10 m) Secondary OT (PSADT < 10 m)	 II A II A
First-line	mCRPC	asymptomatic mildly symptomatic	Abiraterone Enzalutamide Docetaxel *Sipuleucel T* Denosumab – ZA	IA IA IA IA
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Second – line	mCRPC	Post-ABI/ENZ	Docetaxel Enzalutamide/Abiraterone *Sipuleucel T* **Radio 223** Denosumab – ZA	IA IA IA IA
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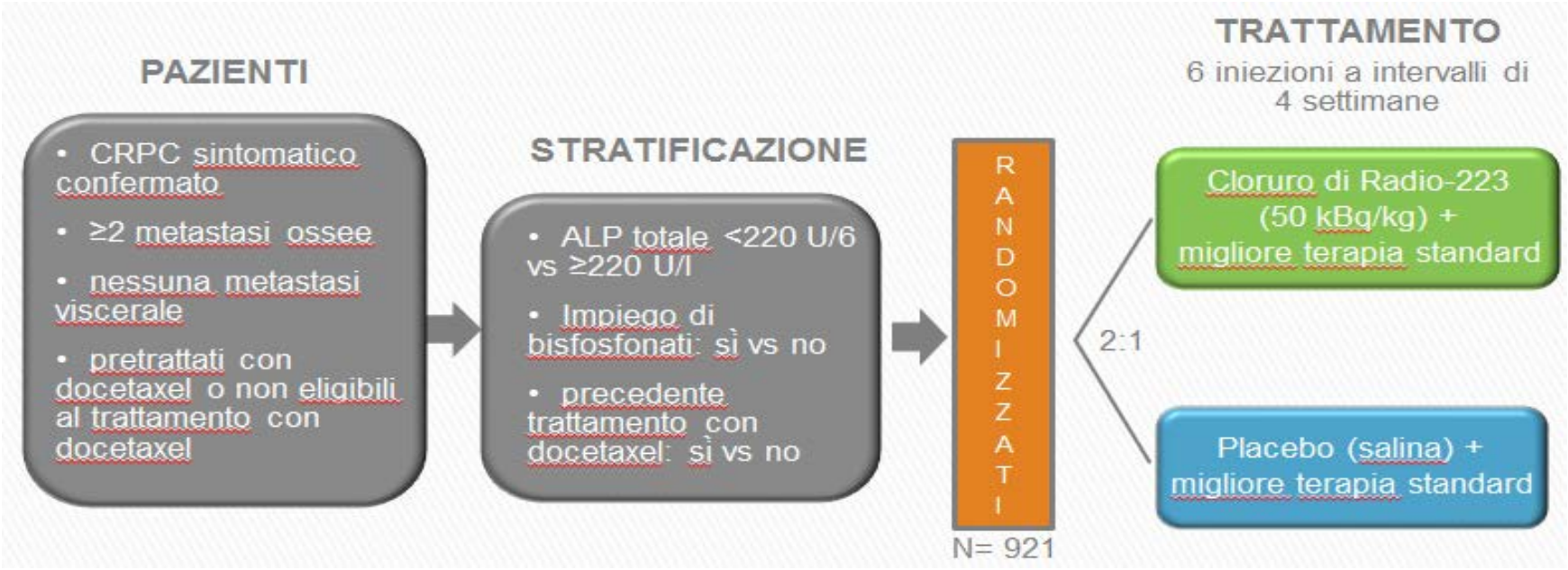
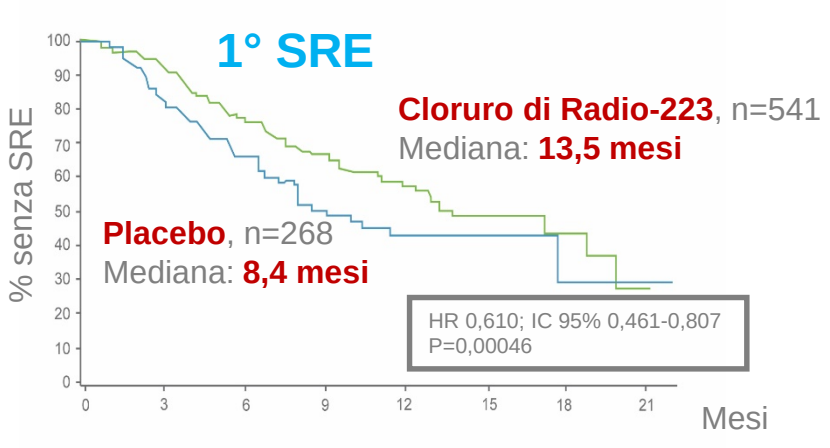
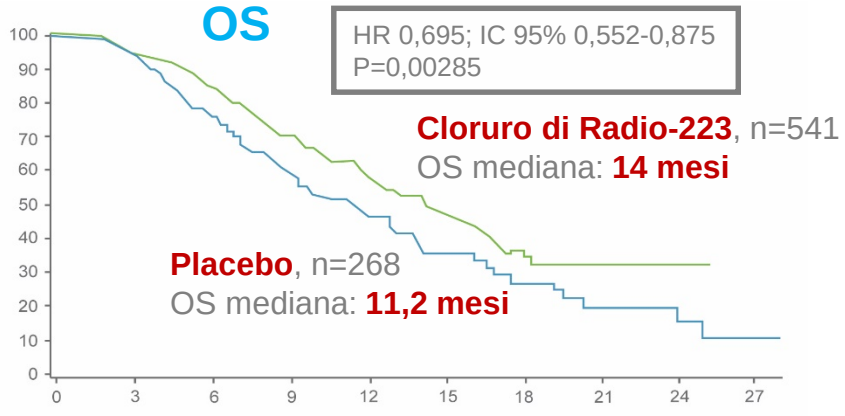
Facchini et al., Curr Cancer Drug Targets. 2017 Feb 8.

ALSYMPCA: Phase III trial







Caso Clinico

mCRPC

Aprile 2016

Dolore lombo-sciatalgico a destra VAS 9
PSA 6 ng/dl vs ***2.5 ng/dl*** *vs* **11.8 ng/dl**
Testosterone <0.04

PET con 18-FDG: iperaccumulo femore destro (SUV max 6 versus 4) + ala iliaca destra (SUV max 5 versus 3.8) + ala iliaca sinistra (SUV max 6 versus 3.4) + L3-L4-L5 (SUV max 3.2). Evidenza di area di iperaccumulo in corrispondenza di L1 (SUV max 5.0) e femore sx (SUV max 6)

PD sierica (PSA in incremento) e strumentale (comparsa di 2 nuove lesioni ossee)

Inizia RADIO 223

Inizia DENOSUMAB 120 mg s.c. q28

Caso Clinico

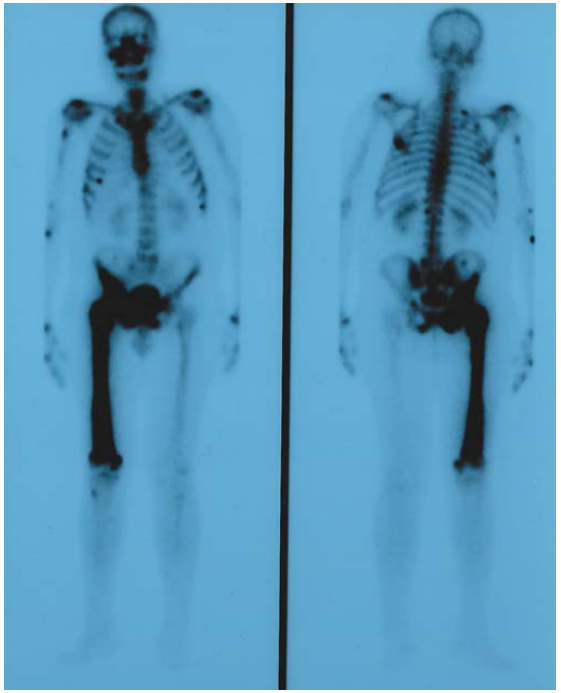
mCRPC

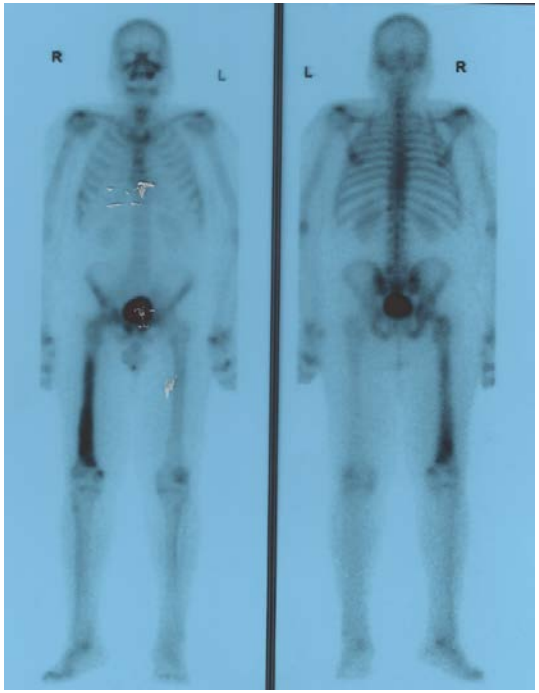
Settembre 2016

TERMINA RADIO 223 – 6 cicli

PSA 15 ng/dl
Testosterone <0.04
Calcemia 7.9 mg/dl (8,6 - 10,2 md/dl)

VAS 2

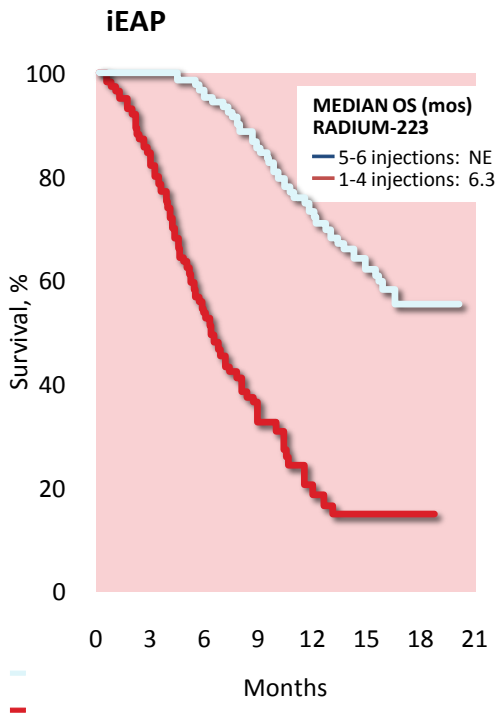


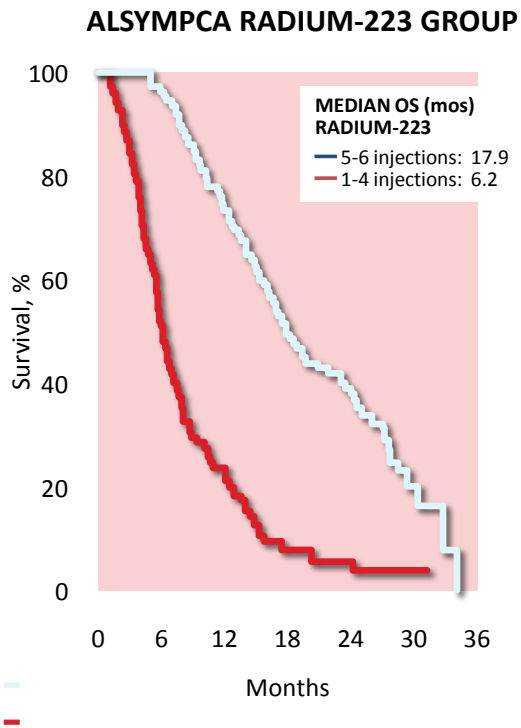


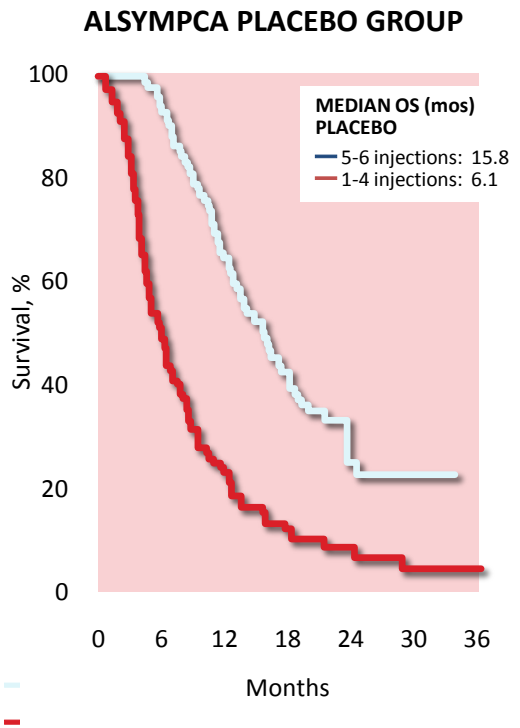
viene inviato a follow up clinico strumentale

Efficacia: Overall Survival per numero di somministrazioni

- Nello Studio ALSYMPCA, la OS mediana è maggiore nei pazienti che ricevono 5-6 iniezioni di Radio 223 vs. quelli che ricevono 5-6 iniezioni di placebo. In entrambi gli Studi: EAP Internazionale e ALSYMPCA (gruppo Radio 223), la OS è maggiore in pazienti che ricevono 5-6 iniezioni su quelli che ne ricevono 1-4
- L'uso precoce di Radio 223 permette al paziente di ricevere tutte e 6 le somministrazioni



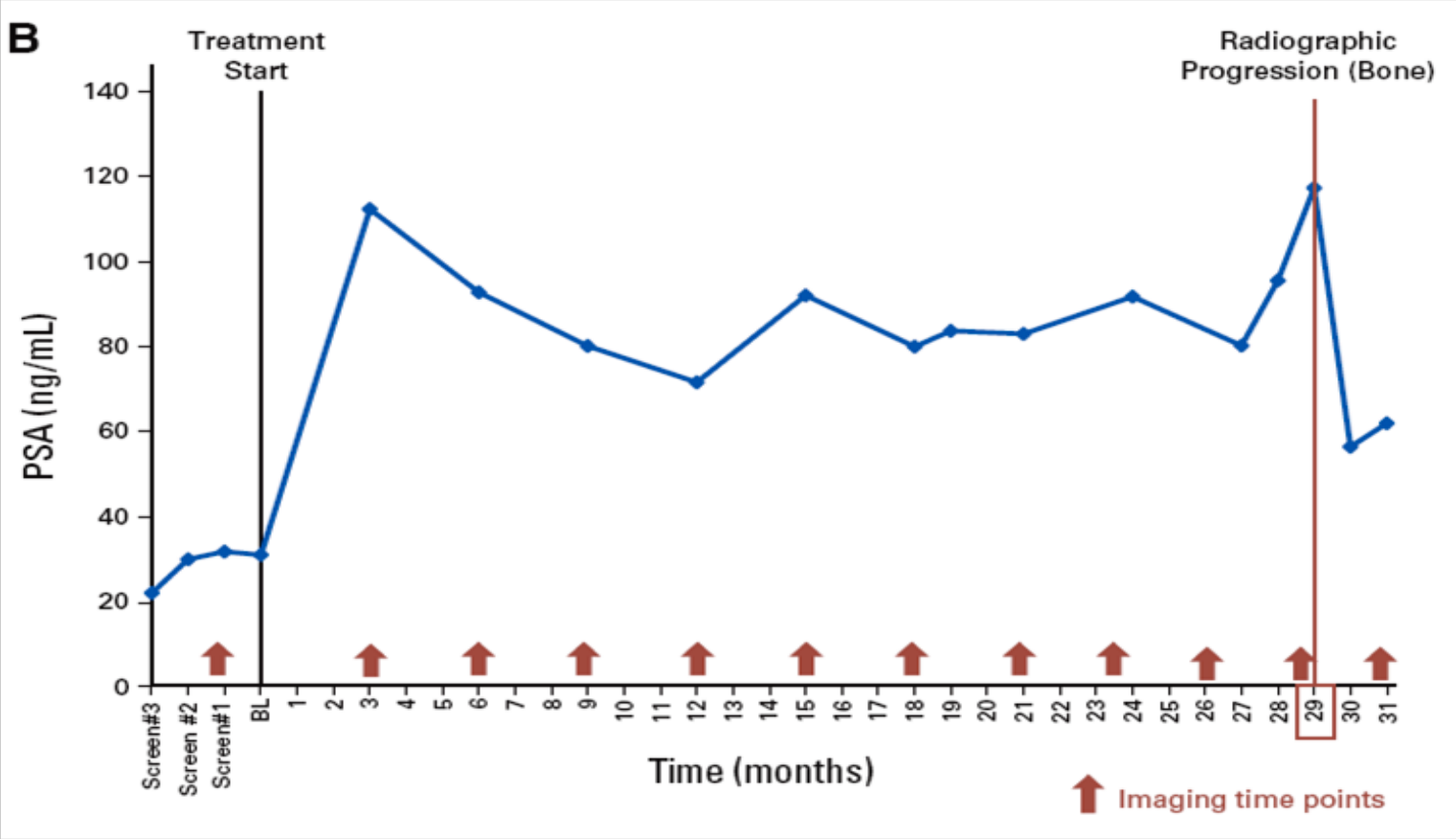




NE = not estimable.

Saad F, et al. *J Clin Oncol.* 34, 2016 (suppl; abstr 5082).

PSA Monitoring



Treating Through Progression vs Stopping Treatment:
A PSA “drifter” for 3,5 years

Scher et al., *J Clin Oncol* 2011

Caso Clinico

mCRPC

Marzo 2017

PSA 27 ng/dl
Testosterone <0.04

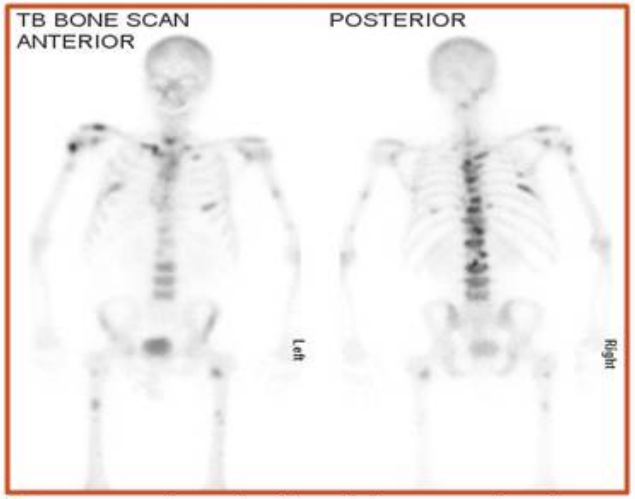
PET con 18- FDG o Colina?: iperaccumulo femore destro (SUV max 10 versus 6) + ala iliaca destra (SUV max 7 versus 5) + ala iliaca sinistra (SUV max 8 versus 6) + L3-L4-L5 (SUV max 8 versus3.2). Evidenza di area di iperaccumulo in corrispondenza di L1 (SUV max 6.0 versus 5), femore sx (SUV max 8 versus 6), **teca cranica (SUV 5max), branca ischio pubica (SUV 6), omero dx e sx (SUV max 8).**

➔ **PD sierica, strumentale e clinica**

Inizia terapia con **Enzalutamide** 160 mg cpr

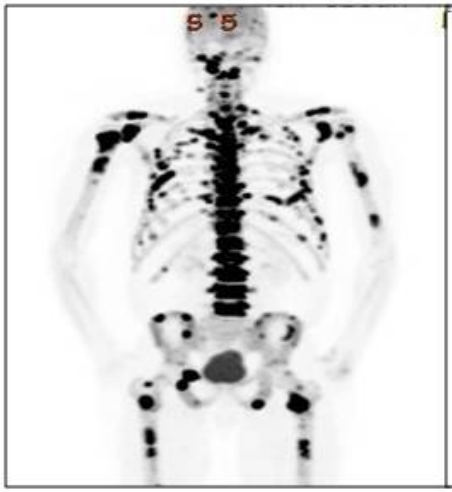
Validation of Imaging Modalities - Analytical and Clinical - Has to be Done One Modality at a Time

Tc-99 MDP

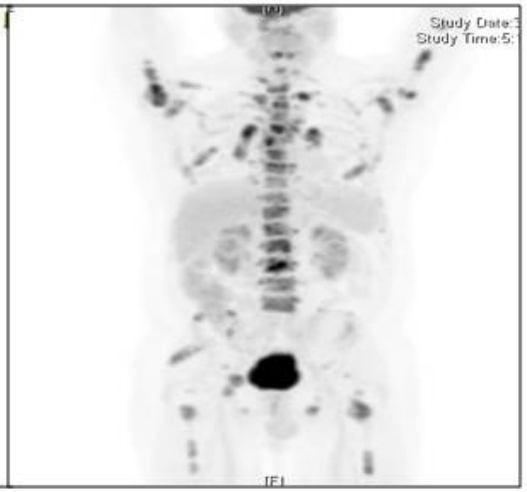


Progression defined by new lesions, **Needed** – assesing growth of existing lesions.

NaF PET



FDG PET



Investigational

Abstract 5075

Updated Results: A Phase 1/2a Randomized Trial of Radium-223 + Docetaxel Versus Docetaxel in Patients With Castration-Resistant Prostate Cancer and Bone Metastases

Michael J. Morris,[1] Yohann Loriot,[2] Christopher Sweeney,[3] Karim Fizazi,[2] Charles J. Ryan,[4] Daniel Shevrin,[5] Emmanuel S. Antonarakis,[6] John Reeves,[7] Kumari Chandrawansa,[7] Martin Kornacker,[8] Celestia Higano[9]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Institut Gustave-Roussy, University of Paris Sud, Villejuif, France; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [5]NorthShore University Health System, Evanston Hospital Kellogg Cancer Center, Evanston, IL, USA; [6]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [7]Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA; [8]Bayer Pharma AG, Berlin, Germany; [9]University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA, USA

BACKGROUND

- Radium-223 dichloride (radium-223), a first-in-class alpha-emitting radiopharmaceutical,
  - Extends overall survival (OS) and delays time to first symptomatic skeletal event in castration-resistant prostate cancer (CRPC) patients with bone metastases[1-3]
  - Has a unique mechanism of action (MOA) and favorable safety profile,[1] making it suitable for combination with other anticancer agents
- Docetaxel is the first chemotherapy agent shown to prolong OS in metastatic CRPC patients[4,5]
- A phase 1/2a trial studied radium-223 + docetaxel in CRPC patients with bone metastases
  - **Phase 1 dose escalation:** results supported proceeding to the expanded phase 2a safety cohort using radium-223 (50 kBq/kg* q 6 wk × 5) + docetaxel (60 mg/m^2 q 3 wk × 10),[7] since no dose-limiting toxicity occurred
  - **Preliminary phase 2a:** results showed that radium-223 (50 kBq/kg* q 6 wk × 5) + docetaxel (60 mg/m^2 q 3 wk × 10) is well tolerated with a favorable impact on prostate-specific antigen (PSA) and alkaline phosphatase (ALP) versus docetaxel alone[8,9]
- ***Here we report updated safety and exploratory efficacy data from phase 2a***

*55 kBq/kg following the National Institute of Standards and Technology (NIST) update.[6]

STUDY RATIONALE

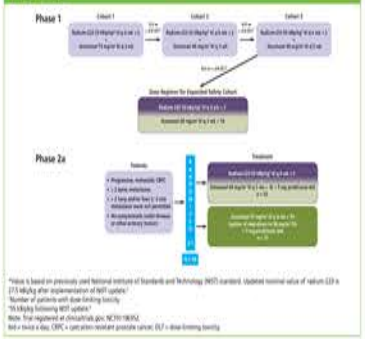
- Treating metastatic CRPC patients using 2 anticancer agents with different MOAs may have a synergistic effect

STUDY OBJECTIVES

- To establish a recommended radium-223 dose for use with docetaxel and evaluate the safety and efficacy of the combination

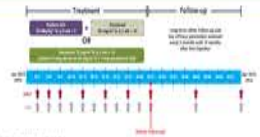
STUDY DESIGN

Figure 1. Phase 1 Dose Escalation and Phase 2a Expanded Safety Cohort Study Design



*Value is based on previously used National Institute of Standards and Technology (NIST) standard. Updated nominal value of radium-223 is 273 kBq/kg after implementation of NIST update.[7]
†Number of patients with dose-limiting toxicity.
‡55 kBq/kg following NIST update.[6]
Note: Trial registered at clinicaltrials.gov; NCT01106352.
bid = twice a day; CRPC = castration-resistant prostate cancer; DLT = dose-limiting toxicity.

Figure 2. Phase 2a Schedule of Evaluations and Assessments



*55 kBq/kg body weight after NIST update.[6]
†No later than week 19.
bALP = bone alkaline phosphatase; bid = twice a day; PPFS = first patient's first visit; LPLV = last patient's last visit; PSA = prostate-specific antigen; qw = week.

- Adverse events (AEs) were assessed at each scheduled visit during treatment and safety follow-up (week 31); samples were analyzed at a central laboratory

RESULTS

Patient and Disease Characteristics

Table 1. Patient Demographics and Baseline Characteristics

	Radium-223 + Docetaxel n = 33	Docetaxel n = 13
Age, median (range), y	68 (49-82)	67 (55-82)
Weight, median (range), kg	87 (61-120)	78 (69-132)
PSA		
> ULN, n (%)*	32 (97)	13 (100)
Median (range), µg/L	99 (3-1000)	43 (4-1042)
Total ALP		
> ULN, n (%)*	20 (61)	10 (77)
Median (range), U/L	167 (62-1016)	186 (74-472)
Bone ALP		
> ULN, n (%)*	23 (70)	11 (85)
Median (range), µg/L	36 (10-331)	47 (16-164)
LDH		
> ULN, n (%)*	6 (18)	2 (15)
Median (range), U/L	191 (123-418)	190 (124-328)
Extent of disease (number of bone lesions), n (%)		
2-4	4 (12)	0
5-9	7 (21)	3 (23)
10-20	9 (27)	4 (31)
> 20	13 (39)	6 (46)

*ULN provided by central lab.
ALP = alkaline phosphatase; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; ULN = upper limit of normal

- 46 patients were enrolled; the majority had extensive disease

Table 2. Selected Therapies Received Prior to Study Entry

	Radium-223 + Docetaxel n = 33	Docetaxel n = 13
Anticancer Therapies, n (%)		
Hormonal therapies		
Abiraterone + prednisone	25 (76)	8 (62)
Enzalutamide	3 (9)	5 (38)
Chemotherapy		
Docetaxel	2 (6)	0
Immunostimulants	1 (3)	0
Sipuleucel-T	6 (18)	4 (31)
Bone-Modifying Agents, n (%)		
Bisphosphonates	13 (39)	5 (38)
Denosumab	12 (36)	3 (23)
Other, n (%)		
Radiation	24 (73)	9 (69)

Table 3. Patient Exposure to Study Drug and Disposition

Exposure to Study Drug, n (%)	Radium-223 + Docetaxel n = 33	Docetaxel* n = 13
Received all 5 radium-223 injections	25 (76)	NA
Received all 10 docetaxel cycles	20 (61)	5 (38)
Disposition, n (%)		
Completed study (through 12-mo follow-up)	23 (70)	9 (69)

*3 (23%) docetaxel patients stepped down to 60 mg/m^2.
NA = not applicable

Safety Outcomes

Table 4. Treatment-Emergent Adverse Events (TEAEs)

	All Grades		Grade 3 or 4	
	Radium-223 + Docetaxel n = 33	Docetaxel n = 13	Radium-223 + Docetaxel n = 33	Docetaxel n = 13
Patients with TEAEs, n (%)	33 (100)	13 (100)	16 (48)	8 (62)
Hematologic, n (%)				
Anemia	3 (9)	1 (8)	1 (3)	0
Neutropenia	10 (30)	5 (38)	10 (30)	5 (38)
Febrile neutropenia	0	2 (15)	0	2 (15)
Leukopenia	2 (6)	2 (15)	2 (6)	2 (15)
Lymphopenia	1 (3)	0	1 (3)	0
Nonhematologic,* n (%)				
Fatigue	17 (52)	9 (69)	0	0
Nausea	16 (48)	8 (62)	0	0
Diarrhea	15 (45)	5 (38)	1 (3)	0
Constipation	11 (33)	5 (38)	0	0
Peripheral edema	12 (36)	5 (38)	0	1 (8)
Decreased appetite	11 (33)	4 (31)	0	0
Dysgeusia	7 (21)	8 (62)	0	0
Peripheral neuropathy	10 (30)	4 (31)	0	0
Alopecia	12 (36)	7 (54)	0	0
Arthralgia	7 (21)	6 (46)	0	0
Back pain	13 (39)	4 (31)	2 (6)	0
Dyspnea	2 (6)	5 (38)	0	0
Gastroesophageal reflux disease	1 (3)	4 (31)	0	0

*All grades occurring in ≥ 25%.

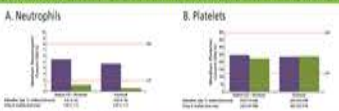
- Compared with docetaxel alone, radium-223 + docetaxel–treated patients had a lower percentage of
  - Grade 3/4 treatment-emergent adverse events (TEAEs) (48% vs 62%)
  - Serious TEAEs (21% vs 31%)
- 2 docetaxel-alone patients had febrile neutropenia
- No patients in either arm had thrombocytopenia
- The majority of nonhematologic events were grades 1 and 2; fatigue was the most common
- There were no grade 5 TEAEs
- During the follow-up period, 2 (6%) radium-223 + docetaxel–treated patients had treatment-emergent adverse drug reactions: 1 anemia and 1 fatigue

Table 5. Incidence of Grade ≥ 3 Hematologic Laboratory Values and Time to Recovery

	Neutrophil Count Decreased		Anemia*		Platelet Count Decreased	
	Radium-223 + Docetaxel n = 33	Docetaxel n = 13	Radium-223 + Docetaxel n = 33	Docetaxel n = 13	Radium-223 + Docetaxel n = 33	Docetaxel n = 13
Incidence of grade ≥ 3, n (%)	18 (55)	11 (85)	1 (3%)	1 (8%)	0	0
Recovery† to grade 2 or lower, n (%)	18 (55)	11 (85)	0	0	NA	NA
Median time‡ to recovery (range), d	11 (7-14)	7 (7-25)	NA	NA	NA	NA

*Based on lab values according to CTCAE version 4.0; lab values for grade 3 = 8.0 g/dL, < 6.5 mmol/L, < 80 g/L.
†If multiple recovery times for single parameter, average was taken prior to summarizing across patients.
‡Time was measured from onset of grade ≥ 3 lab value to onset of subsequent grade < 3 value.
NA = not applicable

Figure 3. Median Neutrophil and Platelet Laboratory Values at Baseline and Day 8

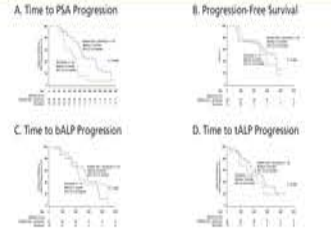


ULN = lower limit of normal; LLN = upper limit of normal

- There were no major differences in median neutrophil and platelet laboratory values between treatment arms
- Granulocyte colony-stimulating factor (GCSF) was used as secondary prophylaxis per investigators' discretion; 3 (9%) radium-223 + doxetaxel–treated patients and 2 (15%) doxetaxel-alone patients received concomitant GCSF

Efficacy Outcomes

Figure 4. Time to PSA Progression,*† Progression-Free Survival,*‡ Time to bALP Progression,* and Time to tALP Progression*



*Per protocol population; intent-to-treat patients who received ≥ 48% of specified number of radium-223 injections or docetaxel, per dose-escalation study results, and have no major protocol violations.
†The Prostate Cancer Working Group 2 (PCWG2). PSA progression for patients with an initial PSA decline from baseline is defined as a PSA increase ≥ 25% and ≥ 2 ng/mL above nadir, confirmed ≥ 3 weeks later. For those with no PSA decline from baseline, progression is defined as a PSA increase ≥ 25% and ≥ 2 ng/mL above baseline after 12 weeks.
‡Progression-free survival is a composite end point of time to first radiographic or clinical progression, or death.
bALP = bone alkaline phosphatase; PSA = prostate-specific antigen; PFS = progression-free survival; tALP = total alkaline phosphatase

Overall Survival

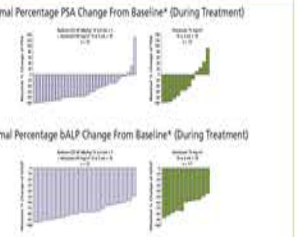
- 12-month survival rates were similar for radium-223 + docetaxel–treated versus docetaxel-alone patients (89% vs 90%)
- Censoring rates for overall survival were 29/32 (91%) for radium-223 + docetaxel–treated and 12/13 (92%) for docetaxel-alone patients; high censoring rates were due to low number of death events

Table 6. PSA And bALP Change From Baseline* (During Treatment)

	PSA		bALP	
	Radium-223 + Docetaxel n = 33	Docetaxel n = 13	Radium-223 + Docetaxel n = 23	Docetaxel n = 11
Any increase, n (%)	3 (9)	4 (31)	0	0
Decrease, n (%)				
≤ 30%	4 (12)	1 (8)	0	0
≥ 30%	26 (79)	8 (62)	23 (100)	11 (100)
> 50%	20 (61)	7 (54)	22 (96)	9 (82)
> 80%	10 (30)	4 (31)	10 (43)	2 (18)
Normalization, n (%)	NA	NA	21 (91)	7 (64)
Median % change from baseline (range)	-75 (-93, 131)	-55 (-98, 92)	-77 (-95, -49)	-59 (-86, -44)

*Changes are described as the percentage of patients who had < 30%, < 50%, or < 80% declines from baseline to lowest value on study, prior to starting new treatments.
†Patients with elevated baseline bALP (> 21 µg/L).
bALP = bone alkaline phosphatase; NA = not applicable; PSA = prostate-specific antigen.

Figure 5. Waterfall Plots of Maximal Percentage PSA and bALP Change From Baseline* (During Treatment)



*Maximal percentage change was calculated from baseline to lowest value on study, before starting any new treatment.
†55 kBq/kg following the NIST update.[6]
‡Patients with elevated baseline bALP (> 21 µg/L).
bALP = bone alkaline phosphatase; PSA = prostate-specific antigen.

CONCLUSIONS

- The combination of radium-223 (50 kBq/kg* q 6 wk × 5) + docetaxel (60 mg/m^2 q 3 wk × 10) was well tolerated
  - A lower percentage of patients had grade 3/4 TEAEs in the radium-223 + docetaxel arm, compared with the docetaxel-alone arm
- Compared with docetaxel alone, patients in the radium-223 + docetaxel arm had
  - A longer median time to PSA progression
  - More pronounced declines of PSA and bALP levels
- These results provide a rationale for further investigating the efficacy and safety of the combination of radium-223 and docetaxel in metastatic CRPC

*55 kBq/kg following the NIST update.[6]

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Abstract TPS5088

ERA 223: A Phase 3 Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-Naïve Patients With Bone-Predominant Metastatic Castration-Resistant Prostate Cancer

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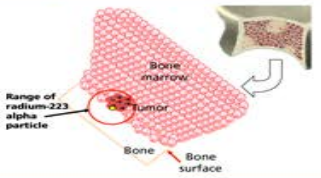
BACKGROUND

- Most metastatic prostate cancer patients are first treated with androgen deprivation therapy; however, the majority develop castration-resistant prostate cancer (CRPC)[1]
- ~50% of patients with metastatic disease are asymptomatic and therefore may not be good candidates for immediate chemotherapy, but may still benefit from alternate therapies[2,3]

Radium-223 Dichloride (Radium-223)

- This first-in-class alpha radiopharmaceutical selectively targets bone metastases. Its particle range (< 100 µm [< 10 cell diameters]) is shorter than that of beta emitters, limiting surrounding tissue damage[4] (**Figure 1**)

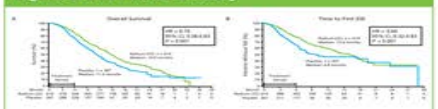
Figure 1. Target of Radium-223



- In ALSYMPCA, radium-223 (50 kBq/kg [55 kBq/kg following National Institute of Standards and Technology (NIST) update*][5] IV every 4 wk x 6) plus best standard of care (BSoC) (eg, local external beam radiation therapy [EBRT], corticosteroids, antiandrogens, ketoconazole, estrogens), versus placebo plus BSoC, in CRPC patients with symptomatic bone metastases
  - Prolonged overall survival (OS) and delayed time to first symptomatic skeletal event (SSE)[6,7] (**Figure 2**)
    - Survival was prolonged regardless of concomitant bisphosphonate use or previous docetaxel use, leading to guidelines recommending radium-223 pre- and post-docetaxel[2,3,8]
  - Was safe, with low rates of myelosuppression.[6] Lack of significant toxicity, particularly when radium-223 is administered with BSoC, supports combining it with other agents

*Value is based on data assessed by previously used NIST standard. Updated nominal value of radium-223 is 55 kBq/kg body weight after implementation of NIST update.[5]

Figure 2. ALSYMPCA Efficacy



SSE = symptomatic skeletal event.

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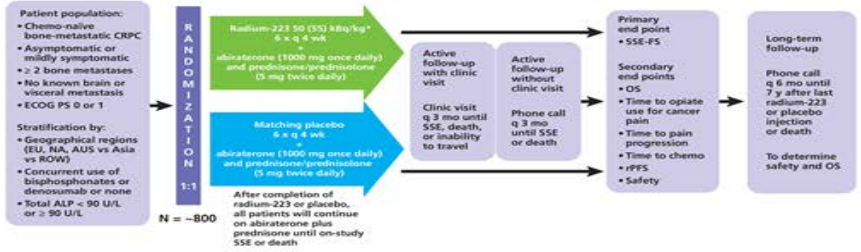
Figure 3. ERA 223 Study Design



*Updated nominal value of radium-223 is 55 kBq/kg body weight after implementation of National Institute of Standards and Technology update.[5]
ALP = alkaline phosphatase; AUS = Australia; CRPC = castration-resistant prostate cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; EU = Europe; NA = North America; OS = overall survival; ROW = rest of world; rPFS = radiologic progression-free survival; SSE = symptomatic skeletal event; SSE-FS = SSE-free survival.

Abiraterone Acetate (Abiraterone)

- This selective irreversible steroidal inhibitor of 17α-hydroxylase/C17,20-lyase targets androgen synthesis in testes, adrenal glands, and prostate cancer cells[9]
- In a large, randomized, placebo-controlled phase 3 trial in patients with asymptomatic or mildly symptomatic chemotherapy-naïve metastatic CRPC,[10] abiraterone 1000 mg 1 x daily plus prednisone 5 mg 2 x daily, compared with placebo plus prednisone,
  - Significantly improved radiologic progression-free survival (16.5 vs 8.2 mo [HR = 0.52; 95% CI, 0.45-0.61; *P* < 0.0001])[11]
  - Showed significant OS improvement (34.7 vs 30.3 mo [HR = 0.81; 95% CI, 0.70-0.93; *P* = 0.0033])[12]
- Abiraterone shows no overlapping toxicity with radium-223
- Abiraterone plus prednisone is a standard of care for CRPC patients who are asymptomatic or mildly symptomatic and therefore not eligible for docetaxel

STUDY RATIONALE

- Treatment options remain limited for asymptomatic or mildly symptomatic patients with bone-predominant metastatic CRPC
- Given the different modes of action and the nonoverlapping safety profiles of radium-223 and abiraterone, the combination is expected to prolong SSE-free survival (SSE-FS), compared with abiraterone alone

STUDY OBJECTIVE

- To evaluate the effects of adding radium-223 to abiraterone and prednisone in patients with asymptomatic or mildly symptomatic chemotherapy-naïve, bone-predominant metastatic CRPC

STUDY DESIGN

- This international, randomized, double-blind, placebo-controlled phase 3 study (ERA 223, NCT02043678) is being conducted in North America, Europe, Asia, Australia, Brazil, and Israel at 168 sites (**Figure 3**)

END POINTS

Primary

- SSE-FS—time from randomization to occurrence of
  - On-study SSE defined as
    - EBRT for skeletal symptoms
    - New symptomatic pathologic bone fracture
    - Spinal cord compression
    - Tumor-related orthopedic surgical intervention

Secondary

- OS
- Time to
  - Opiate use for cancer pain
  - Pain progression
  - Cytotoxic chemotherapy
- Radiologic progression-free survival
- Acute and long-term safety, including hematologic parameters and new primary malignancies

Select Exploratory

- Time to first on-study SSE, alkaline phosphatase (ALP) and prostate-specific antigen progression
- Percentage change in total ALP from baseline
- Time to increase in physical symptoms based on the FACT Prostate Symptom Index: Disease-Related Subscale—Physical score

KEY ELIGIBILITY CRITERIA

Inclusion

- Age ≥ 18 years with life expectancy ≥ 6 months
- Histologically confirmed prostate adenocarcinoma
- Known CRPC, documented progression
- ≥ 2 bone metastases within 4 weeks prior to randomization
- Asymptomatic or mildly symptomatic prostate cancer per worst pain in last 24 hours (question 3) on the Brief Pain Inventory–short form
  - Score of 0 = asymptomatic
  - Score of 1-3 = mildly symptomatic
- Eastern Cooperative Oncology Group performance status, 0 or 1
- Adequate hematologic, hepatic, and renal function

Exclusion

- Prior abiraterone or cytotoxic chemotherapy
- Current or history of visceral or brain metastasis
- Malignant lymphadenopathy > 3 cm in short-axis diameter
- Prior hemibody external radiotherapy or systemic radiotherapy with strontium-89, samarium-153, rhenium-186, rhenium-188, or radium-223
- Opiate use for cancer-related pain currently or during 4 weeks prior to randomization

ASSESSMENTS AND FOLLOW-UP

Treatment

- Patients will be assessed at each visit for efficacy, safety, and health-related quality of life
- Clinic visits every 2 weeks until the fourth injection of radium-223 or placebo, then every 4 weeks until the end-of-treatment visit (4 wk post last dose of abiraterone as investigational medicinal product and prednisone alone or 6 mo post last radium-223 or placebo injection, whichever occurs later)

Follow-up

- Active follow-up (***with*** clinic visits)
  - For patients discontinuing treatment without on-study SSE
  - Evaluations to occur every 12 weeks ± 7 days, extending until an SSE or the patient is unable to travel or dies
- Active follow-up (***without*** clinic visits)
  - For patients unable to travel, evaluations to occur by phone as above
- Long-term follow-up
  - For patients experiencing an SSE at any point
  - Monitoring by phone to occur every 6 months and extend to a maximum of 7 years after the last radium-223 or placebo injection or until loss to follow-up, withdrawal of consent, or death

STATISTICAL METHODS

- Intent-to-treat (all randomized) patients will be used in efficacy analyses
- Safety population (all randomized patients receiving ≥ 1 study drug) will be used in safety analyses
- Overall 2-sided type I error rate for analysis of the primary efficacy end point is 0.05. Multiplicity adjustment will be done for the analyses of secondary end points
- 800 patients are expected to provide 389 SSE-FS events, which are needed to detect a 39% increase in median SSE-FS; ie, an overall 0.05-level 2-sided log-rank test has approximately 90% power to detect a statistically significant difference between the 2 SSE-FS curves, assuming the median SSE-FS is 29.2 months for radium-223 versus 21.0 months for control
- Primary and secondary time-to-event end points will be analyzed using a stratified log-rank test accounting for the 3 randomization stratification factors
- No formal interim analysis is planned for the primary end point; 1 interim (at same time as final primary end point analysis) and 1 final analysis are planned for OS
- Safety variables will be analyzed using frequency tables and descriptive statistics

STUDY STATUS

- This study is currently recruiting patients
- As of May 23, 2016, 630 patients have been randomized

Trial (NCT02043678) sponsored by Bayer HealthCare Pharmaceuticals.
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