CASO CLINICO
FINESTRA TERAPEUTICA

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Sig. L.C. anni 72

APR: ipertensione arteriosa, NSTEMI anterolaterale in CAD monovasale (Aprile 2015).

Anamnesi oncologica:

- Giugno 2005: prostatectomia e linfoadenectomia iliaco-otturatoria. iPSA: 8 ng/mL.
  EI: adenoca moderatamente differenziato, GS 4+3, pT2c pN0, invasione perineurale presente, R1.
- Maggio 2009: radioterapia di salvataggio.
- Luglio 2011: impostata terapia ormonale con Bicalutamide150 mg/die.
- Luglio 2013: PSA 8.17 ng/ml. Scintigrafia ossea TB: lesioni diffuse. Impostato BAT.
- Gennaio 2014: dolore in sede cervicale a ricorrenza saltuaria; EBRT su vertebra C6 (20 Gy).
- Maggio 2014: PSA 1.12 ng/ml
- Ottobre 2014: PSA 3.6 ng/ml. Scintigrafia ossea TB: SD.
- Febbraio 2015: PSA 16.35 ng/ml. Scintigrafia ossea TB: SD. TAC WB con mdc: non malattia viscerale.
- Marzo 2015: PSA 27 ng/ml. Sospesa Bicalutamide. Iniziato Acido Zoledronico, effettuata singola infusione di farmaco.

Giugno 2015:

- Dolore 4-5 sec NRS femore sx e 2 sec NRS colonna dorsale. PSA 62 ng/ml.
- Scintigrafia ossea TB : incremento numerico delle lesioni ossee rispetto al controllo del 10/2013, in particolare si evidenziano lesioni a carico del costato e dello sterno, osso occipitale sx, rachide dorsale, passaggio L-S, ilei, acetaboli, branca ischio-pubica dx, sinfisi pubica, regione sottotrocanterica sx.
- TAC WB + femore bil. con mdc: PD scheletrica, con diffuso sovvertimento strutturale a carattere addensante a carico di tutti i metameri DL, sterno, entrambe le scapole, la maggior parte degli archi costali bilateralmente, sacro, bacino e femori. Non lesioni secondarie viscerali.

Luglio 2015: EBRT diafisi femorale sx (20 Gy).

Quale trattamento?

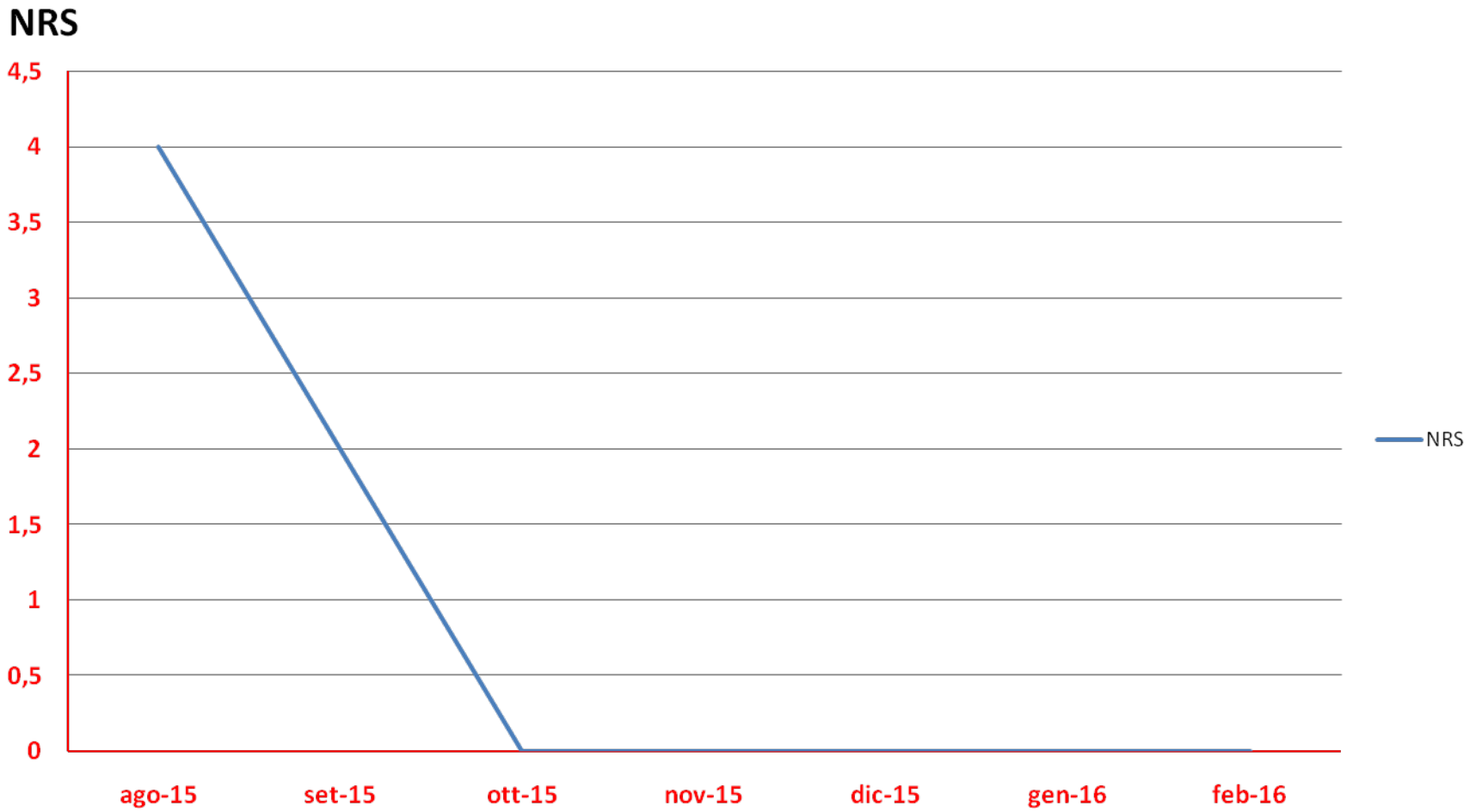
- DOCETAXEL
- ABIRATERONE
- RADIUM 223

Al controllo basale: ECOG PS 1. Dolore 5 sec NRS.

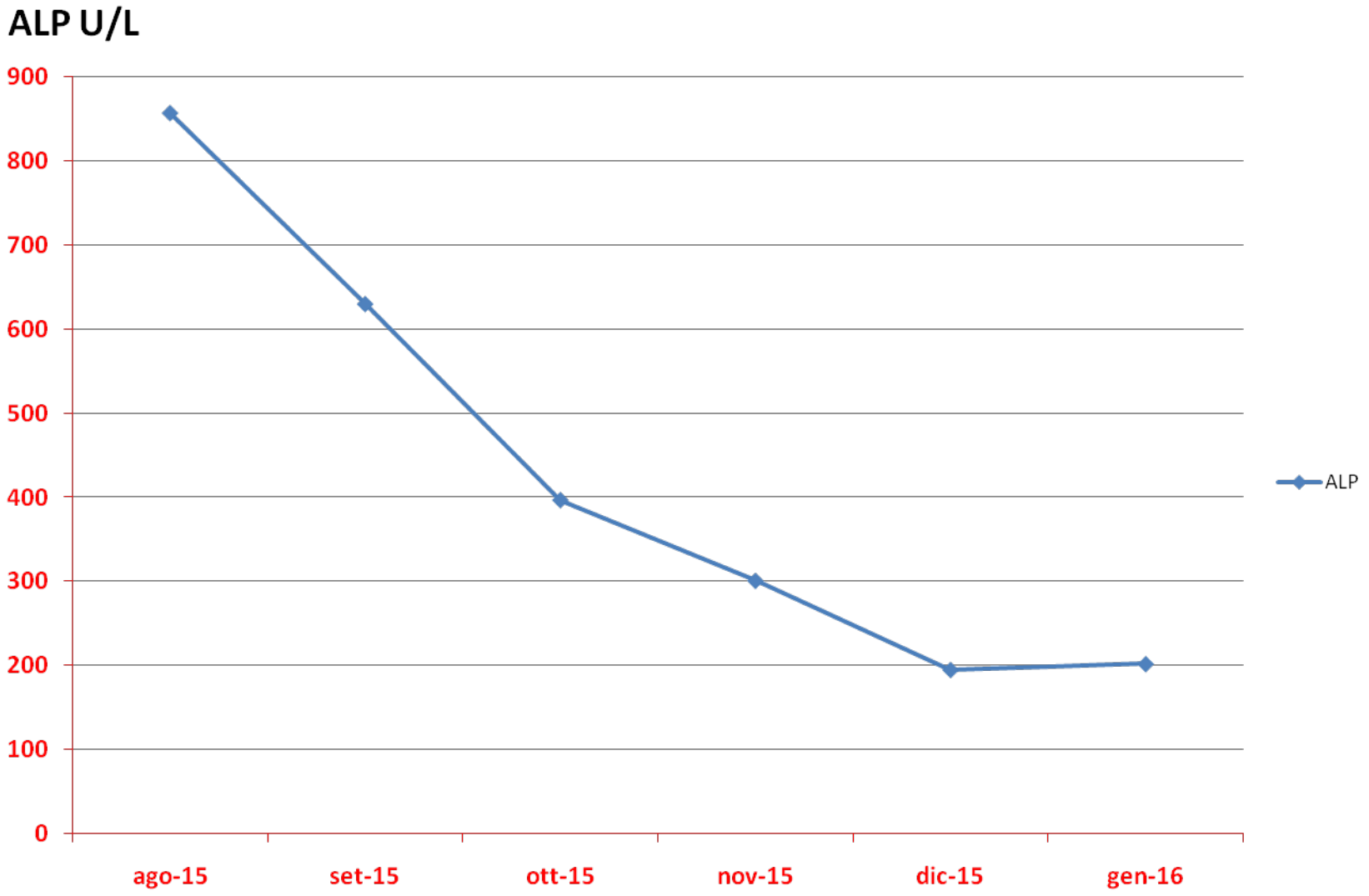
Agosto 2015-Gennaio 2016

6 somministrazioni di Radium 223 50 kBq/Kg ev ogni 28 gg.

Dolore osseo



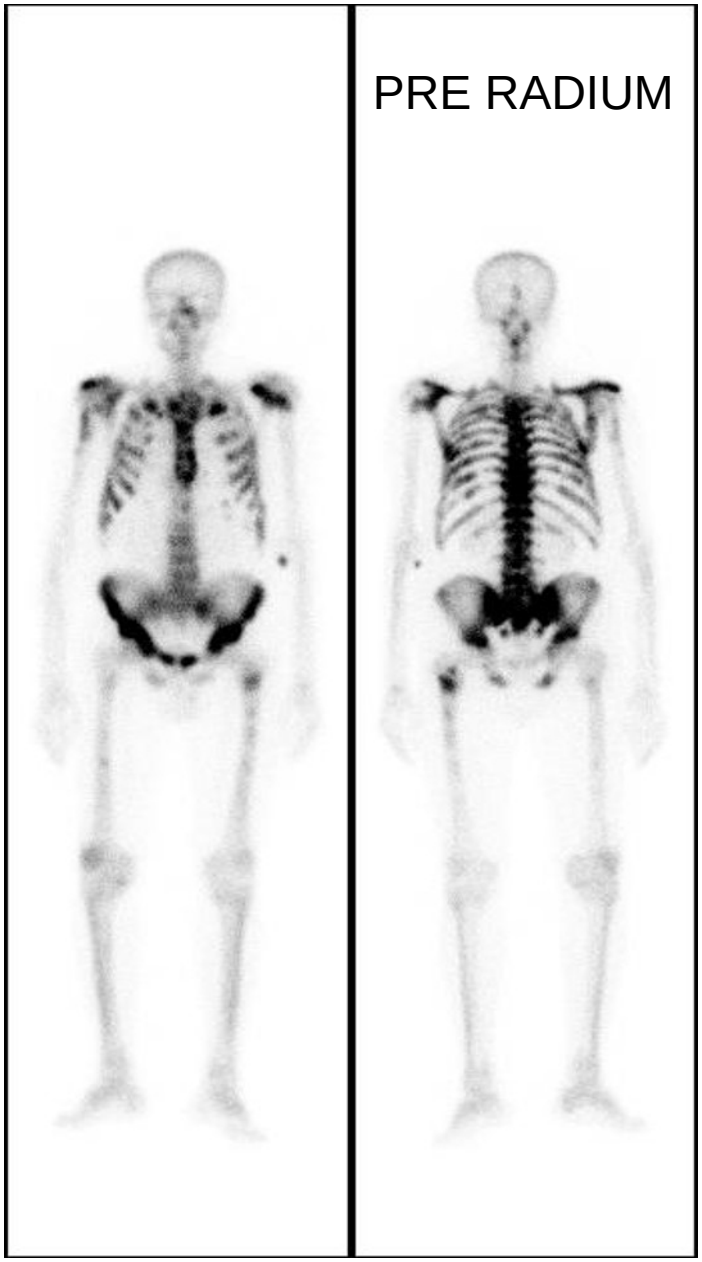
Risposta biochimica (ALP)

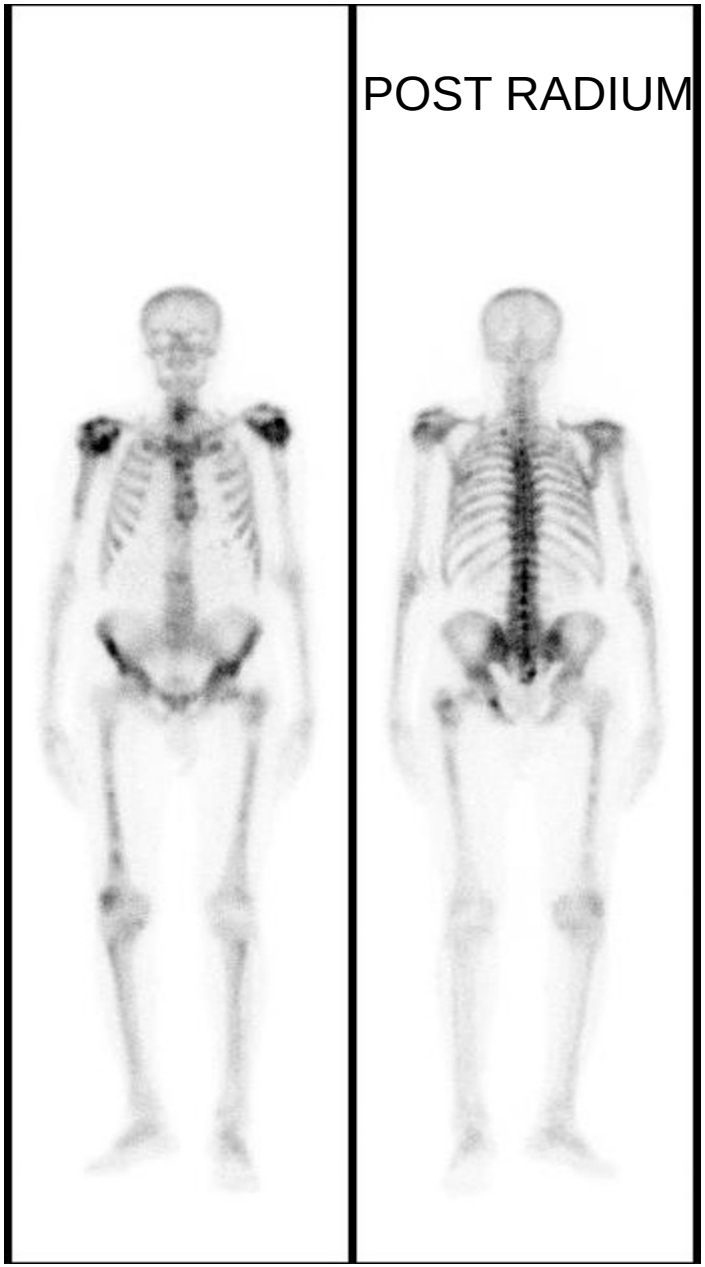


Parametri ematologici

	Ago 2015	Nov 2015	Dic 2015	Feb 2016
Hb g/dl	11	10	9,6	9,2
PLTs 10^3/µl	230	199	187	142
WBC 10^3/µl	7,700	4,500	2,970	3,360
Neu 10^3/µl	2,600	2,520	1,460	1,920
PSA ng/ml	60,54	59,51	46,97	52,38

Rivalutazione strumentale





Aprile 2016: PSA 55 ng/ml; PS 1, paziente asintomatico per dolore.

Luglio 2016:

- Dolore 6 NRS colonna dorsale. PSA 94 ng/ml. ALP 600 U/L.
- Scintigrafia ossea TB : rispetto al controllo del Marzo 2016, PD scheletrica.
- TAC WB + femore bil. con mdc: PD scheletrica, linfoadenopatia ilare polmonare sx di circa 2.5 cm, linfoadenopatie mediastiniche.

Agosto 2016: EBRT D4 (10 Gy).

Quale trattamento?

- DOCETAXEL
- ABIRATERONE
- ENZALUTAMIDE

Al controllo basale:

- ECOG PS 1. Dolore 5 sec NRS.
- Hb 10 g/dL; Plts 135 10^3/µl; WBC 4,23 10^3/µl.
- Ecocardiogramma: ventricolo sx di normali dimensioni con funzione sistolica nella norma; FE 55%.

Agosto 2016-Gennaio 2017

- 8 cicli di Docetaxel 75 mg/mq ev ogni 21 gg + prednisone 10 mg/die
- Acido Zoledronico 4 mg ev ogni 21 giorni

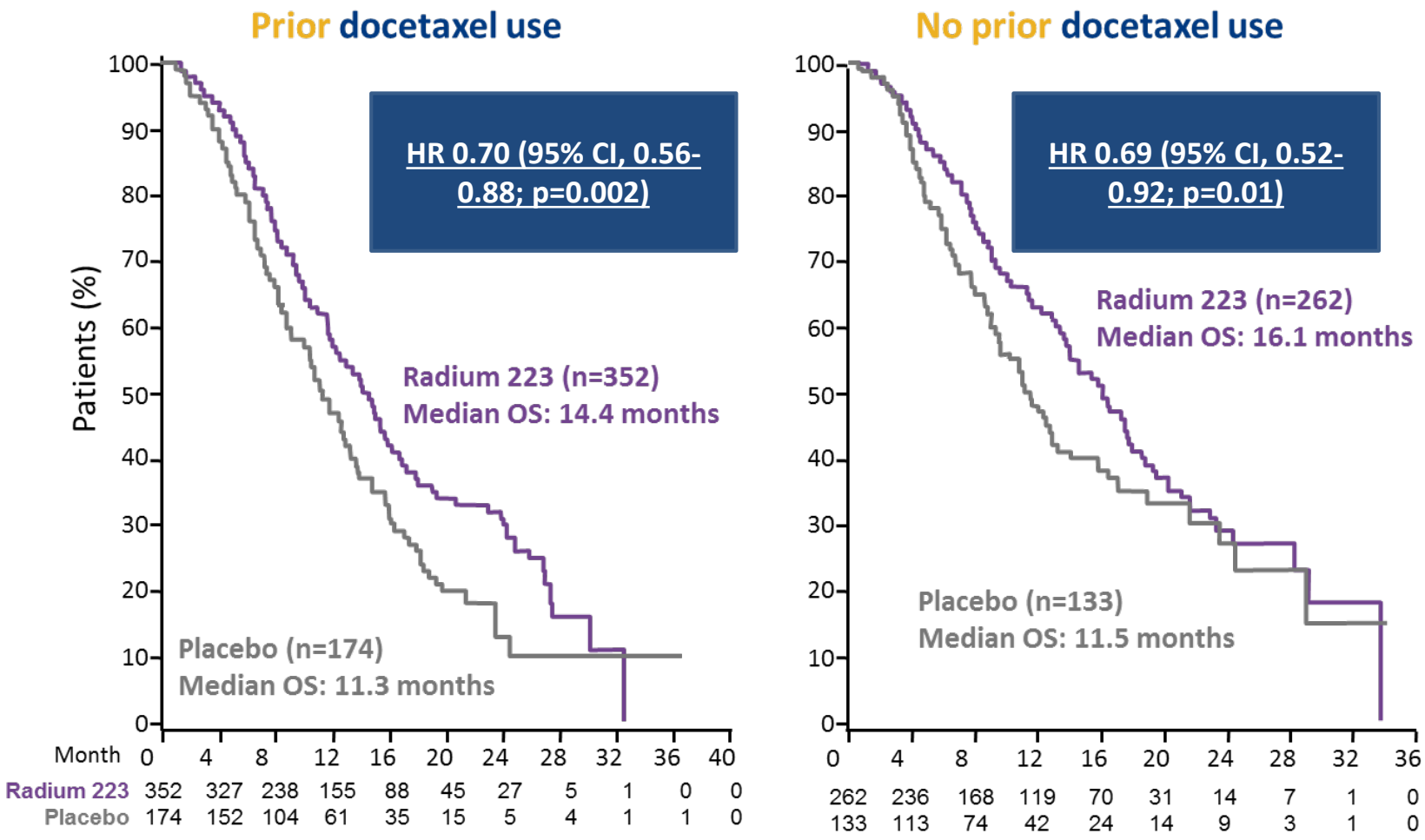
Parametri ematologici

	Ago 2016	Ott 2016	Dic 2016	Gen 2017
Hb g/dl	10,0	9,5	9,0	8,9
PLTs 10^3/µl	135	144	137	132
WBC 10^3/µl	4,23	4,00	3,90	3,40
Neu 10^3/µl	2,23	1,52	1,35	1,34
PSA ng/ml	94,0	53,2	34,0	22,8

Gennaio 2017:

- PS 1. Dolore 2 NRS colonna dorsale. PSA 22,8 ng/ml.
- Scintigrafia ossea TB : SD.
- TAC WB + femore bil. con mdc: SD scheletrica, linfoadenopatia ilare polmonare sx di circa 1 cm, riduzione dimensionale delle linfoadenopatie mediastiniche.

ALSYMPCA Overall Survival by Prior Docetaxel



Hoskin P, et al. Lancet Oncol. 2014;15:1397-1406.

ALSYMPCA Selected Adverse Events

	All Grades		Grades 3 or 4	
	Radium 223 (n=600)	Placebo (n=301)	Radium 223 (n=600)	Placebo (n=301)
Hematological				
Anaemia	187 (31)	92 (31)	77 (13)	40 (13)
Neutropenia	**30 (5)**	**3 (1)**	**13 (2)**	**2 (1)**
Thrombocytopenia	**69 (12)**	**17 (6)**	**38 (6)**	**6 (2)**
Non-haematological				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhoea	**151 (25)**	**45 (15)**	**9 (2)**	**5 (2)**
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (18)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

Data are n (%)

Parker C, et al. N Engl J Med. 2013;369:213-223

ALSYMPCA Low Incidence of Grade 3 or 4 Hematologic AEs, Regardless of Prior Docetaxel Use

- Overall, there was a low incidence of myelosuppression in the docetaxel subgroups
  - The total incidence of grade 3 or 4 thrombocytopenia was significantly higher in patients with prior versus no prior docetaxel use (7% vs 2%, respectively; *P*=0.001)
  - Patients with a history of prior docetaxel had a significantly higher incidence of grade 3 or 4 thrombocytopenia with radium-223 versus placebo (9% vs 3%, respectively; *P*=0.01)
- No statistically significant difference was seen in incidence of anemia or neutropenia between docetaxel subgroups, or between radium-223 and placebo within each docetaxel subgroup

	NO PRIOR DOCETAXEL			PRIOR DOCETAXEL			TOTAL		
PATIENTS WITH GRADE 3 or 4 AEs, n (%)	**RADIUM-223** (n=253)	**PLACEBO** (n=130)	***P* VALUE***	**RADIUM-223** (n=347)	**PLACEBO** (n=171)	***P* VALUE***	**NO PRIOR DTX** (n=383)	**PRIOR DTX** (n=518)	***P* VALUE***
Anemia	27 (11)	15 (12)	NS	50 (14)	24 (14)	NS	42 (11)	74 (14)	NS
Neutropenia	2 (1)	1 (1)	NS	11 (3)	1 (1)	NS	3 (1)	12 (2)	NS
Thrombocytopenia	7 (3)	1 (1)	NS	**31 (9)**	**5 (3)**	**0.01**	**8 (2)**	**36 (7)**	**0.001**

Vogelzang NJ, et al. J Clin Oncol. 31, 2013 (suppl; abstr 5068)

The Prostate 76:905–916 (2016)

Chemotherapy Following Radium-223 Dichloride Treatment in ALSYMPCA

Oliver Sartor,[1,2]* Peter Hoskin,[3] Robert E. Coleman,[4] Sten Nilsson,[5] Nicholas J. Vogelzang,[6] Oana Petrenciuc,[7] Karin Staudacher,[8] Marcus Thuresson,[9] and Christopher Parker[10]

- 142 pz Ra223 and 64 pz placebo dopo Alsympca hanno ricevuto chemioterapia
- 87 pts Ra223 e 37 pts placebo già pretrattati con docetaxel
- Tempo mediano tra la randomizzazione e la chemioterapia successiva 9.1 mesi nel braccio Ra223 e 7.5 nel braccio placebo
- Il pregresso trattamento con Ra223 non sembra compromettere l'uso successivo di chemioterapia, indipendentemente dal pregresso utilizzo di docetaxel

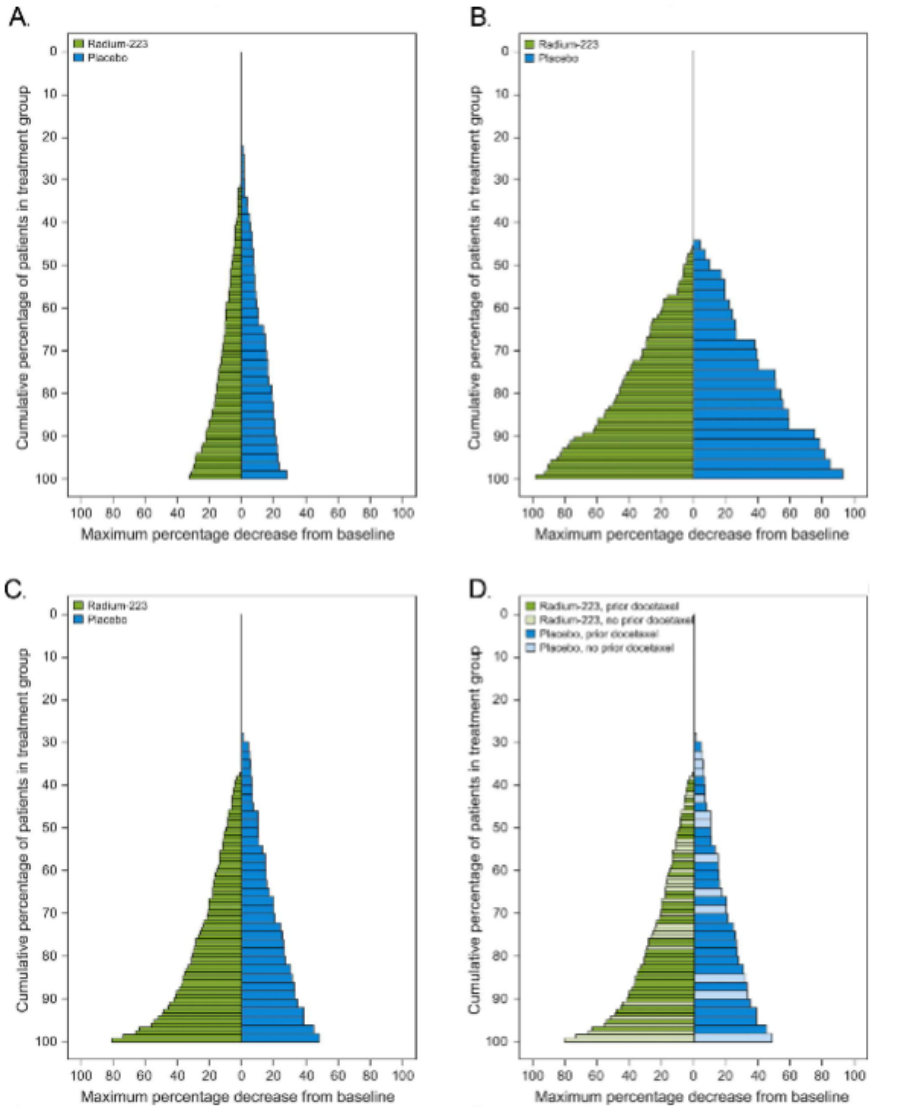


Fig. 2. Maximum percentage decrease from baseline values for hemoglobin (A), neutrophils (B), platelets (C), and platelets by prior docetaxel treatment (D).

External Beam Radiation Therapy Use and Safety With Radium-223 Dichloride in Patients With Castration-Resistant Prostate Cancer and Symptomatic Bone Metastases From the ALSYMPCA Trial

F31

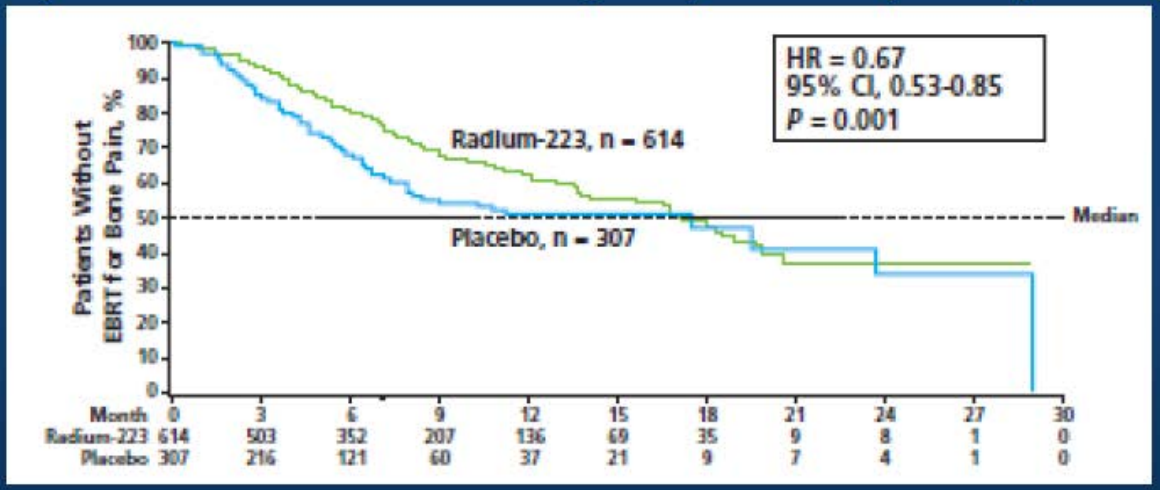
Paganelli Giovanni[1], Rossetti Claudio[2], Aglietta Massimo[3], Messina Caterina[4], Versari Annibale[5], Michalski Jeff M.[6], O'Sullivan Joe M.[7], Parker Chris[8], Garcia-Vargas Jose E.[9], Sartor A.Oliver[10], Finkelstein Steven E.[11]

(Previously presented at ASCO GU 2015, S.E. Finkelstein, et al.).

[1] IRCCS Istituto Scientifico Romagnolo, per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola (FC), IT - Meldola (FC), [2] AO Ospedale Niguarda Cà Granda, Milano, IT - Milano, [3] IRCCS Candiolo (TO), IT - Candiolo (TO), [4] AO Papa Giovanni XXIII, Bergamo, IT - Bergamo, [5] IRCCS AO Arcispedale S. Maria Nuova, Reggio Emilia, IT - Reggio Emilia, [6] Washington University School of Medicine in St. Louis, St. Louis, MO - St. Louis, [7] Centre for Cancer Research and Cell Biology, Queen's University, Belfast,United Kingdom - Belfast, [8] The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, United Kingdom - Sutton, [9] Bayer HealthCare, Whippany, NJ - Whippany, [10] Tulane Cancer Center, New Orleans, LA - New Orleans, [11] 21st Century Oncology, Scottsdale, AZ - Scottsdale.

RESULTS: ON STUDY EBRT (RECOREDED AS A CONCOMITANT PROCEDURE)

- 186/614 (30%) Ra-223 patients and 105/307 (34%) placebo patients received EBRT for bone pain and were included in the secondary endpoint analysis of time to first EBRT.
- Ra-223 significantly reduced the risk of EBRT for bone pain by 33% versus placebo (HR=0.67, P=0.001) (Figure).



- Treatment effect of Ra-223 on consistent across all analyzed subgroups, except patients with >20 mets (HR=1.06).
- Safety profile of Ra-223 was similar with or without concomitant EBRT.
  - Rates of myelosuppression were low regardless of concomitant EBRT use (with EBRT vs without EBRT, all grade): anemia 34% vs 30%; thrombocytopenia 12% vs 11%; neutropenia 6% vs 4%; and leukopenia 3% vs 5%).

Paganelli G, et al. #F31

Current prescribing information recommends that hemoglobin be ≥ 10 g/dL prior to first radium-223 administration. Ongoing protocols allow hemoglobin ≥ 8 g/dL (with transfusions).

No differences between radium-223 and placebo groups exists in frequency of blood transfusions or time to first blood transfusion, a finding that is noteworthy in this mCRPC population.

- Correlazione tra anemia e carico di malattia, ALP e PSA
- Correlazione tra piastrinopenia e livelli basali inferiori di HB e PLT e pregresso docetaxel

Safety e radiosafety

Multivariate Analysis* of Grades 2-4 Anemia (Safety Population; N=901†)

- Grades 2-4 anemia occurred in 173 of 600 (29%) radium-223 patients and 83 of 301 (28%) placebo patients
- Risk of anemia was increased among the following (Table):
  Patients receiving prior docetaxel compared to patients with no history of docetaxel
  Patients with more extensive disease (≥6 metastases/superscan) compared to patients with less extensive disease (<6 metastases)
  Patients with higher baseline ALP levels (≥220 U/L) compared to patients with lower baseline ALP levels (<220 U/L)

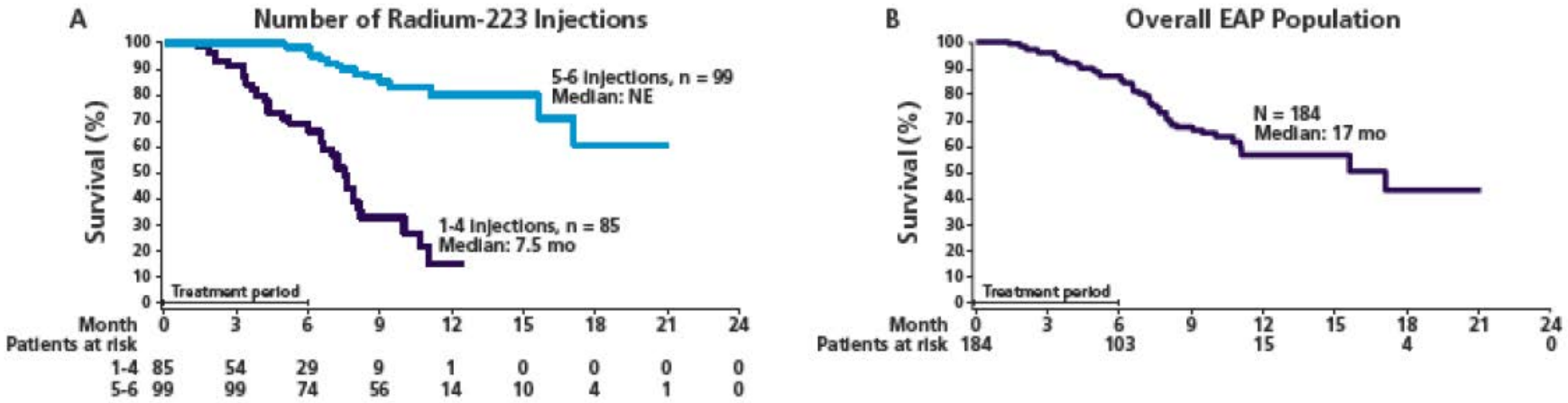
I pazienti con malattia ossea più estesa hanno maggior rischio di sviluppare anemia

BASELINE VARIABLE	HR (95% CI)	*P* VALUE
Treatment group (Radium-223/Placebo)	1.00 (0.77-1.31)	NS
Current bisphosphonate use (Yes/No)	1.13 (0.88-1.45)	NS
Prior docetaxel use (Yes/No)	1.41 (1.08-1.82)	0.0102
Extent of disease, ≥ 6 metastases/superscan (Yes/No)	**4.35 (2.22-8.52)**	**< 0.0001**
Prior EBRT for bone pain (Yes/No)	1.06 (0.83-1.35)	NS
Total ALP ≥220 U/L (Yes/No)	**2.78 (2.14-3.61)**	**< 0.0001**

O'Sullivan, JM et al, 24th International Prostate Cancer Update - February 19 - 22, 2014 - Cascade Conference Center - Vail, Colorado USA

Sartor AO, et al. (Poster 5063)
Ra-223 experience in pretreated patients: EAP setting

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

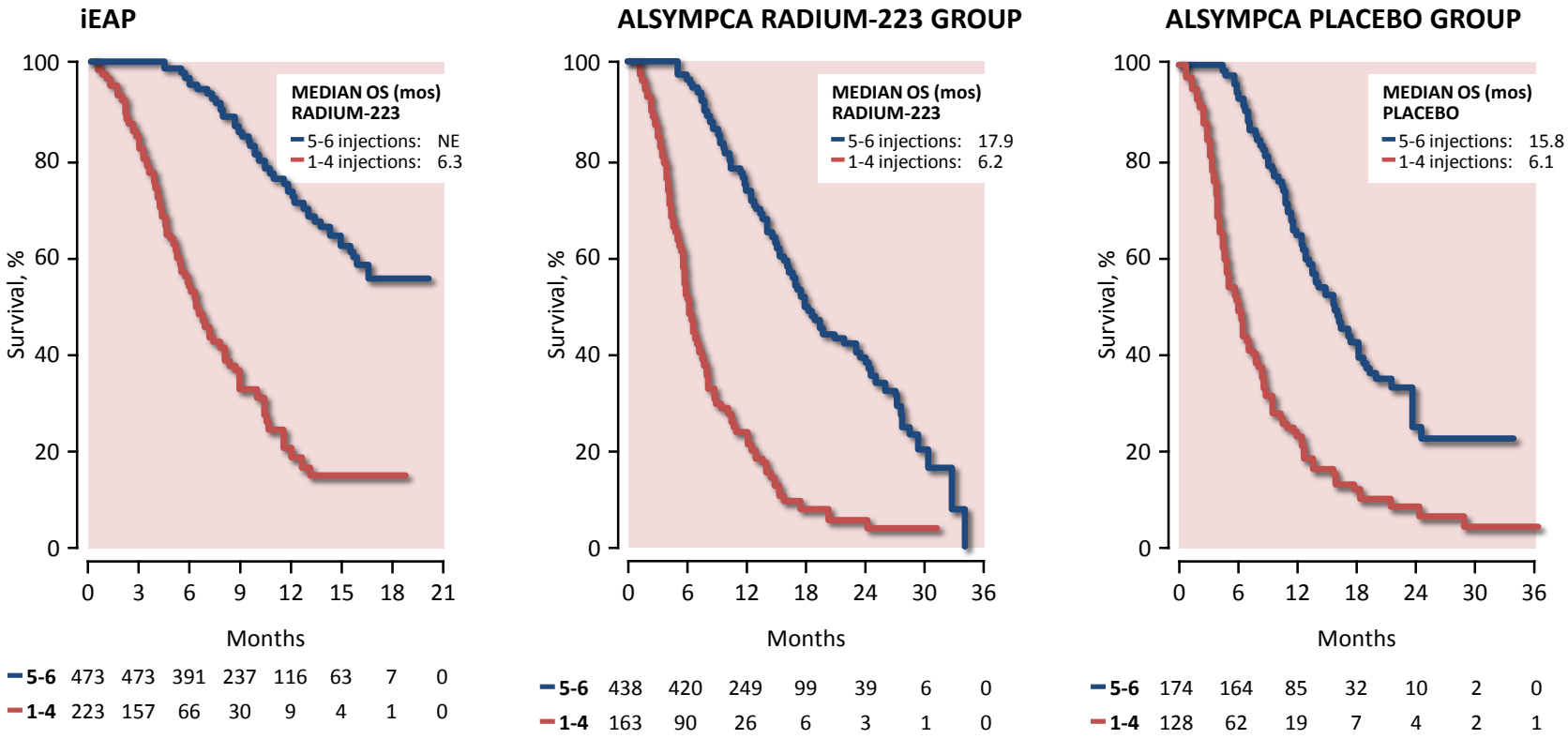


EAP = Expanded Access Program; NE = not estimable due to a short follow-up time and large percentage of patients in the overall population (70%) still alive at the time of analysis.

- A greater percentage of abi and enza naïve pts received all 6 injections (57%)
  - Median OS of pts receiving 5-6 Ra-223 injections (54%) trended longer than that of pts receiving 1-4 injections
  - In the overall EAP population, median OS was 17 mos and 44% of pts received all 6 Ra-223 injections (median, 5 injections)

iEAP e ALSYMPCA: OS per numero di somministrazioni

- In ALSYMPCA, median OS was longer in patients receiving 5-6 injections of radium 223 versus 5-6 injections of placebo. In both iEAP and ALSYMPCA (radium-223 group), OS was longer in patients receiving 5-6 injections versus those who received 1-4 injections
- The use of radium-223 earlier in the treatment paradigm may allow patients to receive the full course of radium-223 treatment



NE = not estimable.

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

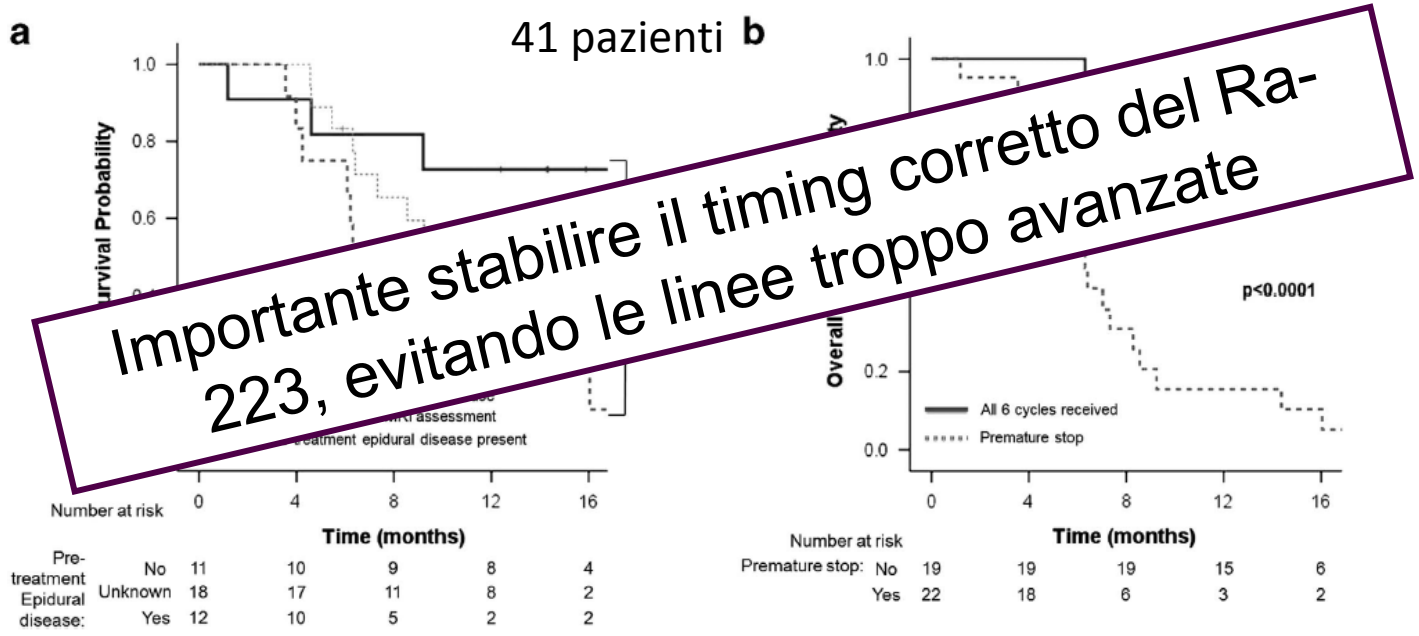
Uso precoce del Radio-223

ORIGINAL ARTICLE

Radium-223 outcomes after multiple lines of metastatic castration-resistant prostate cancer therapy in clinical practice: implication of pre-treatment spinal epidural disease

41 pazienti

Importante stabilire il timing corretto del Ra-223, evitando le linee troppo avanzate



La maggior estensione di malattia ossea al basale, il numero di pretrattamenti e la presenza di malattia alla RM correlano con:

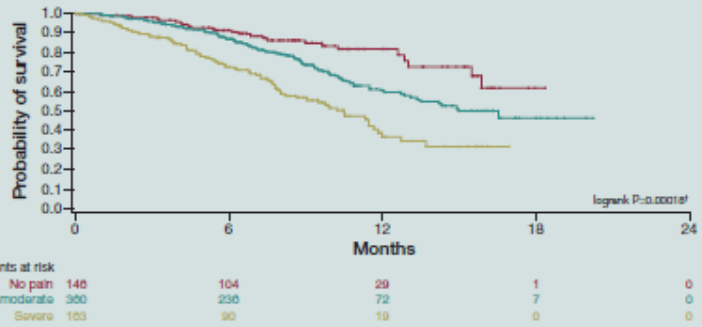
Interruzione precoce della terapia

OS e PFS inferiori

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

Figure 5. OS in EAP patients grouped by baseline pain

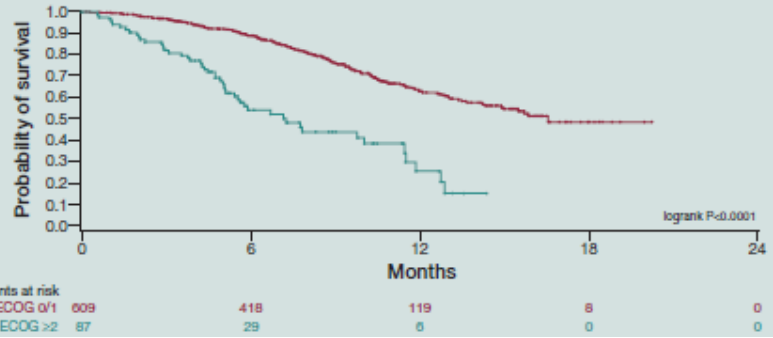
	Baseline pain* (N=669)		
	No pain	Mild–moderate	Severe
Patients, n	146	360	163
No of events (%)	25 (17%)	104 (29%)	72 (44%)
No of censored patients (%)	121 (83%)	256 (71%)	91 (56%)
Median OS, months (95% CI)	NA (16–NE)	15 (13–NE)	11 (8–12)



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 (N=696)	
	0–1	≥2
Patients, n	609	87
No of events (%)	163 (27%)	47 (44%)
No of censored patients (%)	446 (73%)	40 (46%)
Median OS, months (95% CI)	17 (14–NE)	7 (5–11)



Lo studio iEAP conferma i dati di efficacia e safety dello studio ALSYMPCA

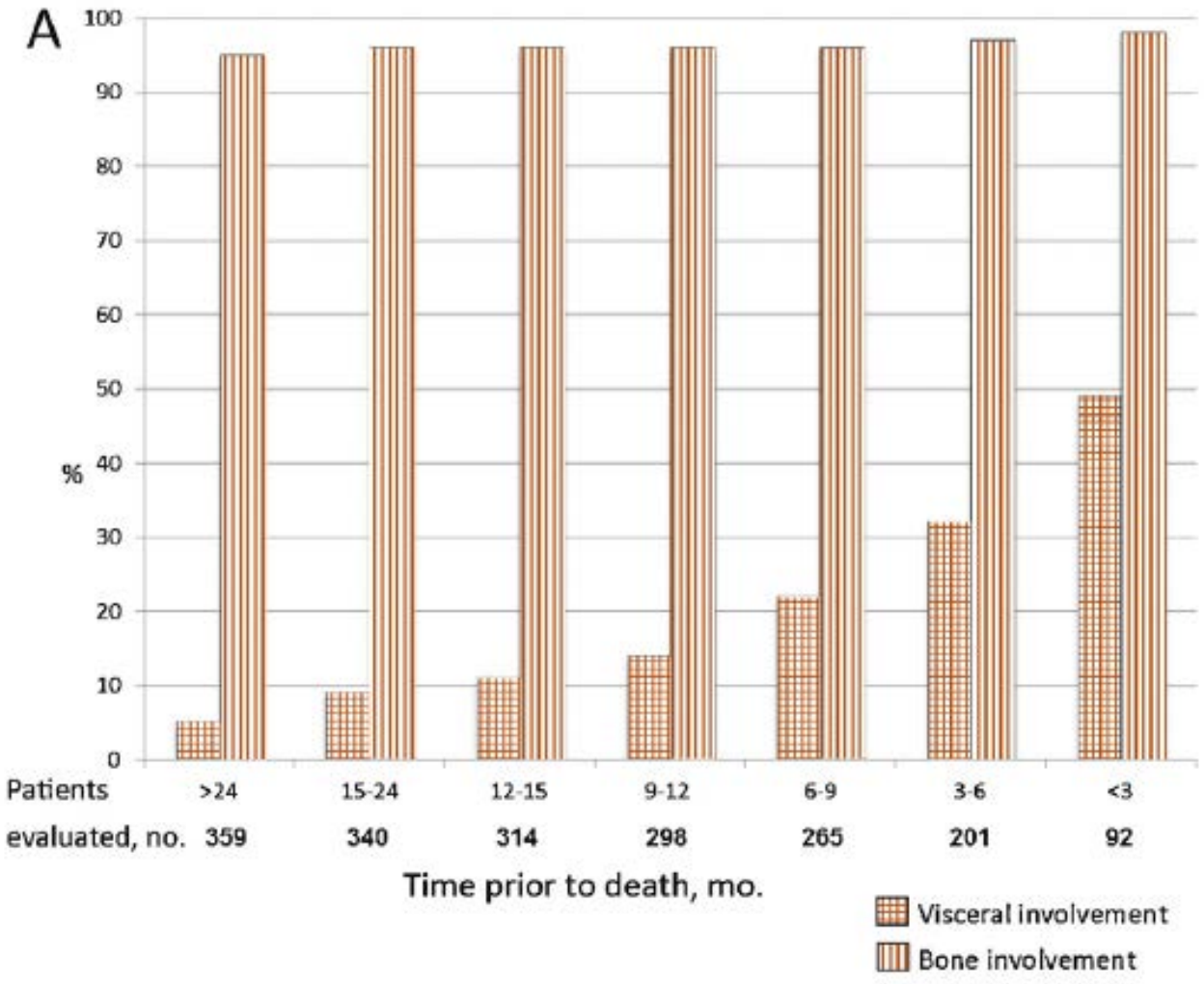
CONCLUSIONS

- 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.

Lo studio iEAP indica che i pazienti con miglior ECOG, assenza di dolore e ALP inferiori hanno una miglior sopravvivenza

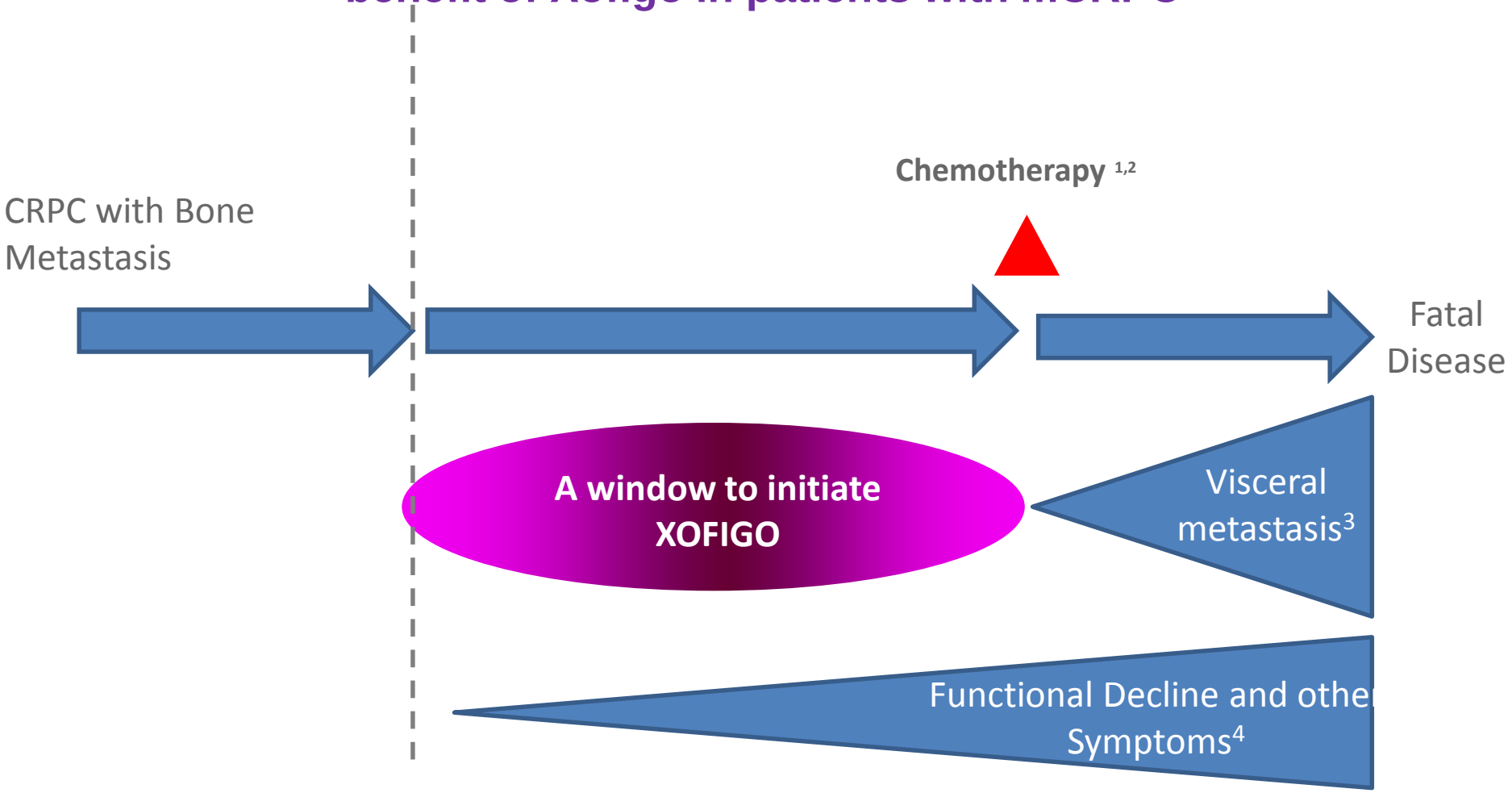
MOST PATIENTS WITH mCRPC ARE CANDIDATES FOR XOFIGO AS VISCERAL METASTES MOSTLY OCCUR IN THE FINAL STAGE OF DISEASE

< 12months of survival



Pezaro et al Eur Urol 2014

There is a well defined window of opportunity to maximise the benefit of Xofigo in patients with mCRPC



1 Ryan et al N Engl J Med 2013;368:138-48
2 Beer et al N Engl J Med. 2014 Jul 31;371(5):424-33
3 Pezaro et al Eur Urol 2014
4 Median Functional decline (Fact-P) after 12.7 months[2]