# Seconda sessione: casi clinici


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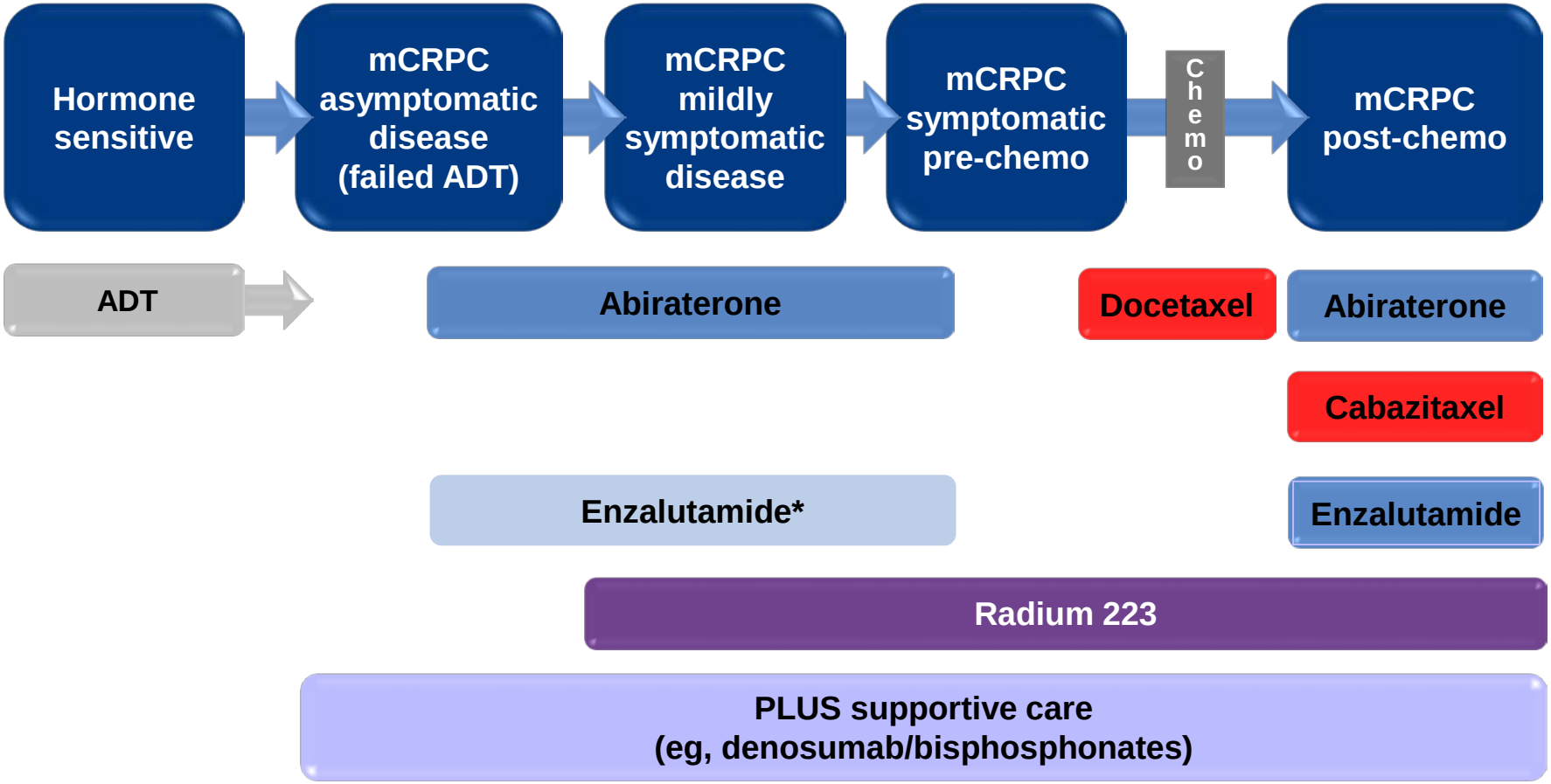
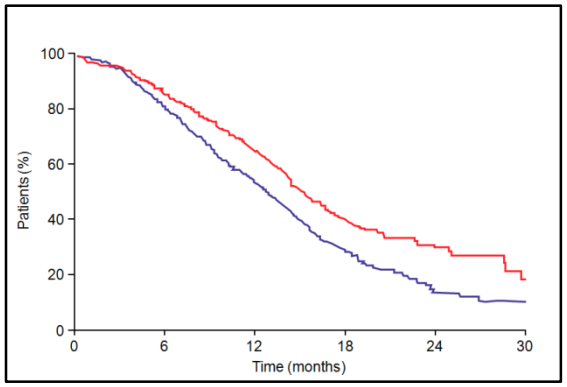
# Treatment options for mCRPC



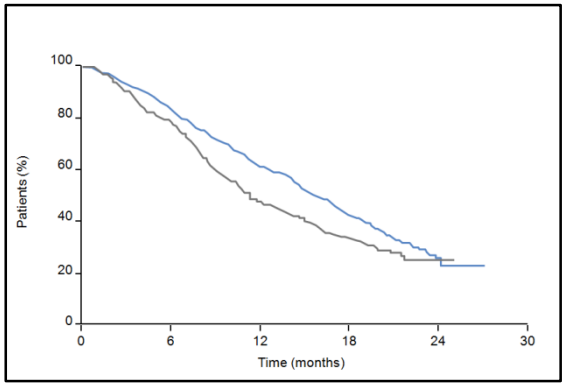

FDA/EMA approved agents
*Positive Phase 3 data and FDA approved

# New therapies with OS benefit in mCRPC

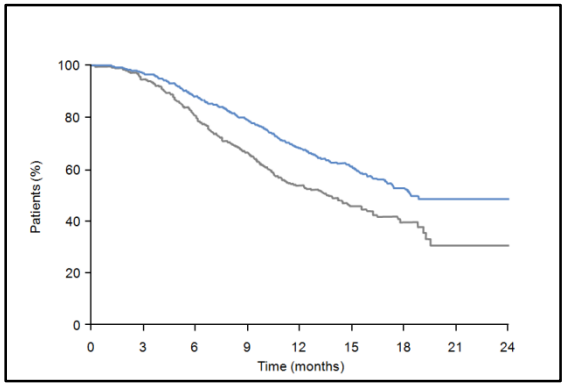
**Cabazitaxel/P** vs mitoxantrone/P[1]



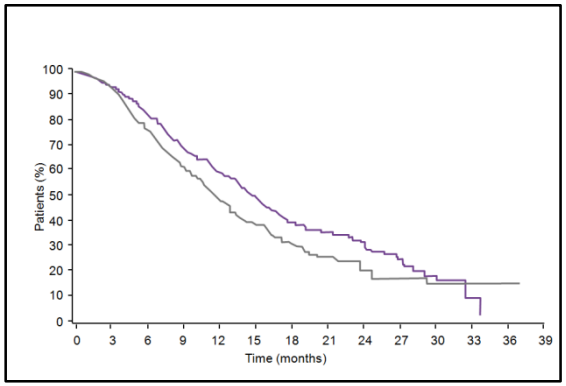

**Abiraterone/P** vs placebo/P[2]




**Enzalutamide*** vs placebo[3]




**Radium 223** vs placebo[4]




**Chemotherapy**

**Novel hormonal agents**

**Novel radiopharmaceutical**

P, prednisone

[1] de Bono JS et al. Lancet 2010;376:1147–54; [2] Fizazi K et al. Lancet Oncol 2012;13:983–92;
[3] Scher HI, et al. NEJM 2012;367:1187–97; [4] Parker C et al. NEJM 2013;369:213–23

# OS benefit in mCRPC

| | Patient setting | Control | Overall survival | | |
|---|---|---|---|---|---|
| | | | Increase in median, months | HR | p value |
| **Docetaxel/P**[1] | First-line | Mitoxantrone/P | 2.9 | 0.79 | p=0.004 |
| **Cabazitaxel/P**[2] | Post-docetaxel | Mitoxantrone/P | 2.4 | 0.70 | p<0.0001 |
| | | | | | |
| **Abiraterone/P**[4] | Post-docetaxel | Placebo/P | 4.6 | 0.74 | p<0.0001 |
| **Abiraterone/P**[5] | Chemo-naïve | Placebo/P | 4.4 | 0.80 | p=0.0027 |
| **Enzalutamide**[6] | Post-docetaxel | Placebo | 4.8 | 0.63 | p<0.001 |
| **Enzalutamide**[7*] | Chemo-naïve | Placebo | 2.2 | 0.71 | p<0.0001 |
| **Radium 223**[8] | Bone metastases | Placebo | 3.6 | 0.70 | p<0.001 |

[1] Berthold DR, et al. JCO 2008;26:242–45; [2] de Bono JS et al. Lancet 2010;76:1147–54;
[3] Kantoff PW et al. NEJM 2010;363:411–22; [4] Fizazzi K et al. Lancet Oncol 2012;13:983–92;
[5] Ryan CJ, et al. Ann Oncol 2014; 25(Suppl.4):iv255–iv279; [6] Scher HI et al. NEJM 2012;367:1187–97;
[7] Beer T. ASCO GU 2014 abstract LBA1^; [8] Parker C, et al. NEJM 2013;369:213–23

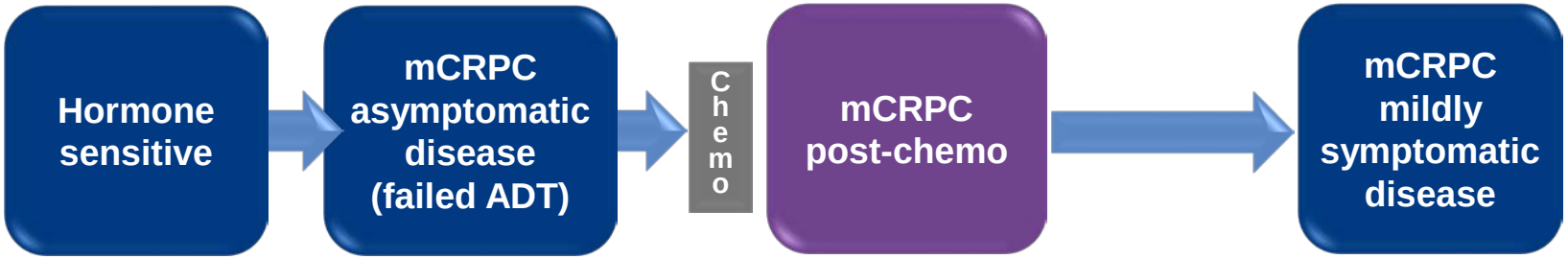
*FDA approved, but not EMA approved

# Differences in safety profiles

| | All adverse events in >10% of patients and ≥2% higher than in placebo |
|---|---|
| **Cabazitaxel/P** vs mitoxantrone/P[1*] | Anaemia (97%); leukopenia (96%); neutropenia (94%); thrombocytopenia (47%); diarrhoea (47%); fatigue (37%); nausea (34%); vomiting (23%); asthenia (20%); constipation (20%); haematuria (17%); back pain (16%); abdominal pain (12%); shortness of breath (12%); fever (12%); joint pain (11%) |
| | |
| **Abiraterone/P** vs placebo/P[3] | Fatigue (47% vs 44%); fluid retention (33% vs 24%); joint pain (30% vs 24%); diarrhoea (20% vs 15%); hypokalaemia (18% vs 9%); cardiac disorders (16% vs 12%); shortness of breath (15% vs 12%); urinary tract infection (13% vs 7%); hypertension (11% vs 8%); abnormalities in liver function tests (11% vs 9%) |
| **Enzalutamide** vs placebo[4] | Fatigue (34% vs 29%); diarrhoea (21% vs 18%); hot flushes (20% vs 10%); musculoskeletal pain (14% vs 10%); headache (12% vs 6%) |
| **Radium 223** vs placebo[5] | Diarrhoea (25% vs 15%); vomiting (18% vs 14%); peripheral fluid retention (13% vs 10%); thrombocytopenia (12% vs 6%) |

[1] de Bono JS et al. Lancet 2010;76:1147–54; [2] Kantoff PW et al. NEJM 2010;363:411–22;
[3] Fizazi K et al. Lancet Oncol 2012;13:983–92; [4] Scher HI et al. NEJM 2012;367:1187–97;
[5] Parker C, et al. NEJM 2013;369:213–23

# Patient case study post chemotherapy:E.A




1996 radical prostatectomy:Adenoca GS 3+2
Adjuvant therapy:LH-RH analogues: 12 m.

## Co-morbidities:

Artritis reumatoides

## Medical Treatment:

-Prednisone 5 mg die
-Prednisone L.A. 5 mg die
-Idroxiclorochina solfato 200 mg x 2 die
-Etoricoxib 90 mg al bis.
-Paracetamolo 500mg+codeina 30mg: 2 die

65 yr

## Treatment history

- 09/2012 Bone metastases
- BAT +Zoledronic acid 4 mg e.v (03/12-08/14)
- Docetaxel (6 cycles: 02-08/2014)PSA=7,9
- Abiraterone+ prednisone (09/14-08/16)PSA=27
- Standard analgesics

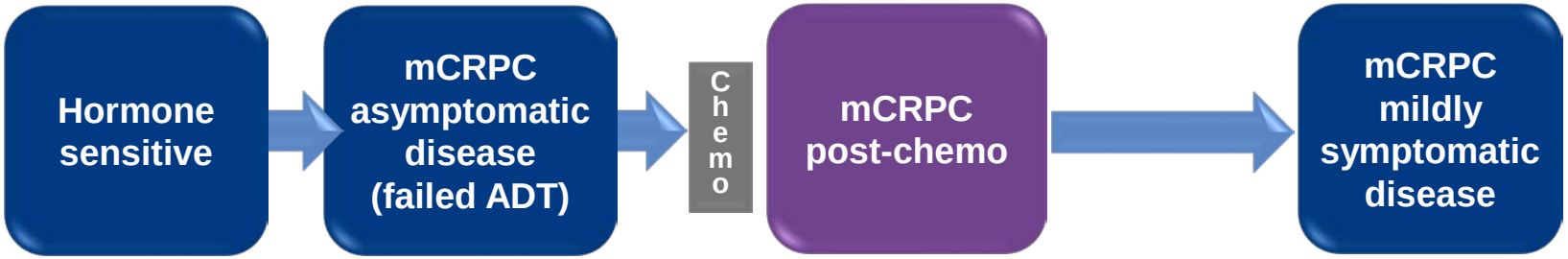
## Symptoms prior to Radium 223

Mild bone pain NRS=5; ECOG=0

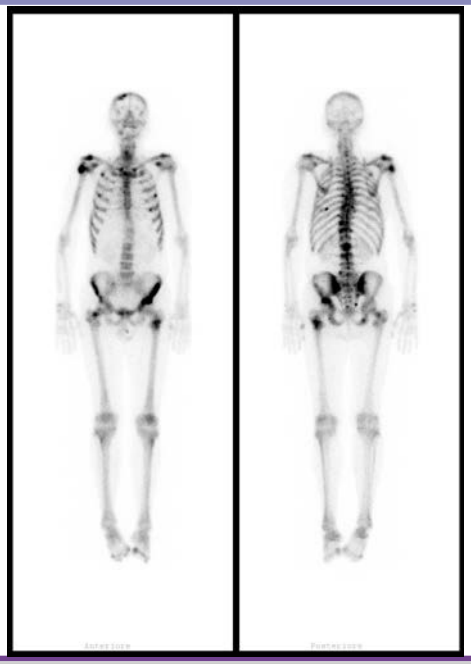
## Scans/tests

Extensive bone metastases on bone scan;
PD on Choline PET TC
Rising PSA 7,9 → 27 µg/L
No visceral metastases
15/9/16:BAP=157 mcg/L;ALP=484U/L

# Patient case study post chemotherapy:E.A




**Sept. 2016: before Radium 223**



65 yr

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Mild bone pain NRS=5; ECOG=0

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PD on Choline PET TC
PSA= 27 µg/L
No visceral metastases
15/9/16:BAP=157 mcg/L;ALP=484U/L

# Selezione del paziente candidabile a Ra223

- *Prima dell'arruolamento e della prima somministrazione*:
- neutrofili (*absolute neutrophil count*, ANC): ≥ 1,5 x $10^9$/L,
- conta piastrinica ≥ 100 x $10^9$/L
- emoglobina ≥ 10,0 g/dL.
- escludere i p. con anamnesi di m. di Crohn e/o colite ulcerosa
- controindicazione relativa : ONJ post-bifosfonati , diverticolosi e poliposi del colon
- *Prima delle somministrazioni successive*:
- ANC: ≥ 1,0 x $10^9$/L
- conta piastrinica ≥ 50 x $10^9$/L.

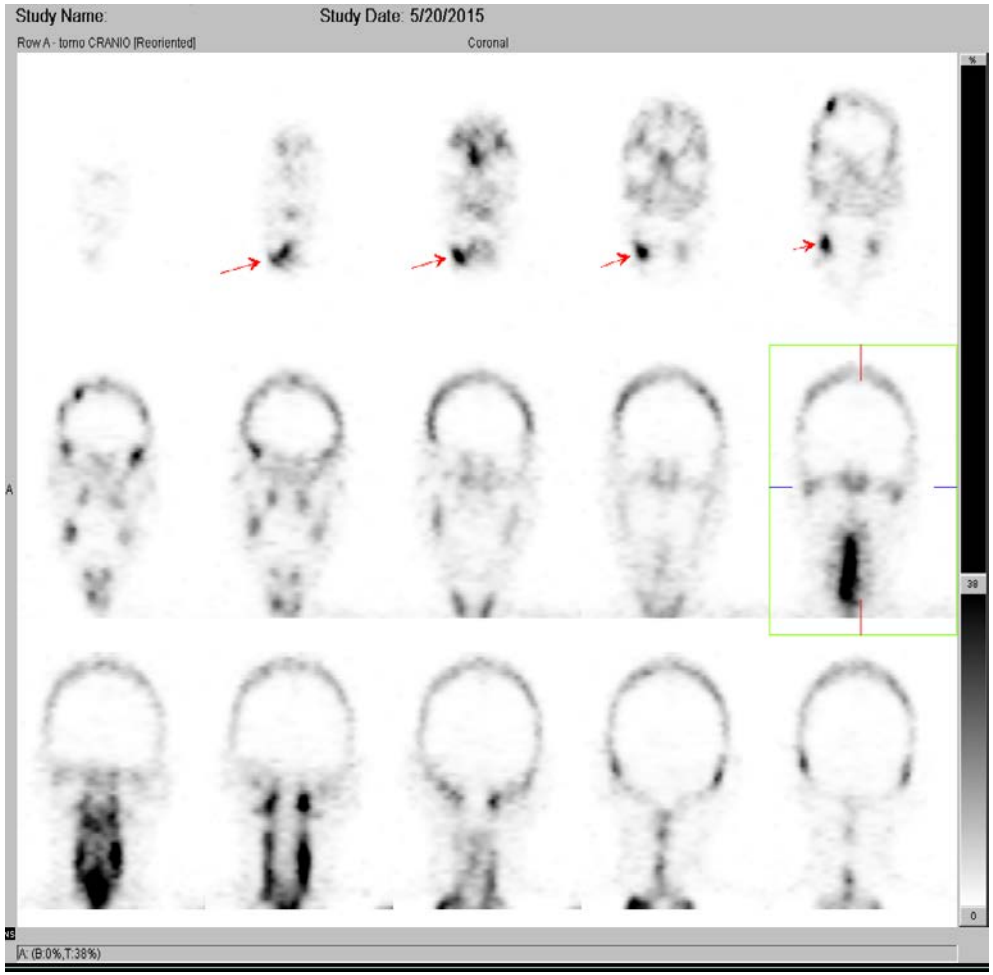
*Se questi valori non rientrano in questi limiti* ***entro 6 sett.dall' ultima*** *somministrazione di Xofigo™* **il trattamento potrà continuare solo dopo un'attenta valutazione del rapporto rischio/beneficio**.

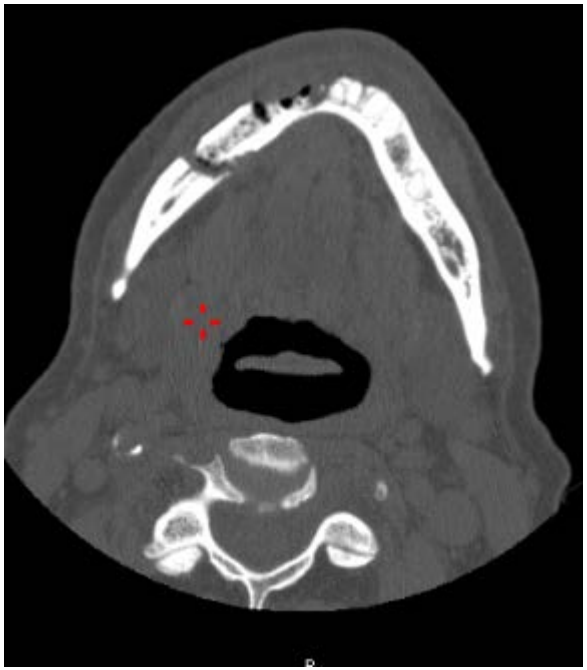
***NB:*** L' evidenza di **riserva midollare ridotta**, dopo precedenti chemioterapie citotossiche e/o radioterapia o pazienti con mCRPC con **diffuse infiltrazioni ossee (EOD4; "superscan")** devono essere **considerati con cautela**.

Un'aumentata incidenza di **reazioni avverse ematologiche, come neutropenia e trombocitopenia G3-4( <1% casistica**), è stata osservata in questi pts nello studio ALSYMPCA III

# Patient case study 1: Radium 223 therapy

-05/2015 ONJ post- bifosphonates T.



# Radio-223 e osteonecrosi della mandibola

- In Letteratura,ad oggi, non sono presenti studi che dimostrino una correlazione tra il trattamento con $^{223}$Ra e l'insorgenza o aggravamento dell' osteonecrosi della mandibola

- Nello studio di fase III sono stati riportati casi di ONJ nello 0,67% (4/600) dei pazienti trattati con $^{223}$Ra e nello 0,33% (1/301) dei pazienti trattati con placebo.

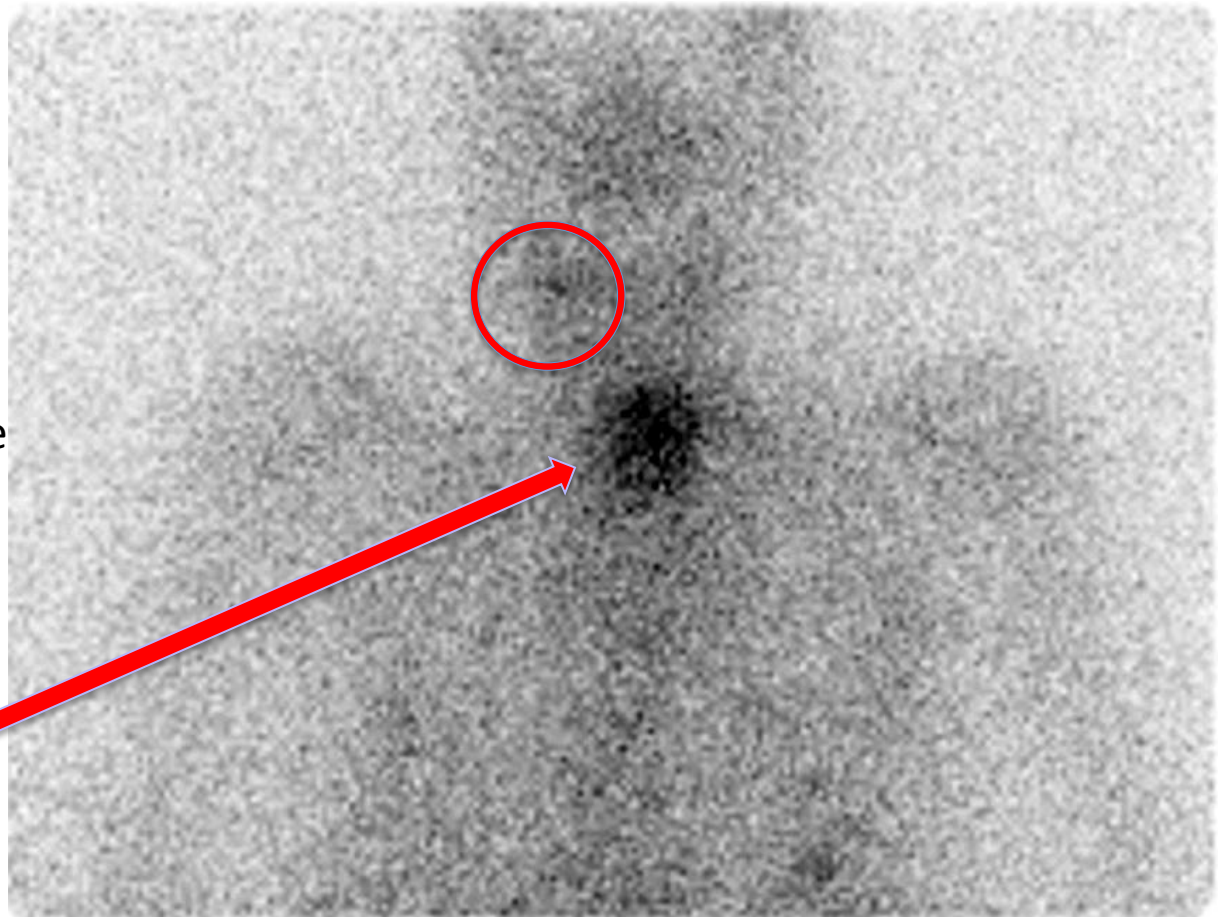
- Anche nella nostra esperienza i pz in trattamento con $^{223}$Ra che presentavano ONJ avevano effettuato, precedentemente, terapia con bifosfonati, denosumab o taxani.


- Parker C et al, NEJM 2013;369:213-223
- Radio-223: Riassunto caratteristiche del prodotto, versione 2016

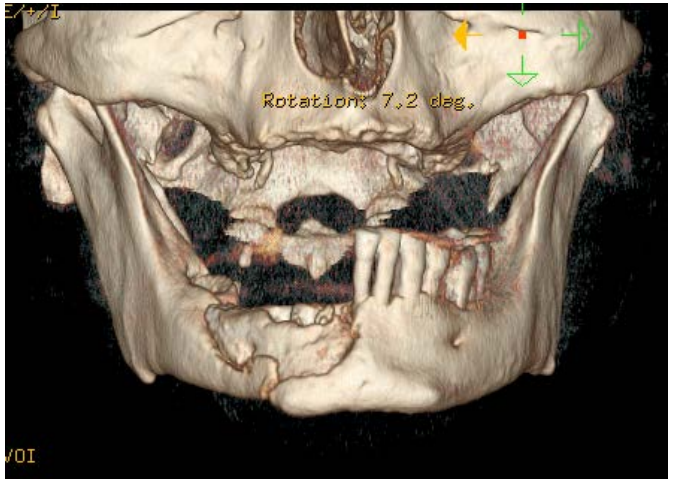
# 82 yrs – Scintigraphy post III 223Radium Treatment 26/3/2015

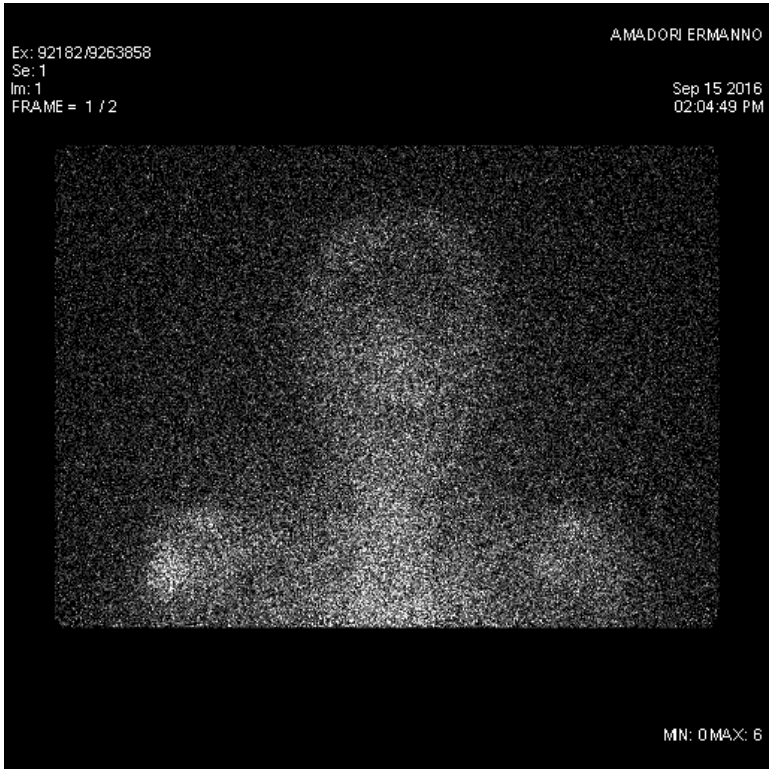
Right mandibular osteonecrosis with moderate uptake of 223 Radium

Bone Lesion



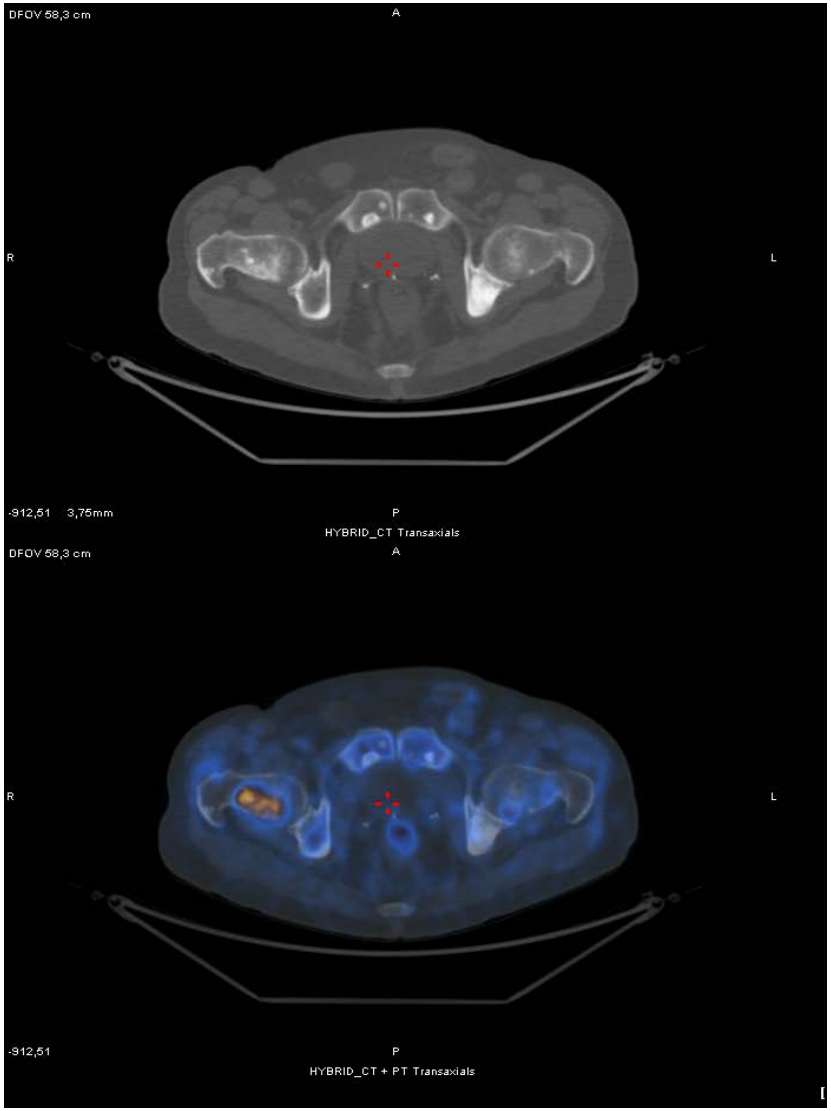
# 65 yrs – Scintigraphy post III 223Radium Treatment 13/10/2016

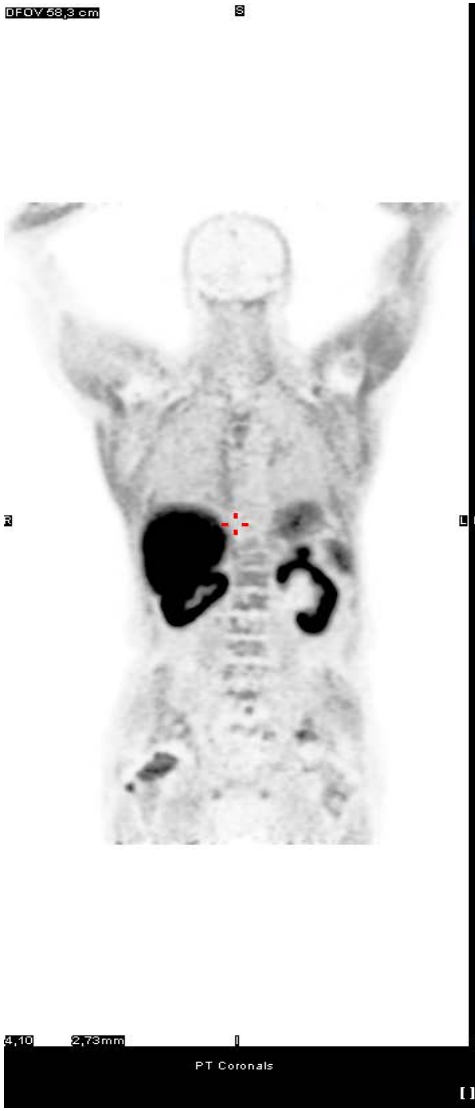


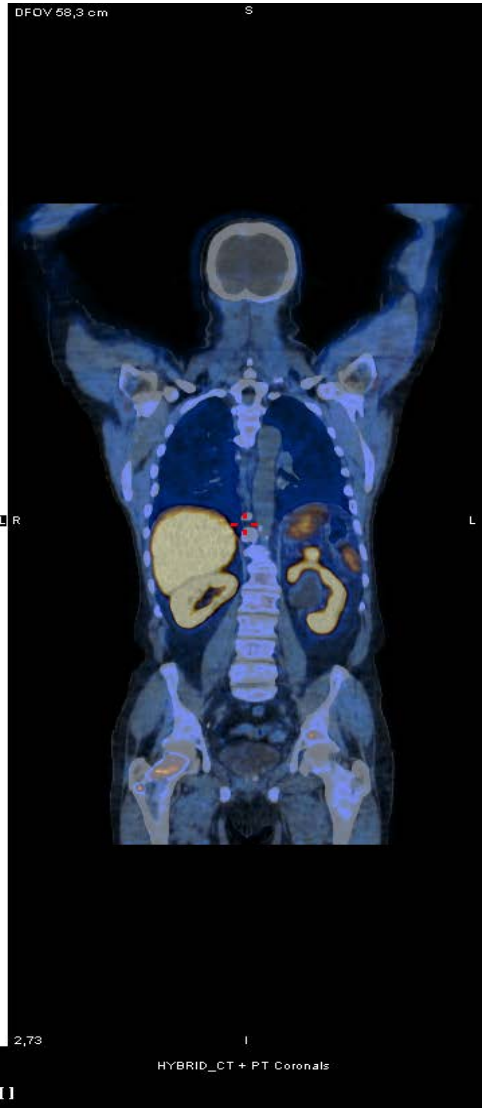




Right mandibular osteonecrosis without significant uptake of 223 Radium

# 30/9/16 NSE=5 : Bone metastases: SSE Risk : inter–trocanteric region femoral ds.



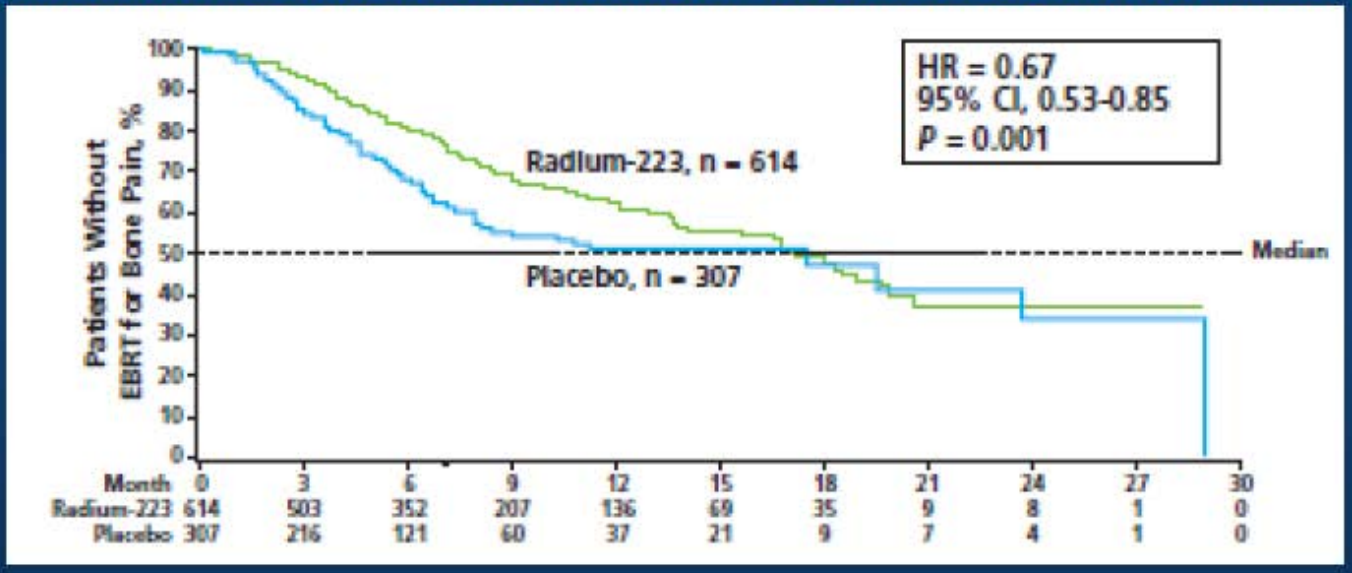



# External beam radiation therapy (EBRT) use and safety with radium-223 dichloride (Ra-223) in patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) from the ALSYMPCA trial. [Finkelstein et al. Abstract 182]

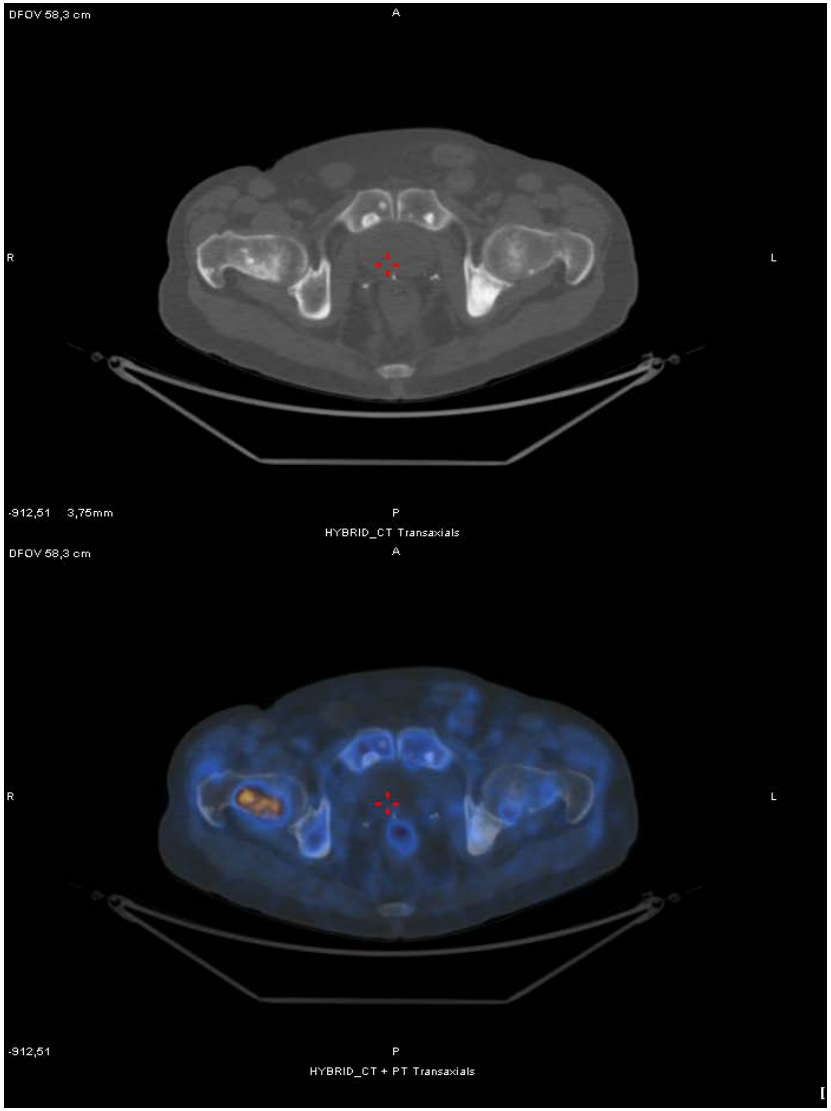
## RESULTS: ON STUDY EBRT (RECOREDED AS A CONCOMITANT PROCEDURE)

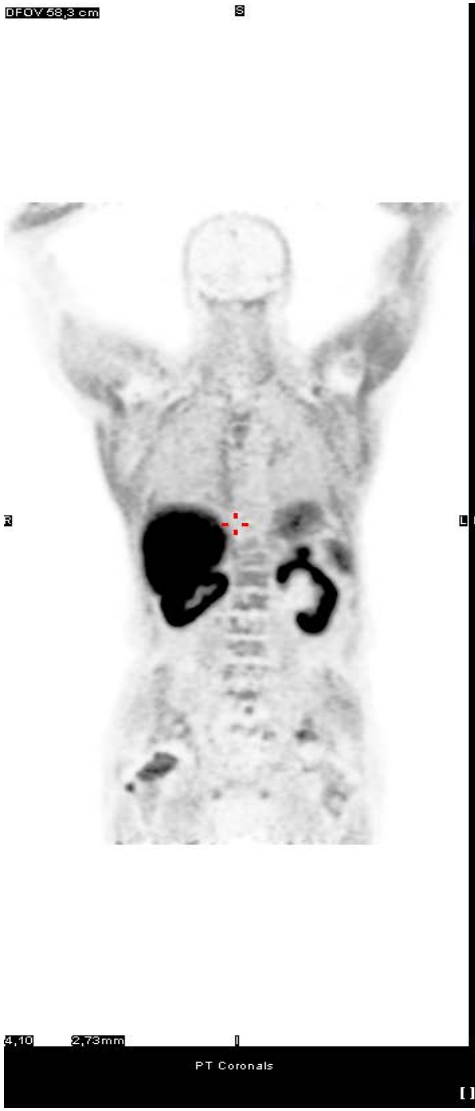
- 186/614 (30%) Ra-223 patients and 105/307 (34%) placebo patients received EBRT for bone pain and were included in the secondary endpoint analysis of time to first EBRT.
- Ra-223 significantly reduced the risk of EBRT for bone pain by 33% versus placebo (HR=0.67, P=0.001) (Figure).

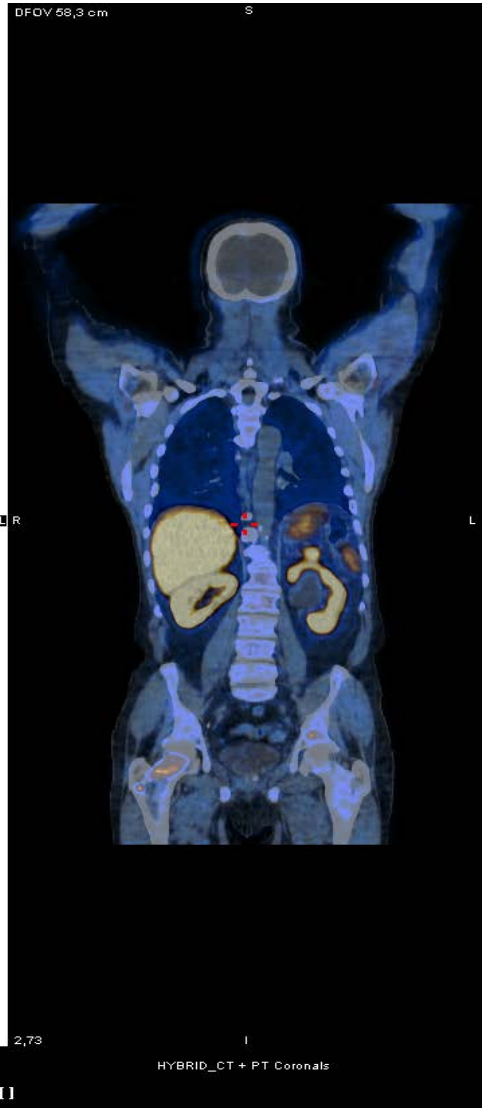



- Treatment effect of Ra-223 on consistent across all analyzed subgroups, except patients with >20 mets (HR=1.06).
- Safety profile of Ra-223 was similar with or without concomitant EBRT.
  - Rates of myelosuppression were low regardless of concomitant EBRT use (with EBRT vs without EBRT, all grade):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

# 30/9/16 RTE 8 Gy single fraction inter–trocanteric region femoral ds.



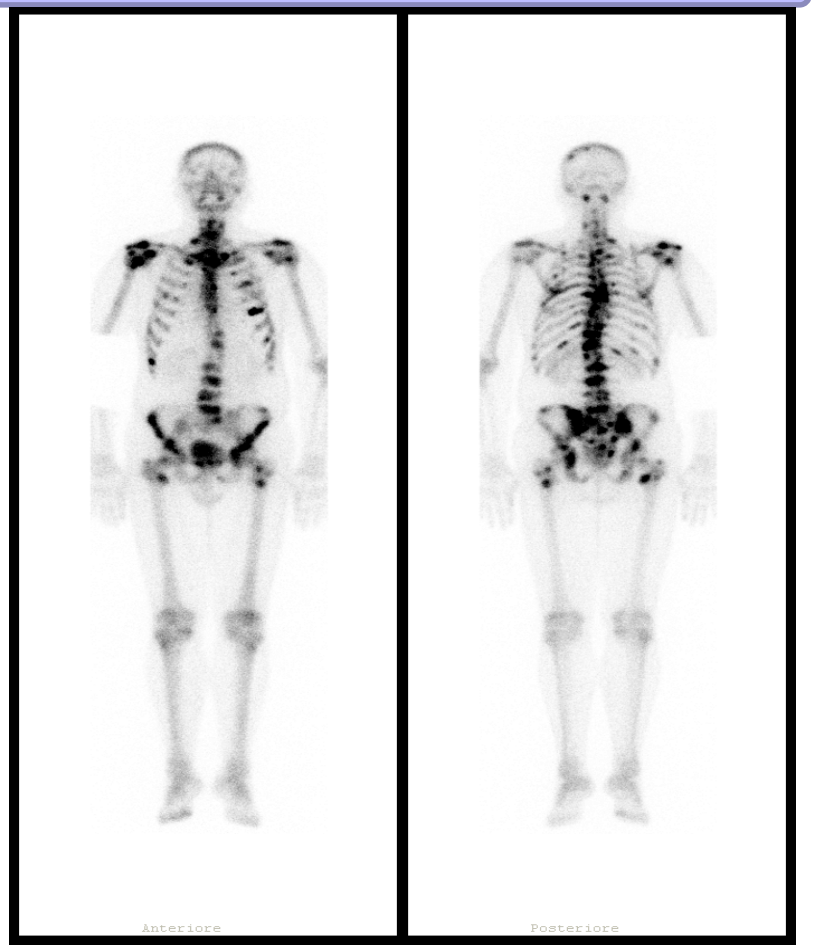
# Patient case study 1: Radium 223 therapy

15 Sept. 2016 − 9 Febr. 2017: six cycles of Radium 223

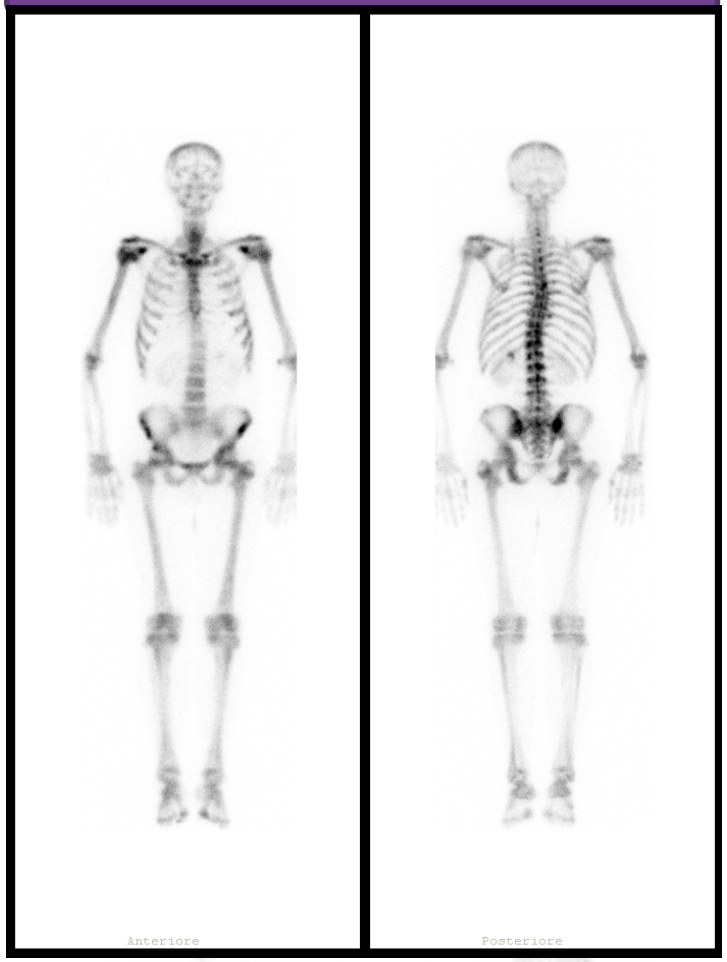
- Some pain flare, thereafter pain ↓ NRS=0 ;
- Mild astenia G1
- ALP ↓ 432 → 90 U/L
- PSA ↑ 27,19 → 47,9 → 91 µg/L

# Patient case study 1: bone scans

**16 Aug 2016: before $^{223}$Ra**

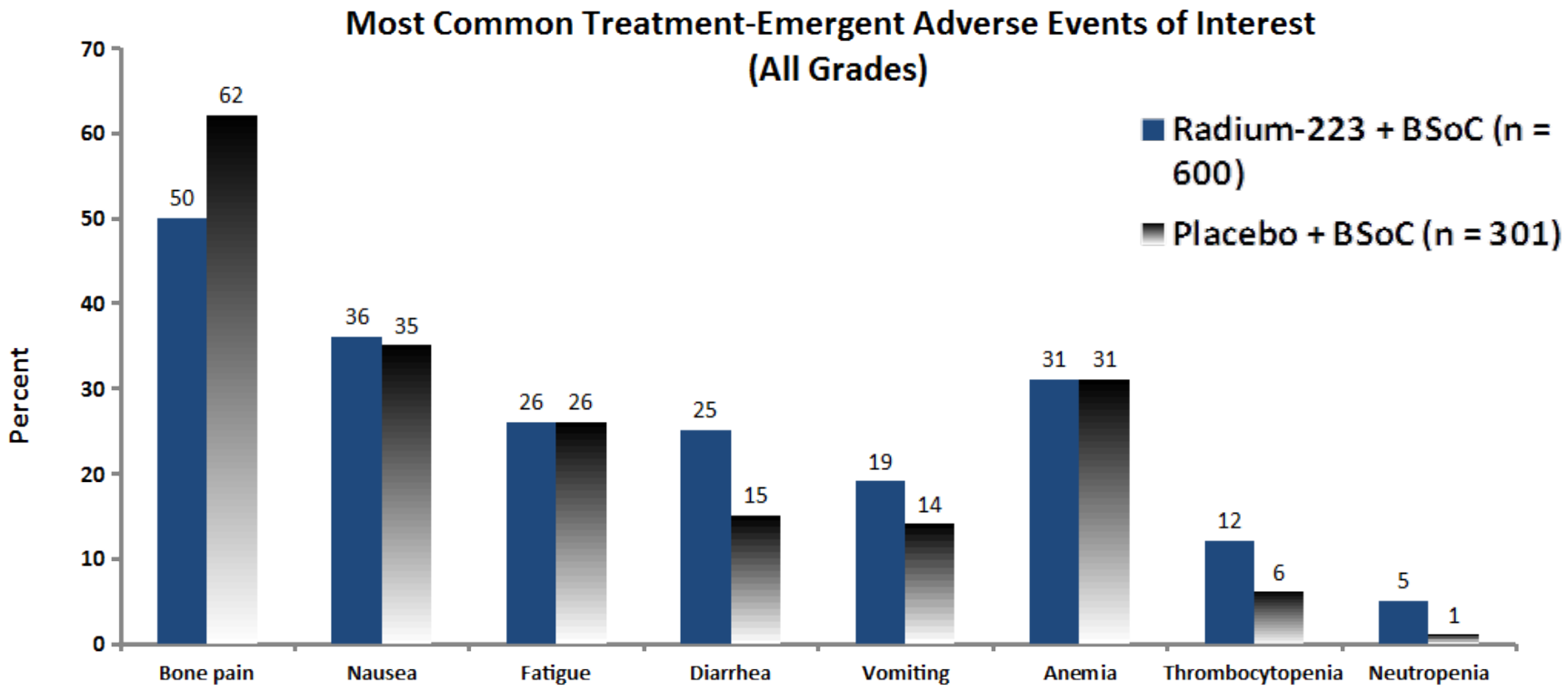



**20 March 2017: after $^{223}$Ra**




***21/3/17 ECOG=0; NRS=0; Feb 2017:TC Body: no visceral metastases; no side effects***

# Studio ALSYMPCA III:EVENTI AVVERSI




**Radium-223 dichloride for the treatment of bone metastatic castration-resistant prostate cancer: an evaluation of its safety**

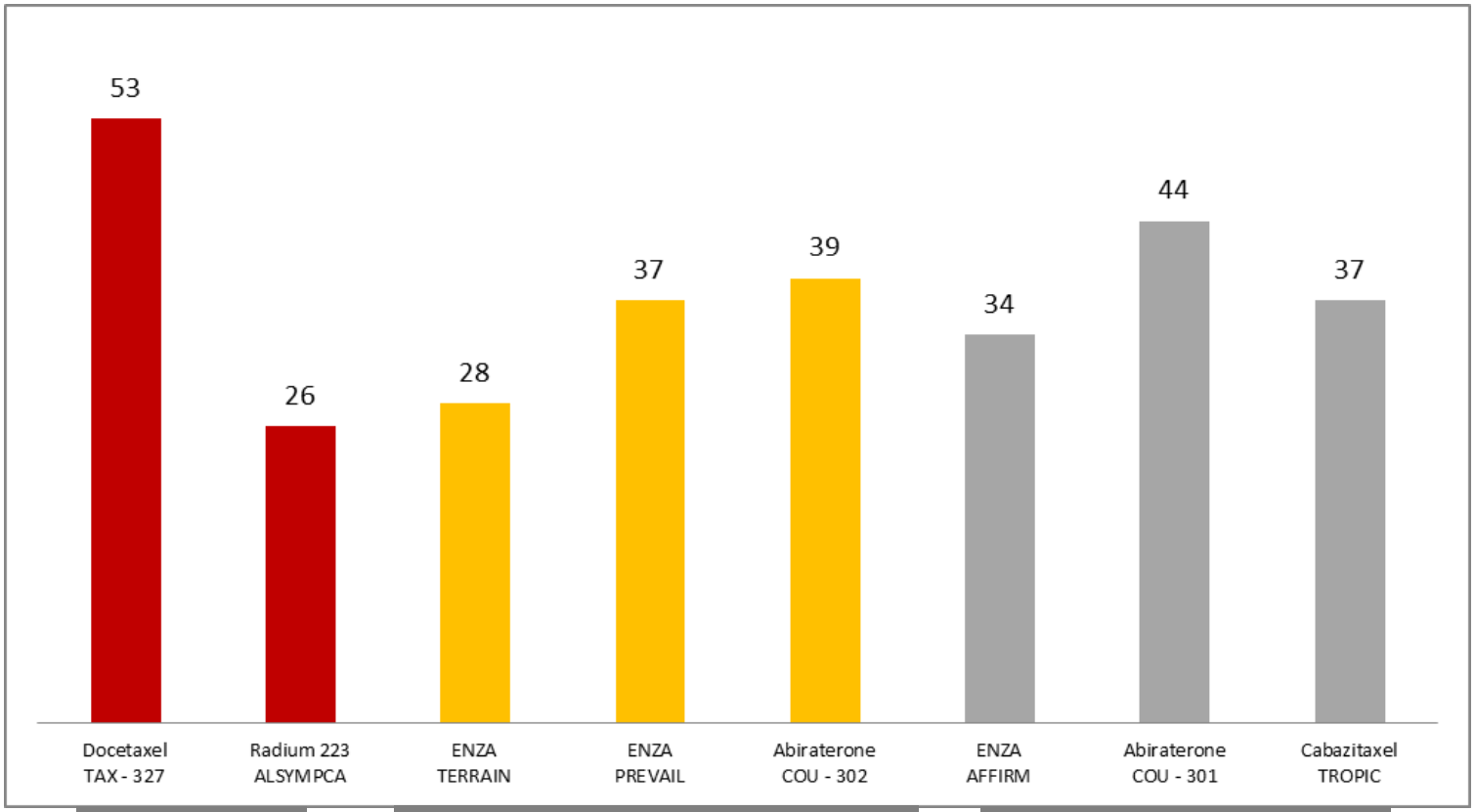
Sten Nilsson Expert opinion in drug safety; vol.14, 2015 issue 7

# Phase 3 ALSYMPCA: adverse events

| | All grades | | Grades 3 or 4 | |
|---|---|---|---|---|
| | Radium 223 (n=600) | Placebo (n=301) | Radium 223 (n=600) | Placebo (n=301) |
| **Haematological** | | | | |
| Anaemia | 187 (31) | 92 (31) | 76 (13) | 39 (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. NEJM 2013;369:213–23

# Fatigue incidence in mCRPC





- Beer TM, et al. N Engl J Med 2014;371:424–33
- Scher HI, *et al. N Eng J Med* 2012;367:1187–97
- Neal D Share et All Lancet Oncology 17(2): 153-163 (2016)
- Fizazi K, *et al. Lancet Oncol* 2012;13:983–92
- Ryan CJ, *et al. N Engl J Med* 2013;368:138–48
- de Bono JS, *et al. Lancet* 2010;376:1147–54
- Parker CP, *et al. N Engl J Med* 2013;369:213–23
- Tannok I et al. N Engl J Med 2004; 351:1502-1512

# Radium 223: recommendations from the clinic

- Radium 223 treatment consists of six cycles
  - Consider the clinical condition when accepting patients → do not use as a last resort treatment as patients may not be able to complete all cycles

- Side effects are generally mild and not difficult to manage, even in patients with advanced disease

- Currently no available markers for response
  - ALP is a potential predictor of treatment effect
  - PSA can vary and is not an accurate biomarker
  - Imaging results are not predictive for treatment outcome

- Always be aware of skeletal lesions that require EBRT:
  → Act on clinical signs and symptoms