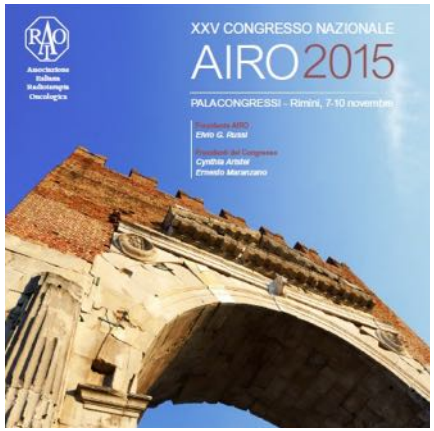


SIMPOSIO AIRO-AIMN

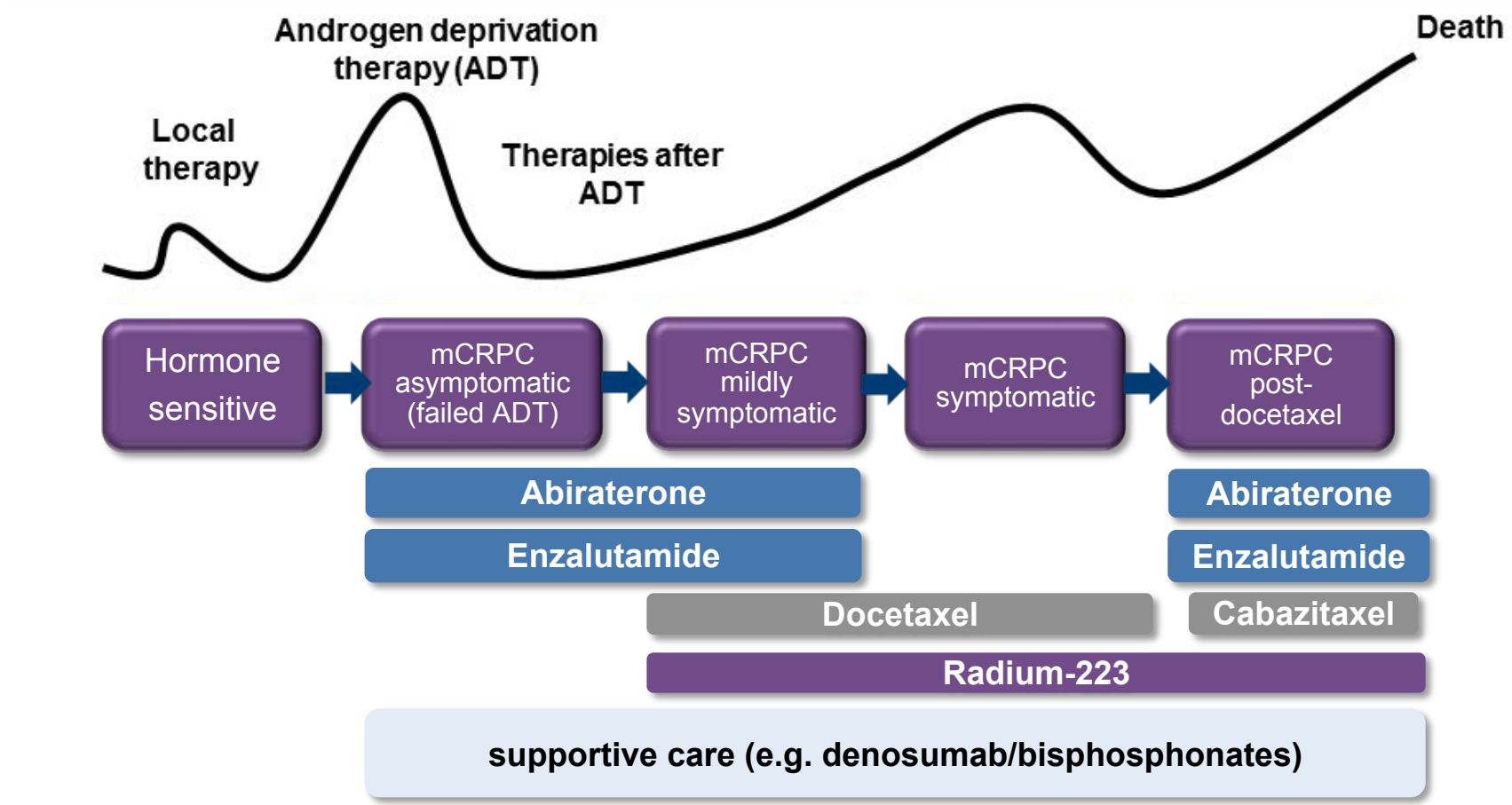
Trattamento delle metastasi ossee nel paziente con tumore della prostata resistente alla castrazione

IMPATTO DEL 223 RADIUM NEL mCRPC

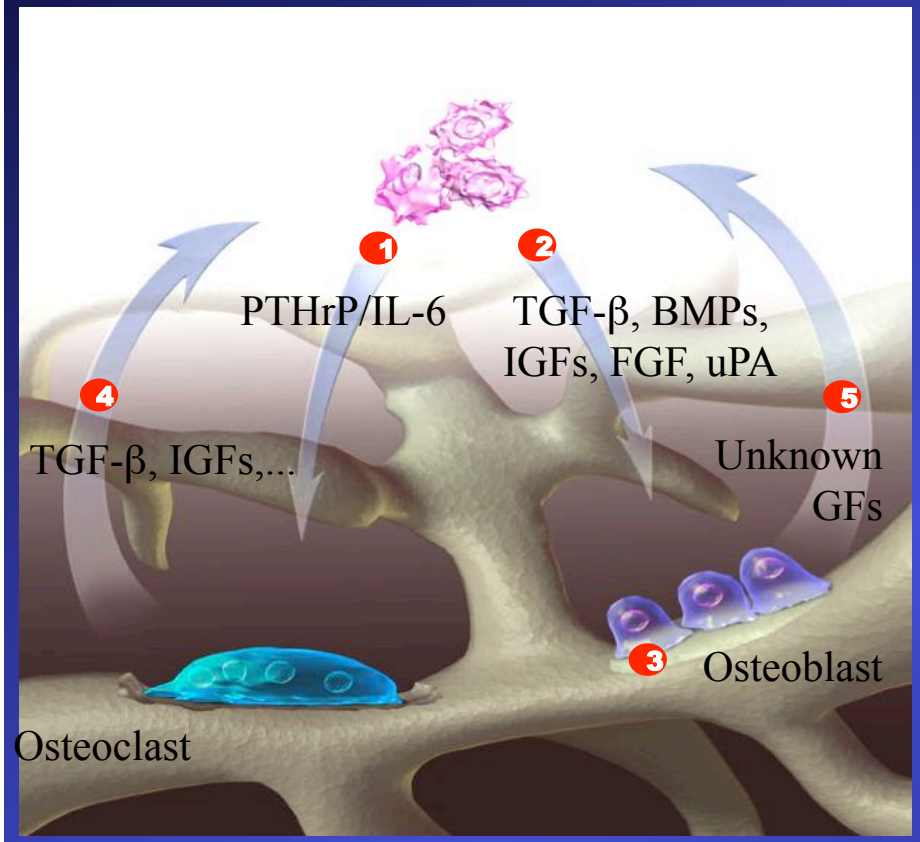
Marcello Tucci

SCDU Oncologia Medica
Azienda Ospedaliero Universitaria San Luigi di Orbassano
Università degli studi di Torino

Current Treatment Paradigm is Evolving



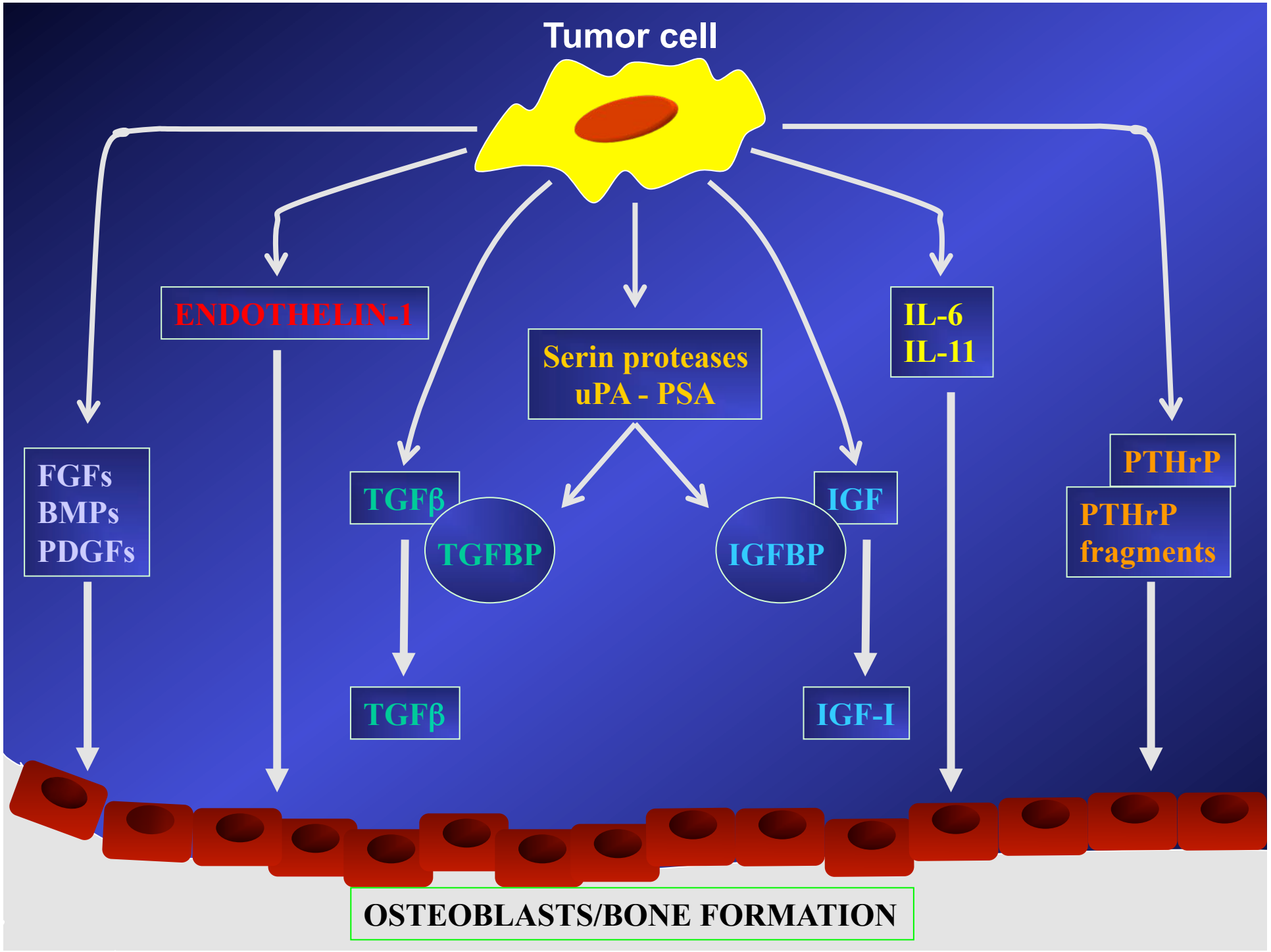
The vicious circle



Factors are released by tumor cells that stimulate both osteoclast 1 and osteoblast 2 activity

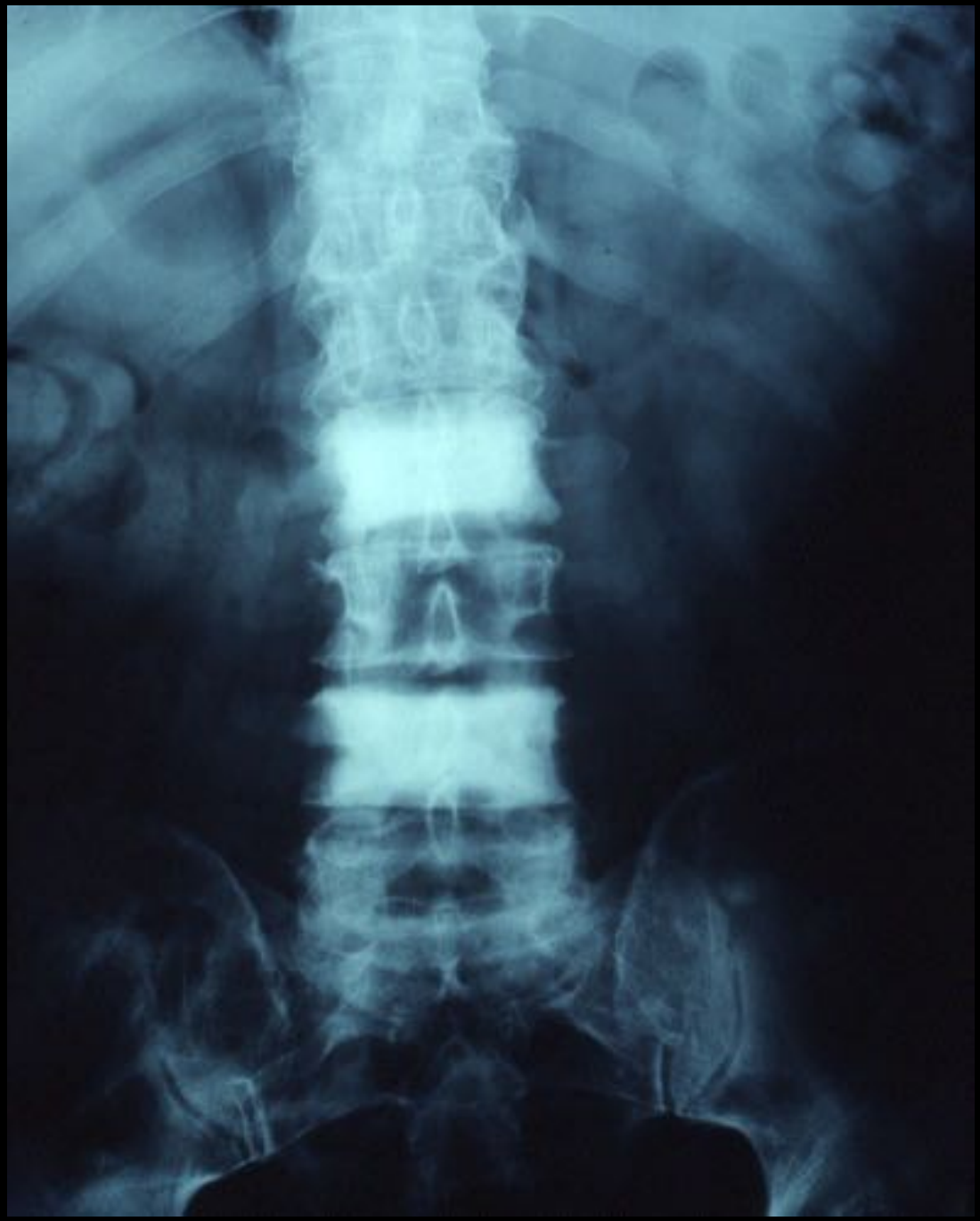
Excessive new bone formation 3 occurs around tumor-cell deposits, resulting in low bone strength and potential vertebral collapse

Osteoclastic 4 and osteoblastic 5 activity releases growth factors that stimulate tumor-cell growth, perpetuating the cycle of bone resorption and abnormal bone growth

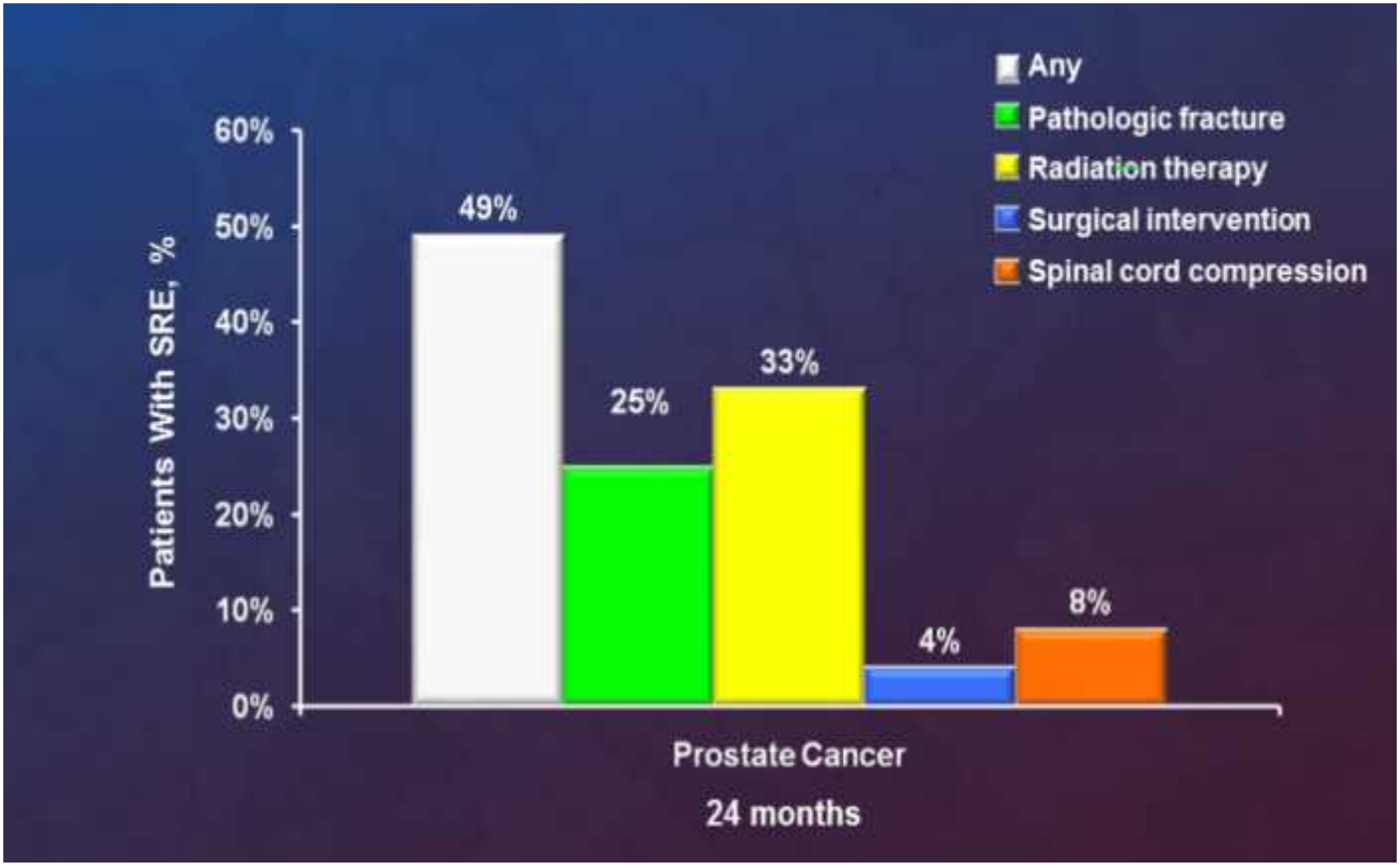

Tumor cell
ENDOTHELIN-1
Serin proteases
uPA - PSA
IL-6
IL-11
FGFs
BMPs
PDGFs
TGFβ
TGFBP
IGF
IGFBP
PTHrP
PTHrP
fragments
TGFβ
IGF-I
OSTEOBLASTS/BONE FORMATION

Cancer and the skeleton

	RX/histology	OB	OC
Multiple myeloma	lytic (>90%)	↑ --> ↓↓	↑ ↑
Breast cancer	lytic (>70%)	↑	↑ ↑
Prostate cancer	sclerotic	↑↑	↑

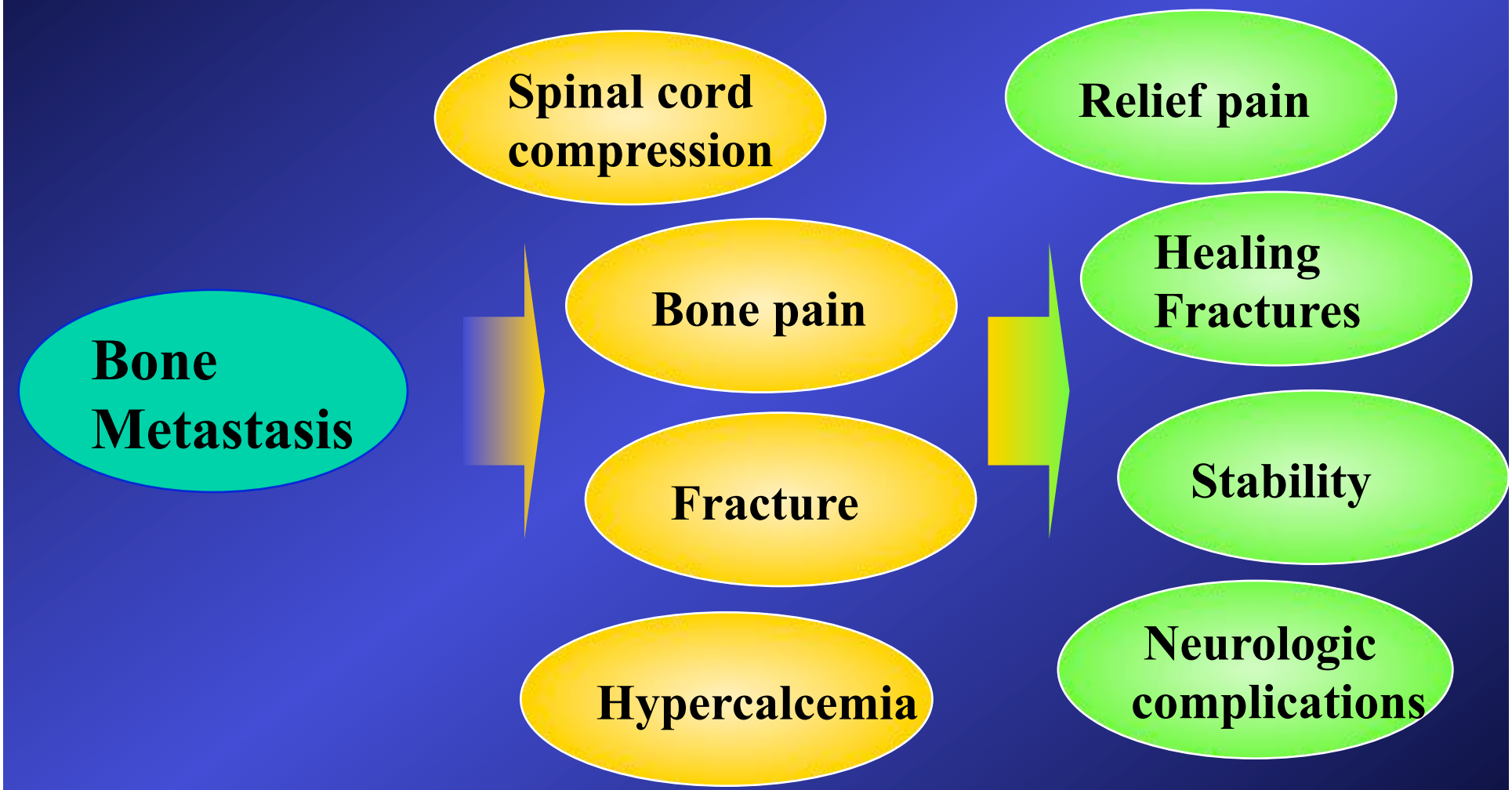


Patients with bone metastases from Pca are at high risk for developing SREs



Saad F, et al. JNCI 2002

Complications of bone metastases



Alpha-Emitter Radium-223 in the Management of Solid Tumors: Current Status and Future Directions

Sten Nilsson, MD, PhD

TABLE 1. Radiopharmaceuticals Used in Metastatic CRPC

Radiopharmaceutical	Survival	Pain	QoL[a]	Toxicity[b]
Alpha-emitter: indicated for treatment of CRPC with symptomatic bone metastases				
Radium-223	3.6 mo	+	+	Myelosuppressive, thrombocytopenia in 6% of patients
Beta-emitters: indicated for treatment of bone pain				
Samarium-153	NA	+	NA	Myelosuppressive, dose-limiting thrombocytopenia in 20-40% of patients
Strontium-89	NA	+	NA	Myelosuppressive, thrombocytopenia in 25-80% of patients

[a]Abbreviations: QoL, quality of life; NA, not applicable.
[b]Grade 3/4 thrombocytopenia in treatment group.

Cell killing and marrow penetration: Two advantages of α-emitters

Large molecule
+
High Linear Energy Transfer

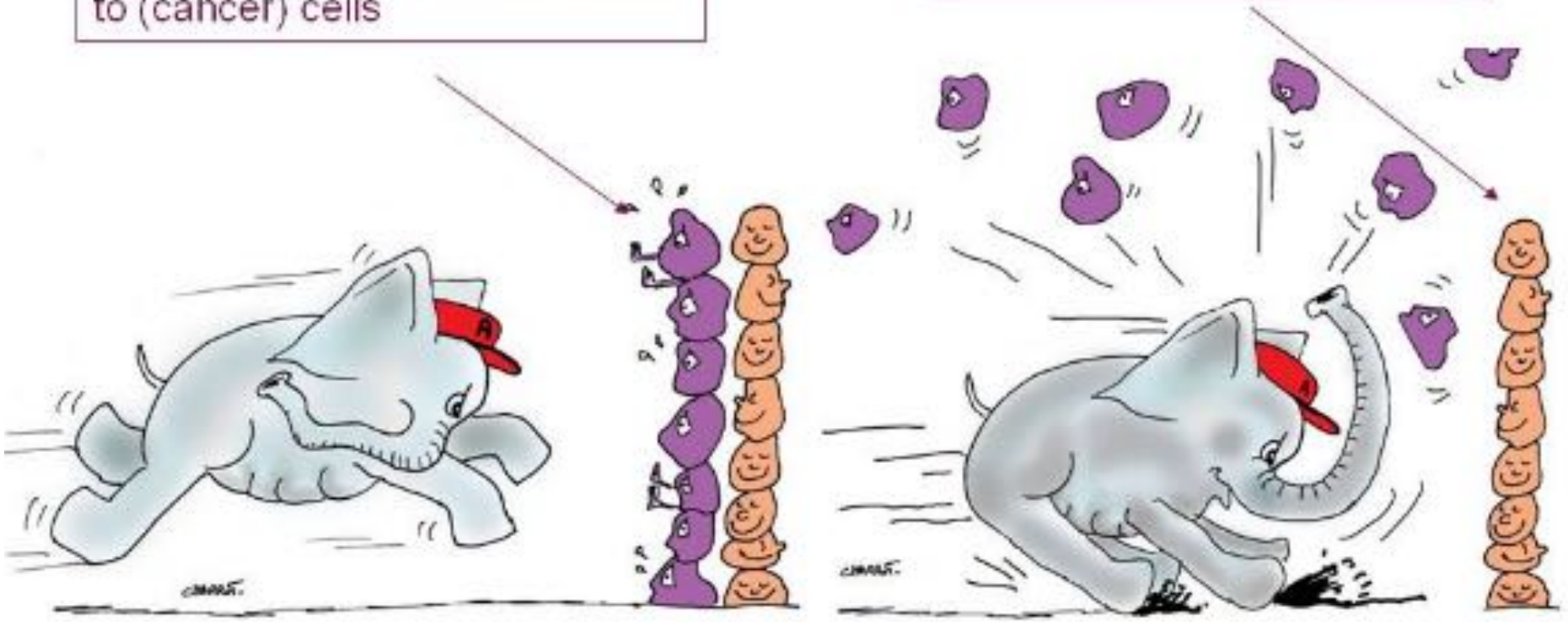
▼

More DNA double-strand breaks to (cancer) cells

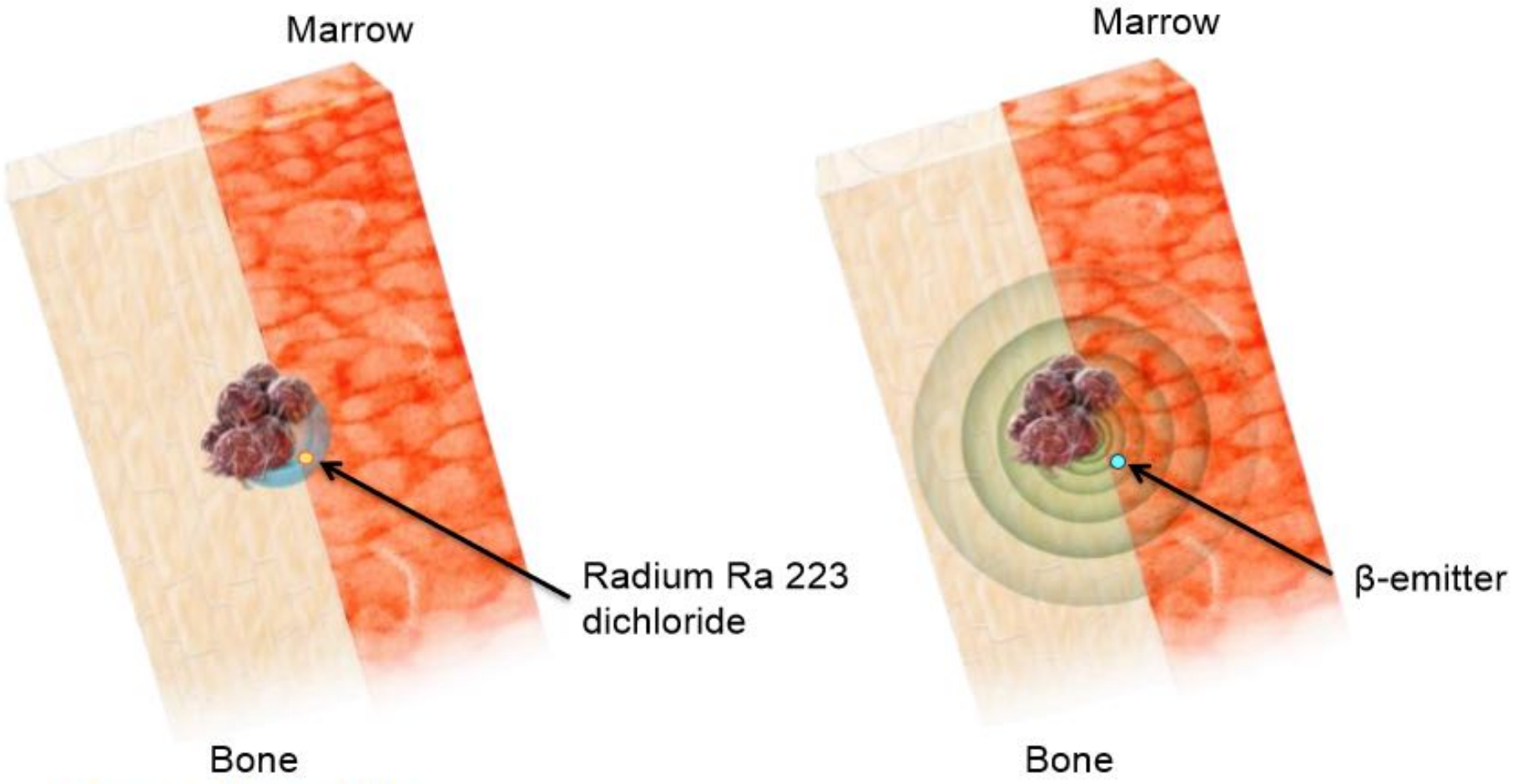
Low marrow penetration (≤100 µm)

↓

Limited hematological toxicity



Short Range of α-Emitters Reduces Bone Marrow Exposure[1]



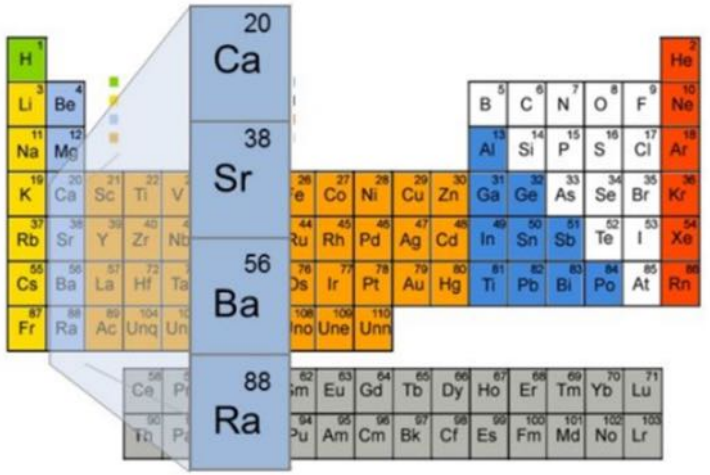
Range of α-particle: (short range – 2 to 10 cell diameters[2])

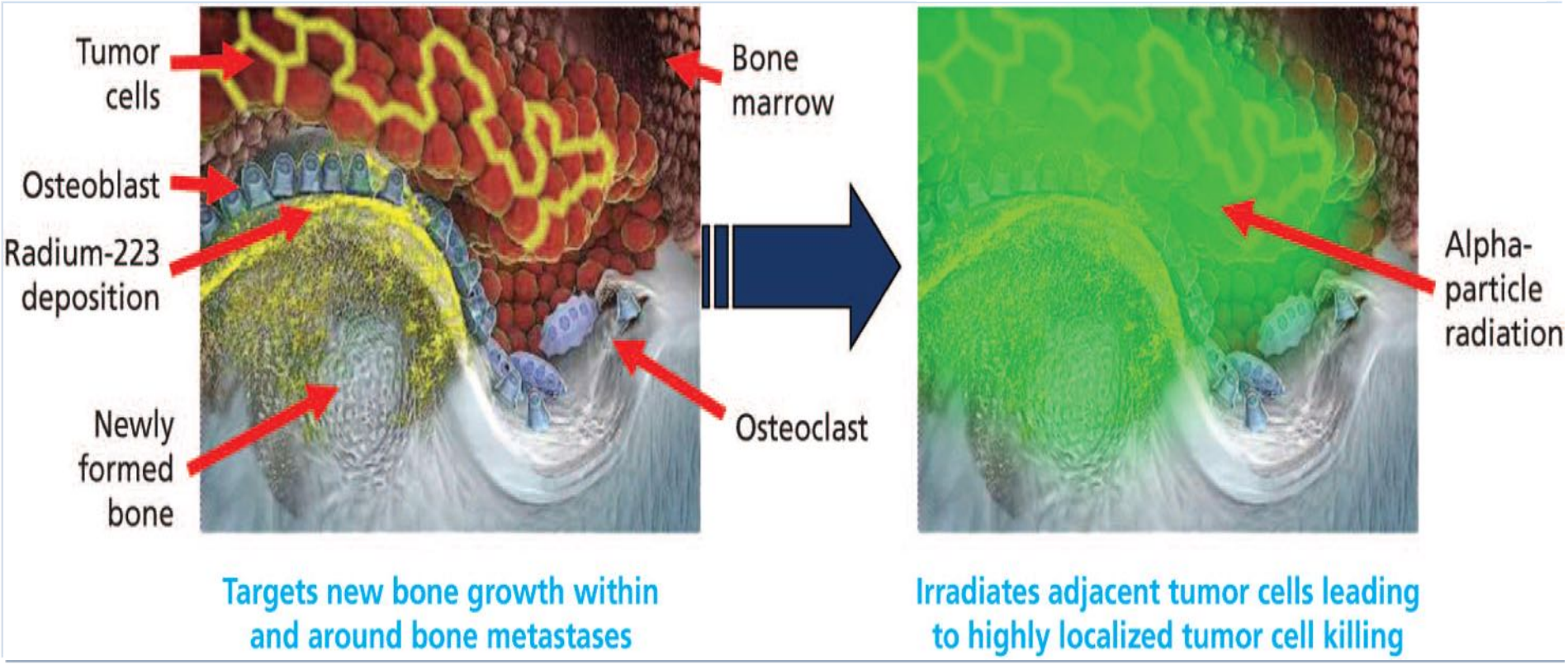
Range of β-particle: (long range – 10 to 1000 cell diameters[2])

1. Henriksen G, et al. *Cancer Res.* 2002;62:3120–3125. **2.** Brechbiel MW. *Dalton Trans.* 2007;43:4918–4928

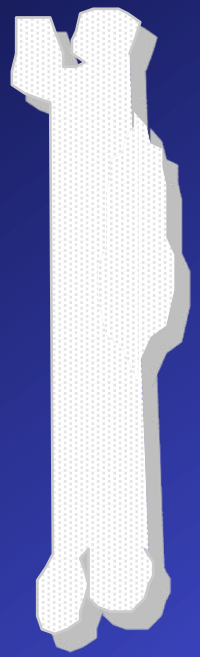
Alpha-Emitter Radium-223 in the Management of Solid Tumors: Current Status and Future Directions

Sten Nilsson, MD, PhD

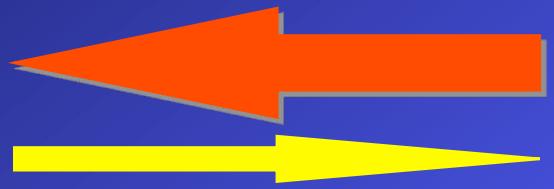




HUNGRY BONE SYNDROME



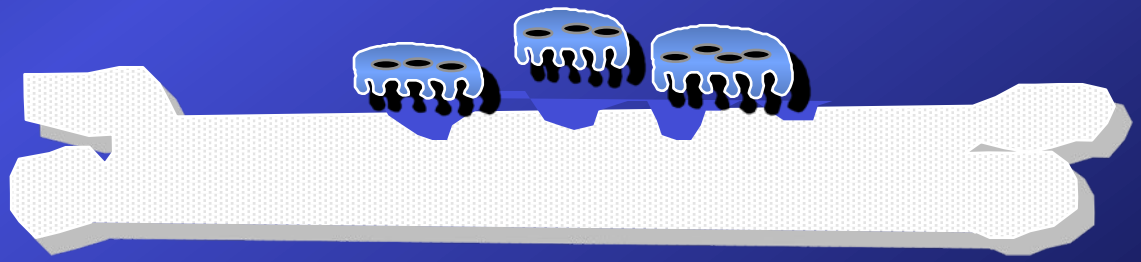
Ca^{++}



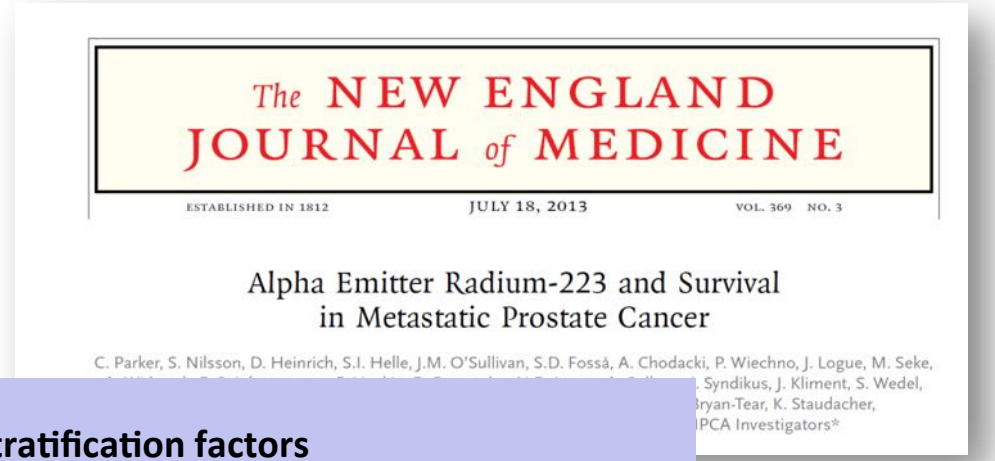
Parathyroid Gland

PTH

Osteoclasts



ALSYMPCA Study design



6 injections (50 kBq/Kg) at 4-week intervals

n=921 mCRPC

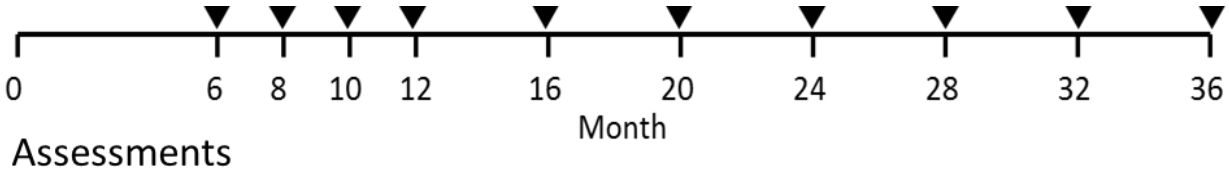
Randomization 2:1

Radium 223 + best standard of care

Placebo + best standard of care

Stratification factors
- Total ALP < 220 U/L vs ≥ 220 U/L
- Bisphosphonate use (Yes vs No)
- Prior docetaxel (Yes vs No)

Key inclusion criteria
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel



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

ALSYMPCA Study Endpoints

Primary endpoint: OS
Secondary endpoints: time to first SSE, time to total ALP progression, total ALP response, total ALP normalization, time to PSA progression, safety and QoL

	Best Standard of care: EBRT, corticosteroids, antiandrogens, oestrogens, estramustine, analgesics, bisphosphonates

SSE: use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour related orthopaedic surgical intervention

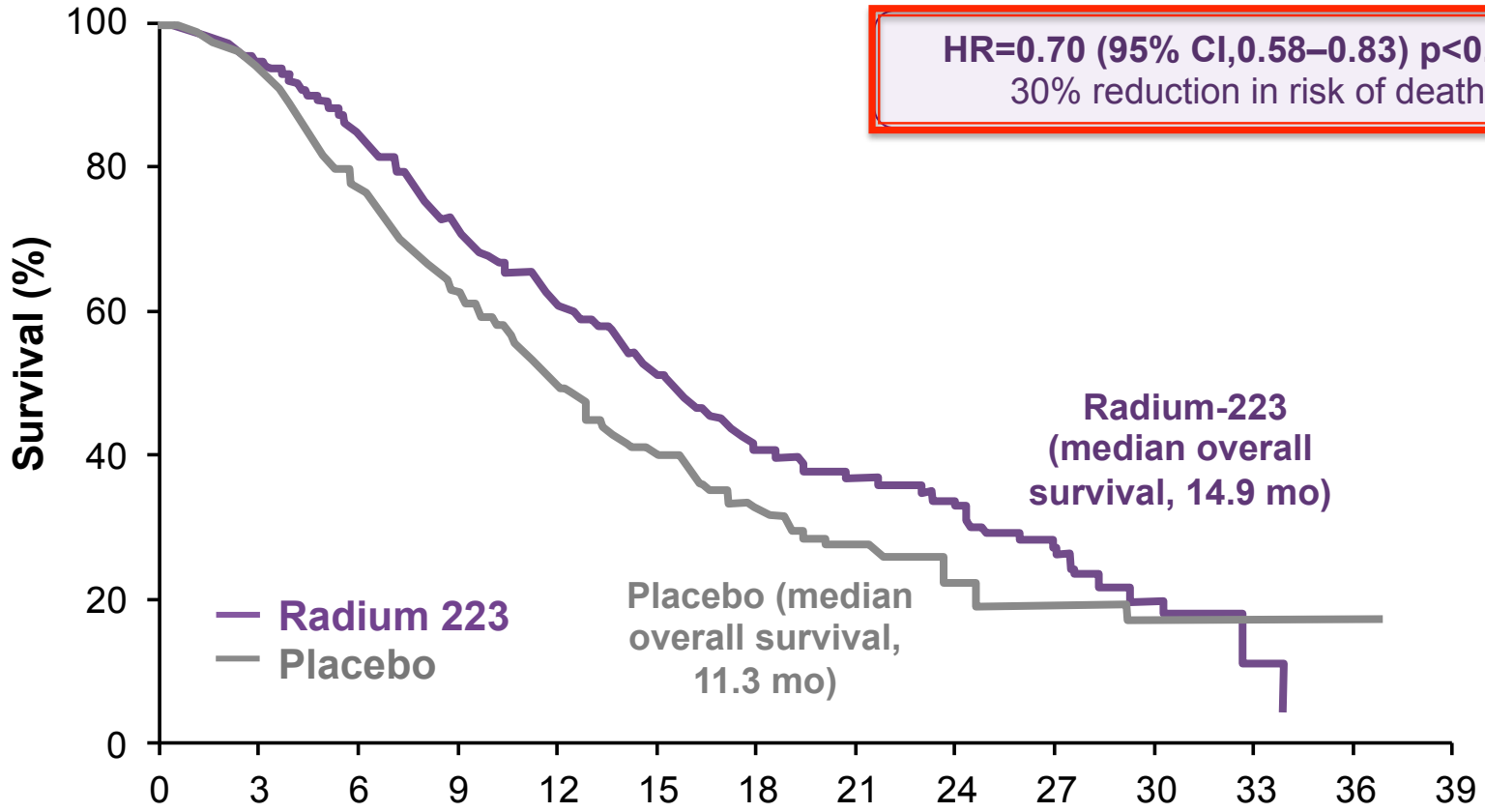
Parker C, et al. N Engl J Med. 2013;369:213-223

ALSYMPCA Baseline Characteristics of the Patients

	Radium-223 (N = 614)	Placebo (N = 307)
Age		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	**575 (94)**	**290 (94)**
Total alkaline phosphatase — no. (%)		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)
Any previous use of docetaxel — no. (%)		
Yes	352 (57)	174 (57)
No	262 (43)	133 (43)
ECOG performance-status score — no. (%)‡		
0	165 (27)	78 (25)
1	371 (60)	187 (61)
≥2	77 (13)	41 (13)
WHO ladder for cancer pain — no. (%)§		
1	257 (42)	137 (45)
2	151 (25)	78 (25)
3	194 (32)	90 (29)
Extent of disease — no. (%)		
<6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
>20 metastases	195 (32)	91 (30)
Superscan¶	54 (9)	30 (10)
External-beam radiation therapy within 12 wk after screening — no. (%)		
Yes	99 (16)	48 (16)
No	515 (84)	259 (84)
Median biochemical values (range)‖		
Hemoglobin — g/dl	12.2 (8.5–15.7)	12.1 (8.5–16.4)
Albumin — g/liter	40 (24–53)	40 (23–50)
Total alkaline phosphatase — U/liter	211 (32–6431)	223 (29–4805)
Lactate dehydrogenase — U/liter	315 (76–2171)	336 (132–3856)
PSA — µg/liter	146 (3.8–6026)	173 (1.5–14500)

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

ALSYMPCA Overall Survival



No. at Risk														
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

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

ALSYMPCA Main Secondary Endpoints

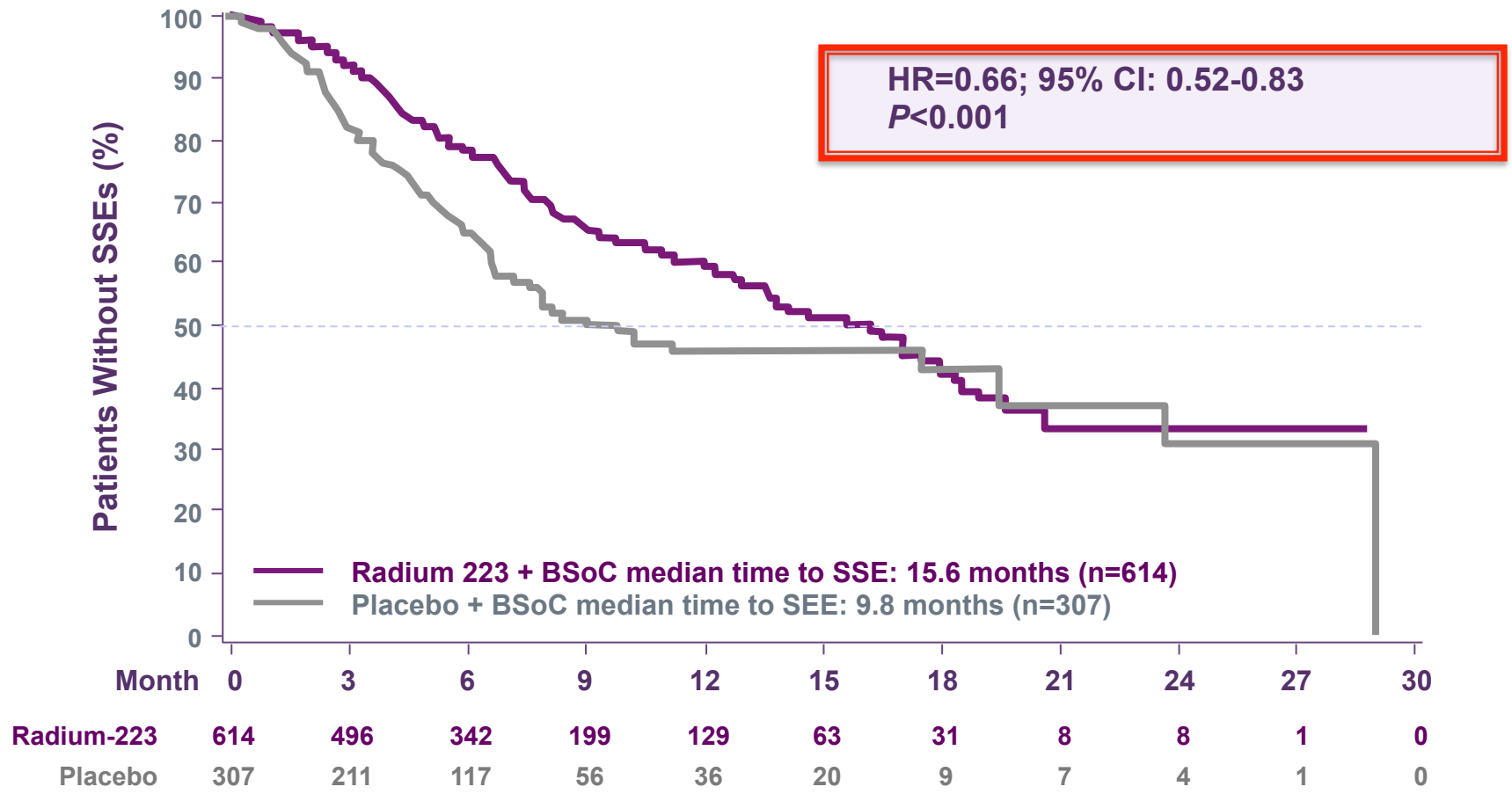
Secondary Efficacy Endpoints	Radium-223 (n=614)	Placebo (n=307)	Hazard Ratio (95% CI)	P Value
Median time to first SSE (months)	15.6	9.8	0.66 (0.52-0.83)	<0.001
Median time to increase in total ALP level (months)	7.4	3.8	0.17 (0.13-0.22)	<0.001
Median time to increase in PSA level (months)	3.6	3.4	0.64 (0.54-0.77)	<0.001
Total ALP response (≥30% reduction) n/total n (%)	233/497 (47)	7/211 (3)	—	<0.001
Total ALP normalisation n/total n (%)	109/321 (34)	2/140 (1)	—	<0.001

All main secondary endpoints favour radium-223 (+ BSoC) compared with placebo (+ BSoC)

ALP, alkaline phosphatase; BSoC, best standard of care; PSA, prostate-specific antigen; SSE, symptomatic skeletal event

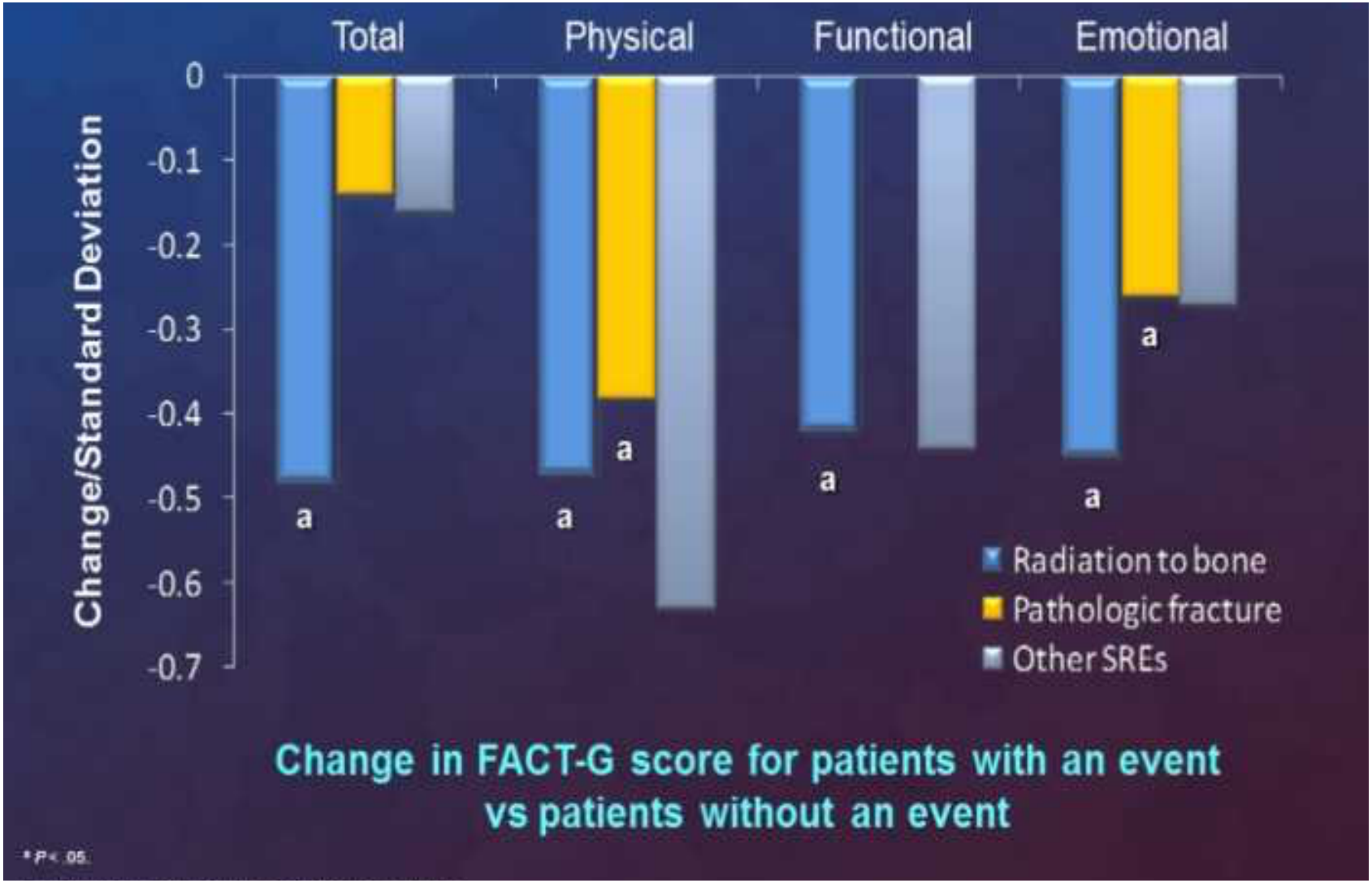
Parker C, et al. N Engl J Med. 2013;369:213-223.

ALSYMPCA Median Time to First SSE



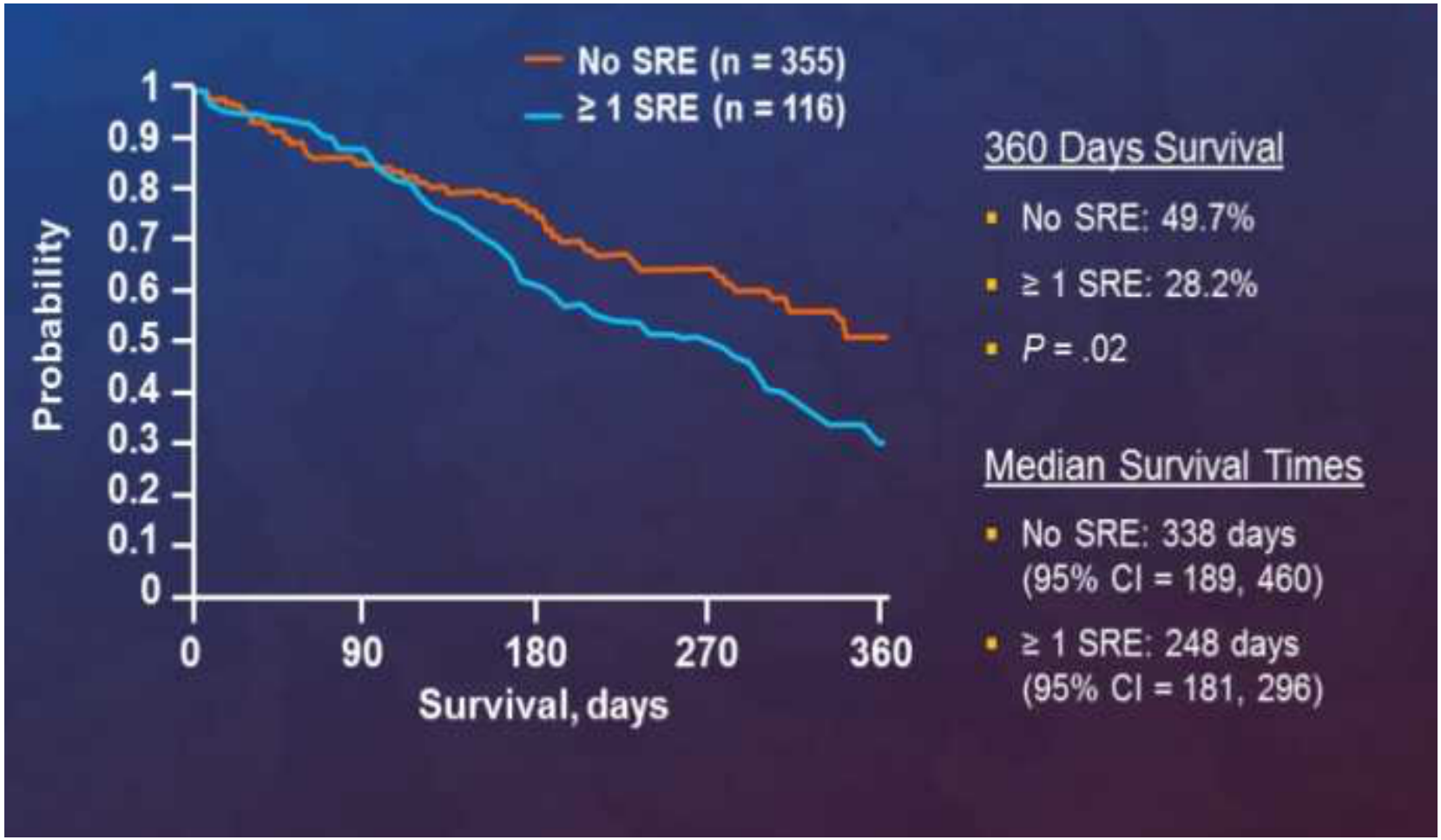
Parker C, et al. N Engl J Med. 2013;369:213-223.

Skeletal complications reduce quality of life in prostate cancer patients



Weinkfurt KP, et al. Ann Oncol 2005

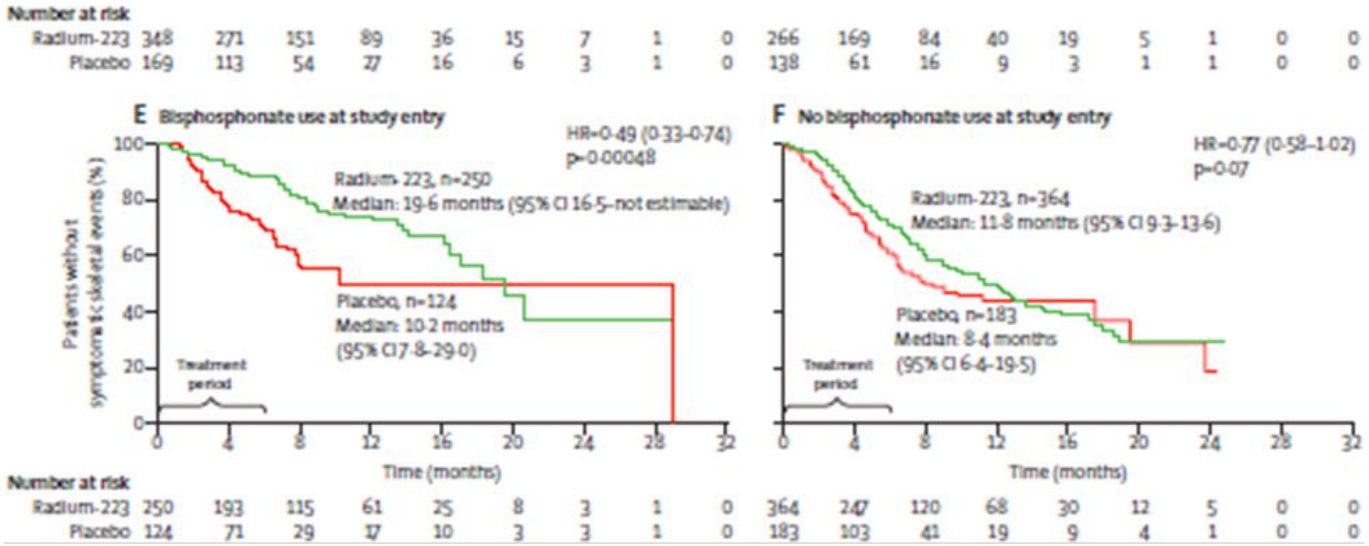
SREs are associated with lower survival in prostate cancer



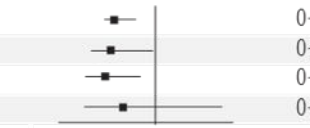
DePuy V, et al. Support Care Cancer 2013

ALSYMPCA Efficacy on SSE

- Aumento significativo del tempo al primo SSE per tutti i gruppi di stratificazione
- Riduzione significativa del rischio di compressione midollare e necessità di EBRT



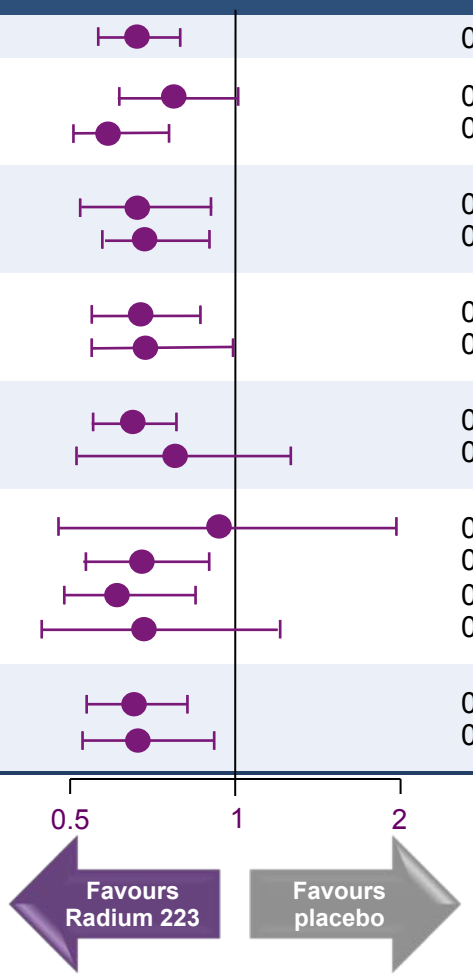
	Number of patients (%)	Median time to first event, months (95% CI)	Number of patients (%)	Median time to first event, months (95% CI)	HR (95% CI)	p value
Individual symptomatic skeletal event components						
External beam radiotherapy	186 (30%)	17·1 (14·1–19·8)	105 (34%)	17·5 (7·9–29·0)	0·67 (0·53–0·85)	0·00117
Symptomatic pathological bone fracture	32 (5%)	NE	20 (7%)	NE	0·62 (0·35–1·09)	0·10
Spinal cord compression	25 (4%)	NE	21 (7%)	NE	0·52 (0·29–0·93)	0·03
Tumour-related orthopaedic surgical intervention	12 (2%)	NE	7 (2%)	NE	0·72 (0·28–1·82)	0·48



Sartor O. The Lancet Oncology 15.7 (2014): 738-746.

ALSYMPCA Overall Survival Across Patient Subgroups

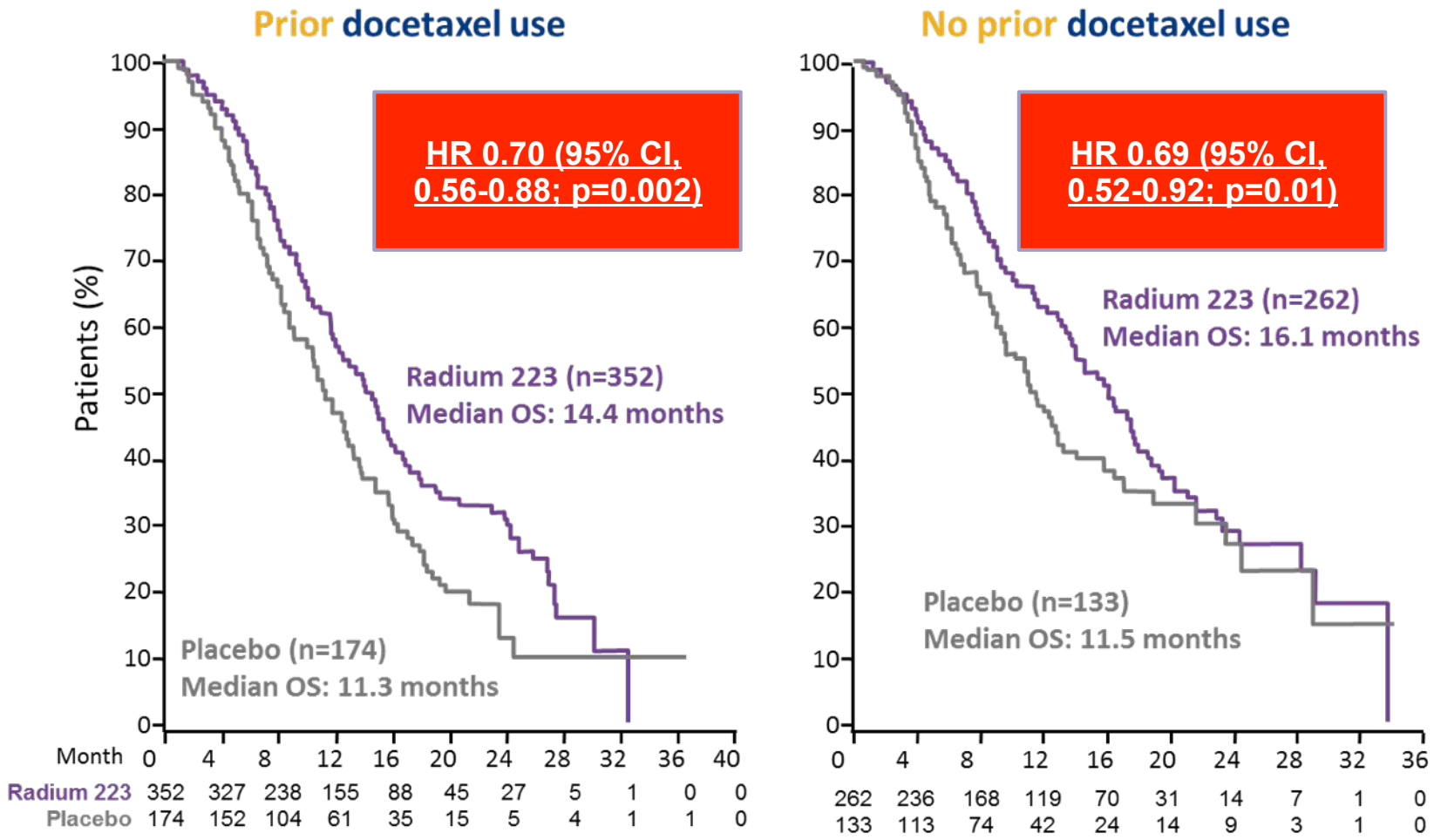
Subgroup	Number of Patients		Median Overall Survival (months)		Hazard Ratio (95% CI)	
	Radium-223	Placebo	Radium-223	Placebo		
All patients	614	307	14.9	11.3	0.70	0.58-0.83
Total ALP						
<220 U/L	348	169	17.0	15.8	0.82	0.64-1.07
≥220 U/L	266	138	11.4	8.1	0.62	0.49-0.79
Current use of bisphosphonates						
Yes	250	124	15.3	11.5	0.70	0.52-0.93
No	364	183	14.5	11.0	0.74	0.59-0.92
Prior use of docetaxel						
Yes	352	174	14.4	11.3	0.71	0.56-0.89
No	262	133	16.1	11.5	0.74	0.56-0.99
Baseline ECOG PS						
0 or 1	536	265	15.4	11.9	0.68	0.56-0.82
≥2	77	41	10.0	8.4	0.82	0.50-1.35
Extent of disease						
<6 metastases	100	38	27.0	NE	0.95	0.46-1.95
6-20 metastases	262	147	13.7	11.6	0.71	0.54-0.92
>20 metastases	195	91	12.5	9.1	0.64	0.47-0.88
Superscan	54	30	11.3	7.1	0.71	0.40-1.27
Opioid use						
Yes	345	168	13.9	10.4	0.68	0.54-0.86
No	269	139	16.4	12.8	0.70	0.52-0.93



ALP, alkaline phosphatase; ECOG PS, *Eastern Cooperative Oncology Group* Performance status; NE, not evaluated

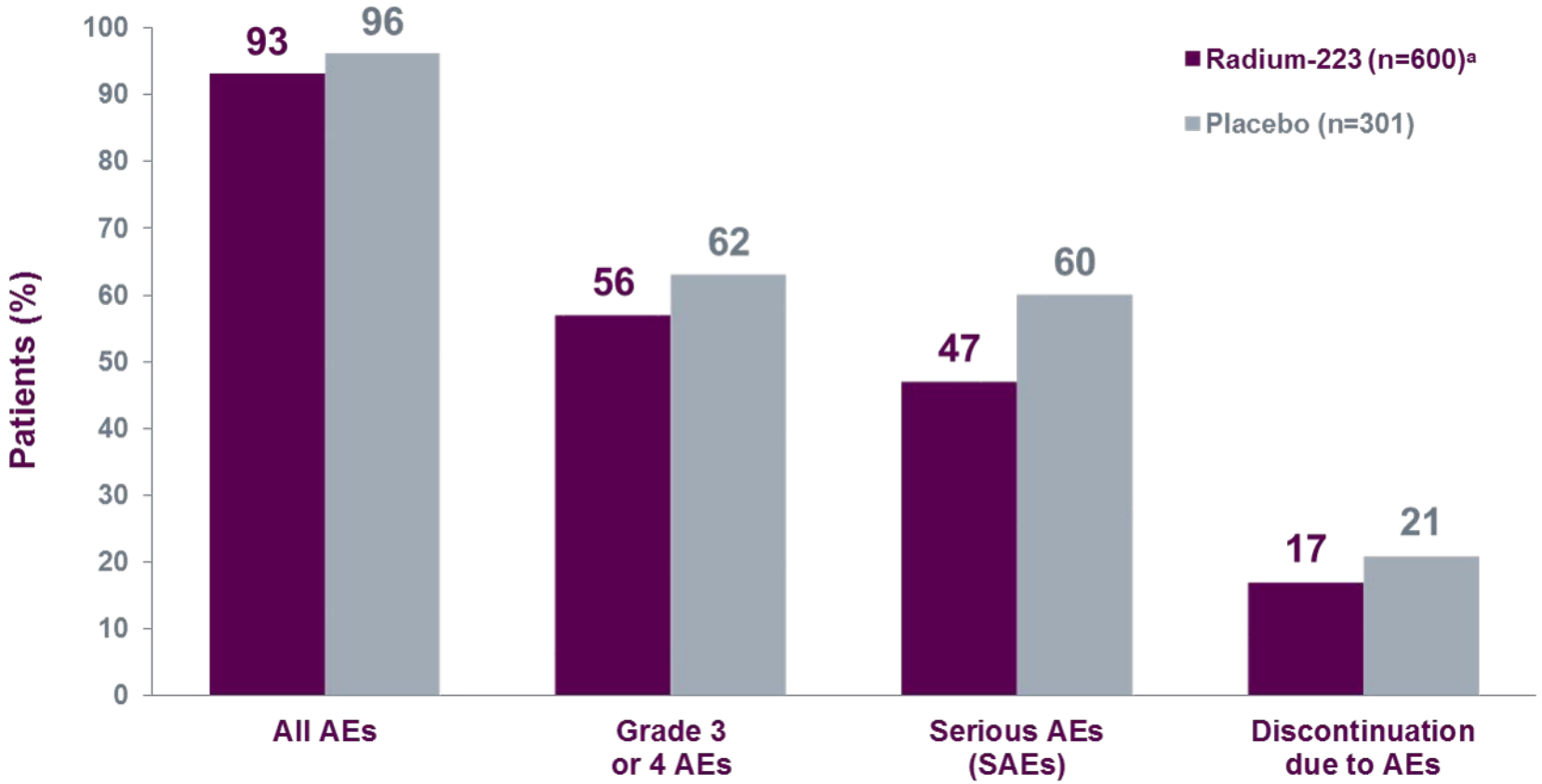
Parker C, et al. N Engl J Med. 2013;369:213-223.

ALSYMPCA Overall Survival by Prior Docetaxel



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

ALSYMPCA Safety and Tolerability



[a]Safety population comprised patients who received at least 1 dose; 1 patient in the placebo group received 1 injection of radium-223 (week 0) and is included in the radium-223 safety analysis.
AE, adverse event
Parker C, et al. N Engl J Med. 2013;369:213-223.

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)

3-Year Safety Follow-up of Radium-223 Dichloride (Ra-223) in Patients (Pts) With Castration-Resistant Prostate Cancer (CRPC) and Symptomatic Bone Metastases (Mets) From ALSYMPCA. [Parker et al. Abstract 195]

STUDY

- Final results reported for the 3-year follow-up (i.e., 3 years after the last patient entered first injection).
- All AEs collected until 12 weeks after last injection; thereafter, only AEs deemed treatment-related were collected.

RESULTS

- **Secondary Malignancies:** There were no reports of AML or MDS.
- Aplastic anemia reported in 1 Ra-223 patient and considered probably related to study drug by the investigator.
- No reports of new primary bone cancer.
- New primary cancers in other organs identified in 2 Ra-223, 3 placebo, and 2 crossover patients and considered not related to study drug (Table).

Radium-223 (n=600)	Placebo (n=301)	Crossover (n=24)
Bladder cancer (follow-up visit 1)	Squamous cell carcinoma of the left hand (follow-up visit 2)	Squamous cell carcinoma of the skin (follow-up visit 1)
Lymph node metastases not originating from prostate cancer (follow-up visit 6)	Adenocarcinoma rectum and adenocarcinoma sigmoideum (follow-up visit 4)	Meningioma (follow-up visits 2 and 4)
	Skin cancer (follow-up visits 7 and 8)	

3-Year Safety Follow-up of Radium-223 Dichloride (Ra-223) in Patients (Pts) With Castration-Resistant Prostate Cancer (CRPC) and Symptomatic Bone Metastases (Mets) From ALSYMPCA. [Parker et al. Abstract 195]

STUDY AND RESULTS

- 27/600 (5%) Ra-223 patients, 8/301 (3%) placebo patients, and 2/24 (8%) crossover patients experienced ≤1 posttreatment follow-up AEs (Table).
- Treatment-related serious AEs (12 weeks after last injection to the end of the 3-year follow-up period):
  - Ra-223: 1 anemia, 1 aplastic anemia, 1 constipation, 1 diarrhea, 1 multiorgan failure, and 1 pneumonia.
  - Placebo: 1 anemia, and 1 cardiopulmonary failure
  - Crossover: 1 pancytopenia and 1 femoral neck fracture.

	All Grades			Grsde 3 or 4, n (%)		
POSTTREATMENT FOLLOW-UP AEs	**Radium-223 (n=600)**	**Placebo (n=301)**	**Crossover (n=24)**	**Radium-223 (n=600)**	**Placebo (n=301)**	**Crossover (n=24)**
All Hematologic AEs						
Anemia	11 (2)	5 (2)	0	5 (1)	1 (<1)	0
Neutropenia	2 (<1)	0	1 (4)	2 (<1)	0	1 (4)
Leukopenia	2 (<1)	0	0	2 (<1)	0	0
Thrombocytopenia	3 (1)	0	0	0	0	0
Pancytopenia	0	0	1 (4)	0	0	1 (4)
Aplastic anemia	1 (<1)	0	0	1 (<1)	0	0
Nonhematologic AEs						
Diarrhea	1 (<1)	0	0	1 (<1)	0	0
Nausea	1 (<1)	1 (<1)	0	0	0	0
Vomiting	1 (<1)	0	0	0	0	0
Constipation	1 (<1)	0	0	0	0	0
Fatigue	1 (<1)	1 (<1)	0	0	0	0

ALSYMPCA Efficacy Summary

Compared with placebo, Radium-223 (50kBq/kg x 6)

- Significantly prolonged median OS by 3.6months[1]
- Significantly delayed time to first SSE by 5.8 months[1]

OS, overall survival; SSE, symptomatic skeletal event

1. Parker C, et al. N Engl J Med. 2013;369(3):213-223

ALSYMPCA Safety Summary

Radium-223 treatment (50kBq/kg x 6) is well tolerated

- Fewer adverse events in radium-223 group[1]
- Small differences in haematologic AEs[1]
- No additional safety issues identified ~3 years after last injection[2]

AE, adverse event

1. Parker C, et al. Presented at ASCO GU 2012. 2. Nilsson S, et al. Presented at ASCO GU 2014.

Radium-223 dichloride (Ra-223) in U.S. expanded access program (EAP). [Vogelzang et al. Abstract 247]

STUDY

- Phase 2 prospective, interventional, open-label, multicenter United States EAP Study (15995)
- Provided Ra-223 access to CRPC patients with symptomatic bone metastases; acute and long-term safety evaluated

PATIENTS AND TREATMENT

- Of 253 patients enrolled in the EAP 184 patients received treatment with ≥1 injection of Ra-223.
- Median number of injections was 5 in the EAP vs 6 for ALSYMPCA.
- % of patients receiving 6 injections
  - EAP: 44%
  - ALSYMPCA: 63%
  - Primary reasons for not receiving all 6 injections of Ra-223: EAP, disease progression (31%); ALSYMPCA, AEs (16%)
- Delays/interruption:
  - EAP: 14%
  - ALSYMPCA: 56%

CHARACTERISTIC	EAP (N=184)	ALSYMPCA Radium-223 Arm (N=600)
Age, years, Median (range)	70 (47-97)	71 (49-90)
≥65 years, n (%)	135 (73)	447 (75)
Weight, Median, Kg	86	82
ECOG PS 0-1, %	90	88
Gleason score at diagnosis, %		
2-4	1	1
5-7	43	45
8-10	51	43
Missing	5	12
Time since PC diagnosis, Median, years	7	5
Time since bone mets diagnosis, Median, years	2	2
tALP <220 U/L, %	67	58
PSA, Median, ug/L	130	146
Prior use of, %		
Docetaxel	60	58
Cabazitaxel	18	NA
Abiraterone	65	NA
Enzalutamide	32	NA

ASCO GU 2015

Radium-223 dichloride (Ra-223) in U.S. expanded access program (EAP). [Vogelzang et al. Abstract 247]

EFFICACY RESULTS

CHARACTERISTIC	EAP (N=184)	ALSYMPCA Radium-223 Arm (N=614)
Patients with SSE, % Median time to 1st SSE, mo Received EBRT for bone pain, %	10 NE 7	33 15.6 30
Median time to: **Disease progression, mo** tALP progression, mo PSA progression, mo	 **10** NE 4	 **NA** 7.4 3.6
Patients with confirmed tALP decline from baseline, % ≥ 30% decline ≥ 50% decline	 33 16	 47 27
Patients with a confirmed PSA response, % [≥50% decline from baseline]	 6	 8
OS*, Median, mo	**17**	**14.9**

NA, not available; NE, not estimable. *Due to a shorter follow-up time in EAP versus ALSYMPCA, there was a greater percentage of patients censored in EAP (134/184 [73%] versus the ALSYMPCA radium-223 arm (281/614 [46%]).

ASCO GU 2015

Prior and concurrent use of abiraterone and enzalutamide with Ra-223 in an expanded access setting

	Abi N = 35 n	Abi N = 35 %	Enza N = 25 n	Enza N = 25 %	Overall N = 184 n	Overall N = 184 %
Age, median, yrs	68		70		70	
Race, white	31	89	23	92	169	92
Weight, median, kg	87		90		86	
ECOG, ≤ 1	35	100	24	96	165	90
Total ALP ≥ 220 U/L	8	23	8	32	56	30
Current bisphosphonate, yes	6	17	6	24	18	10
Prior docetaxel, yes	14	40	15	60	109	59
Pts receiving all 6 injections	20	57	15	60	81	44

Conclusions: In this EAP, Ra-223 concurrently administered with either abiraterone or enzalutamide was safe and well tolerated

J Clin Oncol 33, 2015 (suppl 7; abstr 253)

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

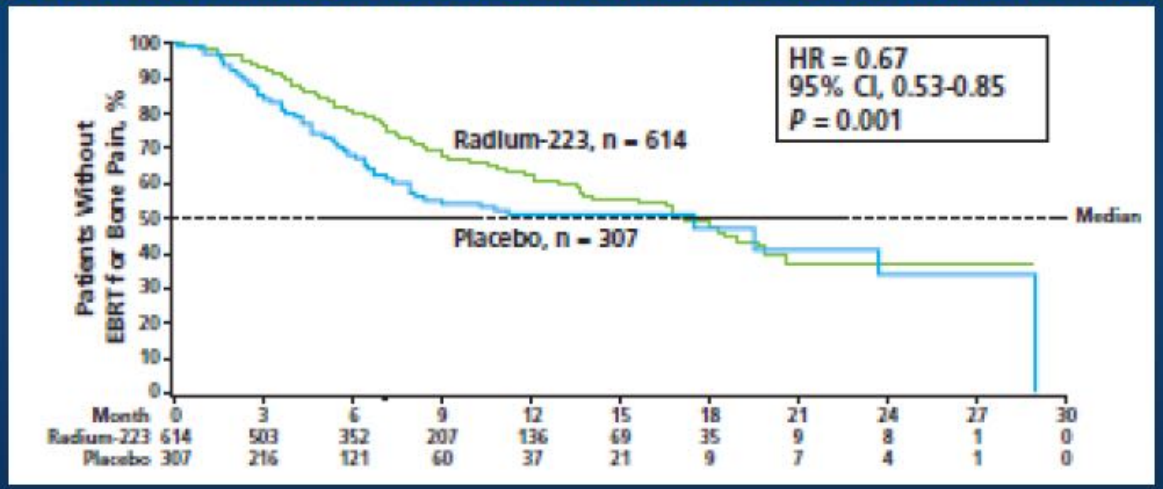
Paganelli Giovanni[1], Rossetti Claudio[2], Aglietta Massimo[3], Messina Caterina[4], Versari Annibale[5], Michalski Jeff M.[6], O'Sullivan Joe M.[7], Parker Chris[8], Garcia-Vargas Jose E.[9], Sartor A.Oliver[10], Finkelstein Steven E.[11]

(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

Chemotherapy after Radium 223 in ALSYMPCA study

- In patients receiving chemotherapy after the last dose of study drug (n = 147), median values of hemoglobin, neutrophils, and platelets were similar for the radium-223 vs placebo group from baseline to month 12
- Administering chemotherapy after radium-223 had no deleterious effect on patient OS
- Hematologic safety profiles for patients receiving chemotherapy after radium-223 were similar to those for patients receiving chemotherapy after placebo

Sartor et al.. Abs 936p ESMO 2012 meeting (Vienna)

Front-line options that improve survival

Treatment	Trial	Visceral disease allowed	HR	Survival (mos)
Docetaxel/prednisone vs Mitoxantrone/prednisone	TAX 327[1]	Yes	0.79	18.9 vs 16.5
Sipuleucel-T vs control	IMPACT[2]	No	0.78	25.8 vs 21.7
Abiraterone/prednisone vs Placebo/ prednisone	COU-302[3]	No	0.81	34.7 vs 30.3
Enzalutamide vs Placebo	PREVAIL[4]	Yes	0.70	32.4 vs 30.4
Radium 223 vs Placebo/BSC	ALSYMPCA[5]	No	0.70	14.9 vs 11.3

[1]Tannock et al. N Engl J Med 2004;351(15):1502-1512, [2]Kantoff et al. N Engl J Med 2010;363(5):411-422, [3]Ryan et al. N Eng J Med 2013;368:138–48, [4]Beer et al. N Engl J Med 2014, [5]Parker et al. NEJM 2013;369(2):213-223

Sequencing in post-docetaxel setting

Trial	Disease State	Trial Design	HR for OS	Survival (months)
TROPIC N=755	Post docetaxel	Cabazitaxel/prednisone vs. mitoxantrone/prednisone	0.70	15.1 vs. 12.7
COU-AA-3001 N=1195	Post docetaxel	Abiraterone/prednisone vs. placebo/prednisone	0.74	15.8 vs. 11.2
AFFIRM N=1199	Post docetaxel	MDV3100 vs. placebo	0.63	18.4 vs. 13.6
ALSYMPCA N=921	Post docetaxel (or unsuitable)	Ra223/BSC vs. placebo/BSC	0.70	14.9 vs. 11.3

How to choose therapy for mCRPC?

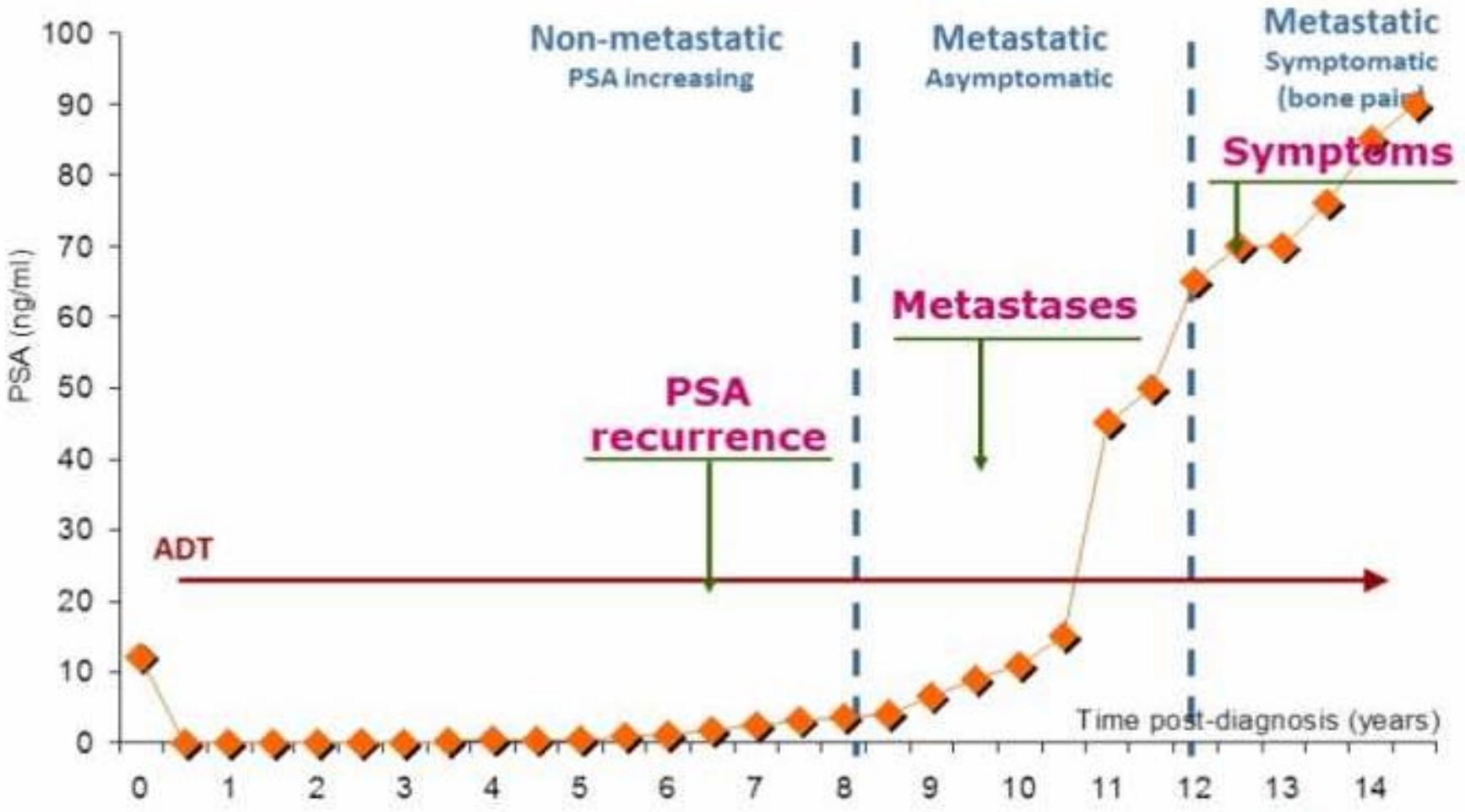
- No predictive markers

- No head-to-head trials

- No prospective sequencing trials

Clinical trials design and results

Pattern of progression of CRPC



Pain predicts overall survival in men with metastatic CRPC

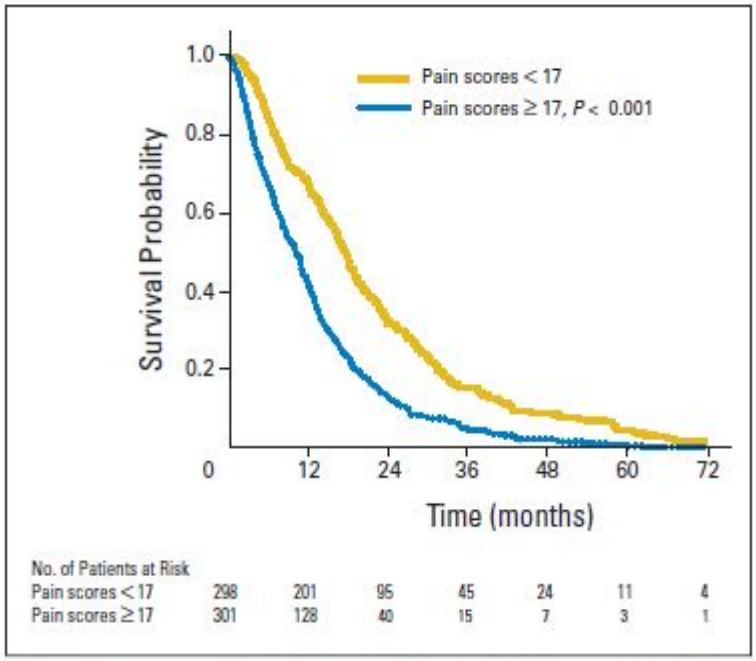


Fig 1. Kaplan-Meier survival curves by pain interference scores at baseline.

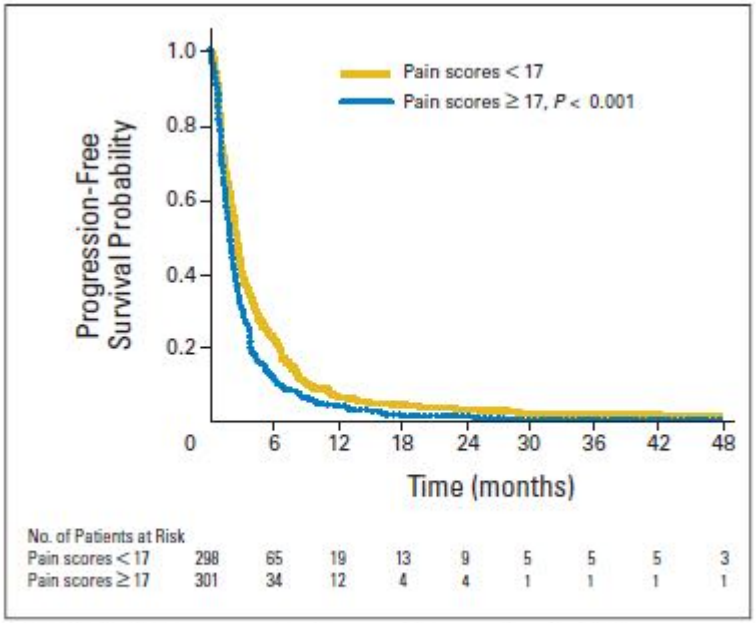
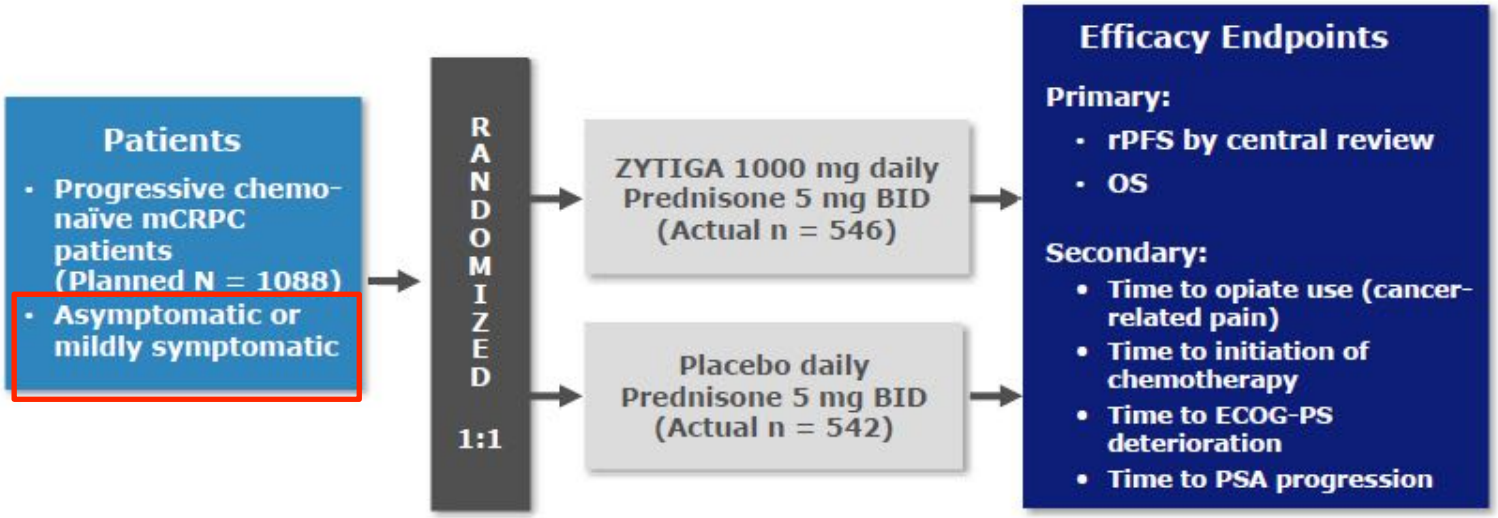


Fig 2. Kaplan-Meier progression-free survival curves by pain interference scores at baseline.

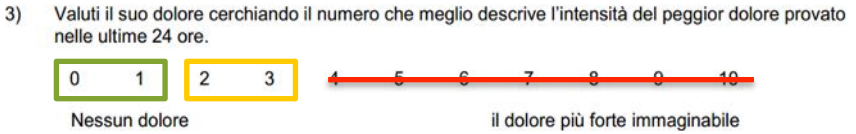
Halabi S, et al. J Clin Oncol 2008

Abiraterone: COU-AA-302 - Design

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Study permitted patients with ECOG performance status of O or 1; this was stratified between study arms
- All subjects had previous antiandrogen therapy followed by documented PSA or radiographic progression after discontinuing antiandrogen therapy

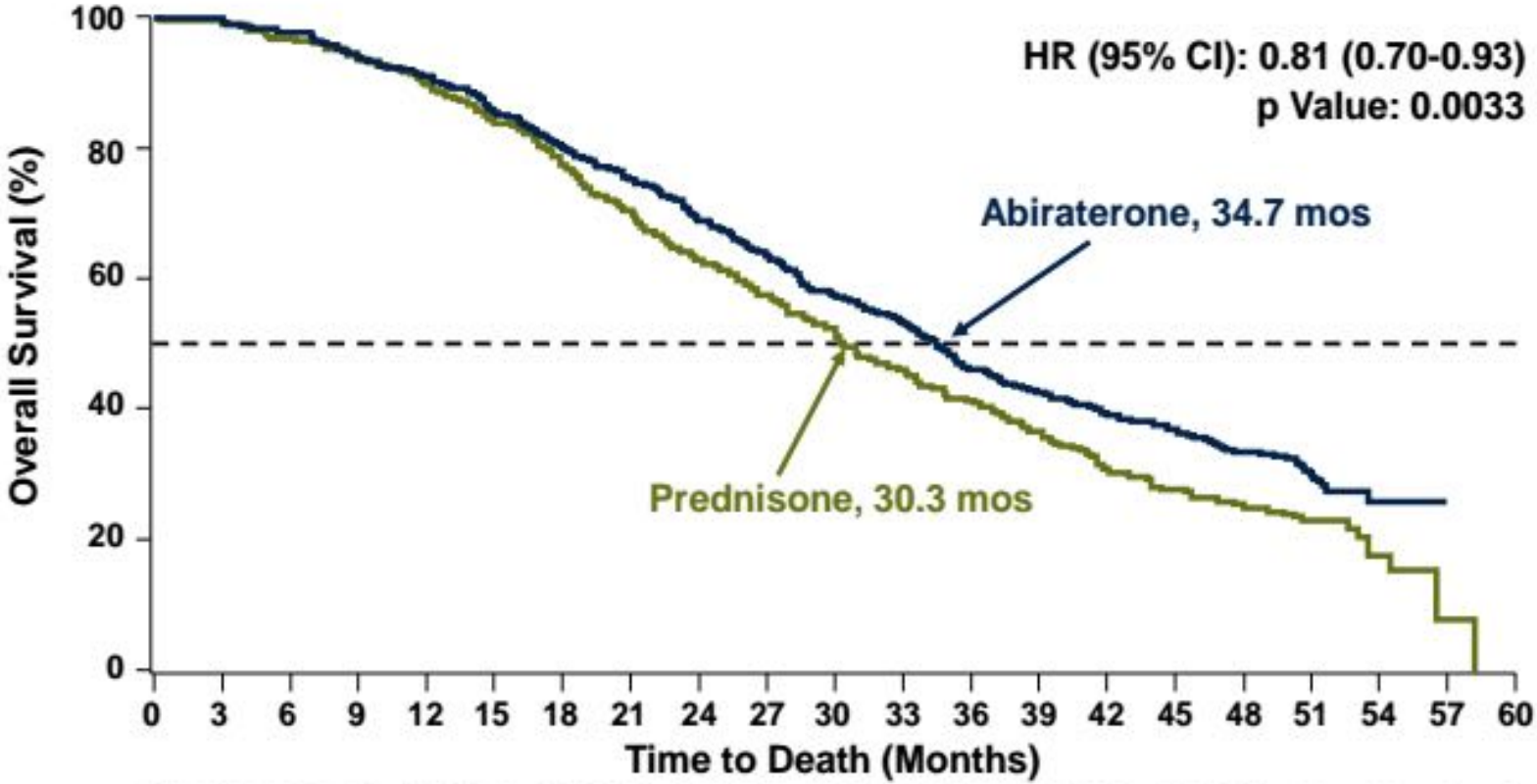


Exclusion Criteria: visceral metastases



Ryan CJ, et al. N Engl J Med 2013;368:138-48.

Final OS Analysis

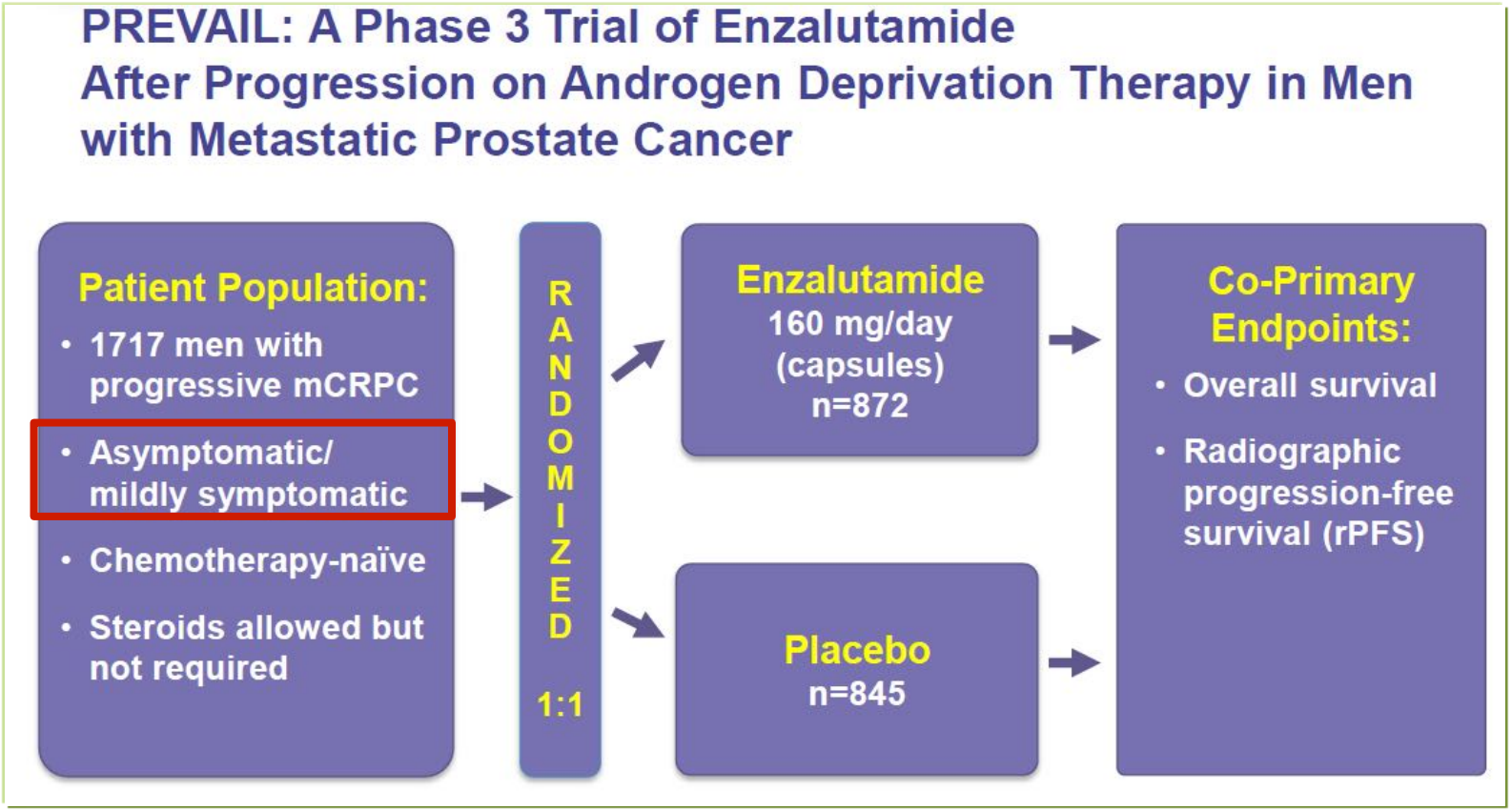


Abiraterone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

- Median follow-up of 49.2 mos
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

Ryan CJ, ESMO 2014

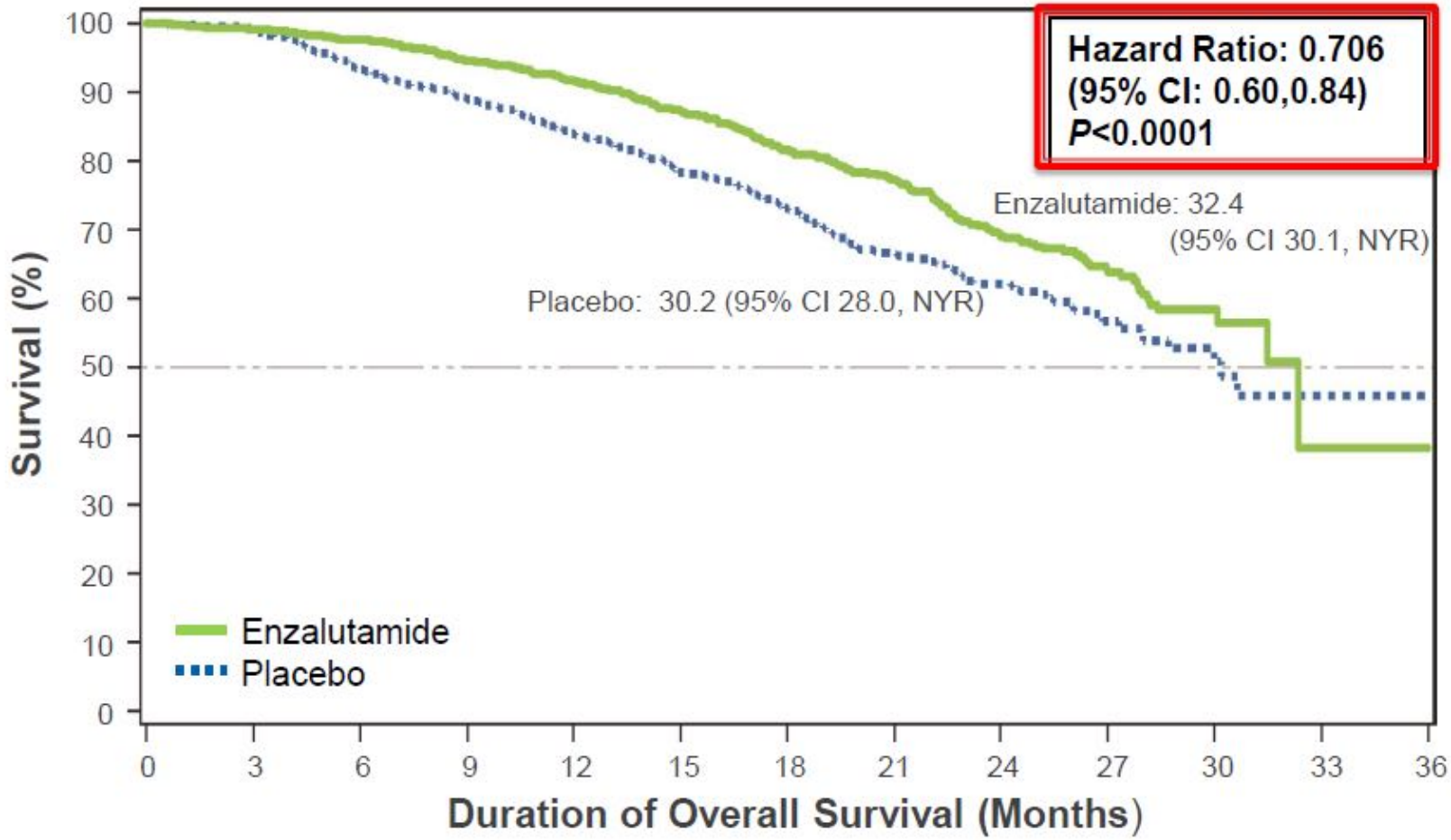
Enzalutamide: PREVAIL- Studio di fase III



▶ **Patients with visceral disease were allowed.**

Beer TM, et al. N Engl J Med 2014

PREVAIL Interim Analysis: Enzalutamide Reduced Risk of Death by 29%



Patients at Risk

Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0

Median Follow-up 22 Months

Beer et al. N Engl J Med. 2014; 371(5):424-33

Docetaxel: TAX 327 - Study design

Metastatic
CRPC
Stratify

Pain level
PPI ≥ 2 or AS ≥ 10
vs
PPI < 2 or AS < 10
KPS ≤70 vs ≥ 80

RANDOMIZATION

→ Docetaxel **75** mg/m² q3 wks + Prednisone **5** mg bid

→ Docetaxel **30** mg/m² wkly 5 of 6 wks + Prednisone **5** mg bid

→ Mitoxantrone **12** mg/m² q3 wks + Prednisone **5** mg bid

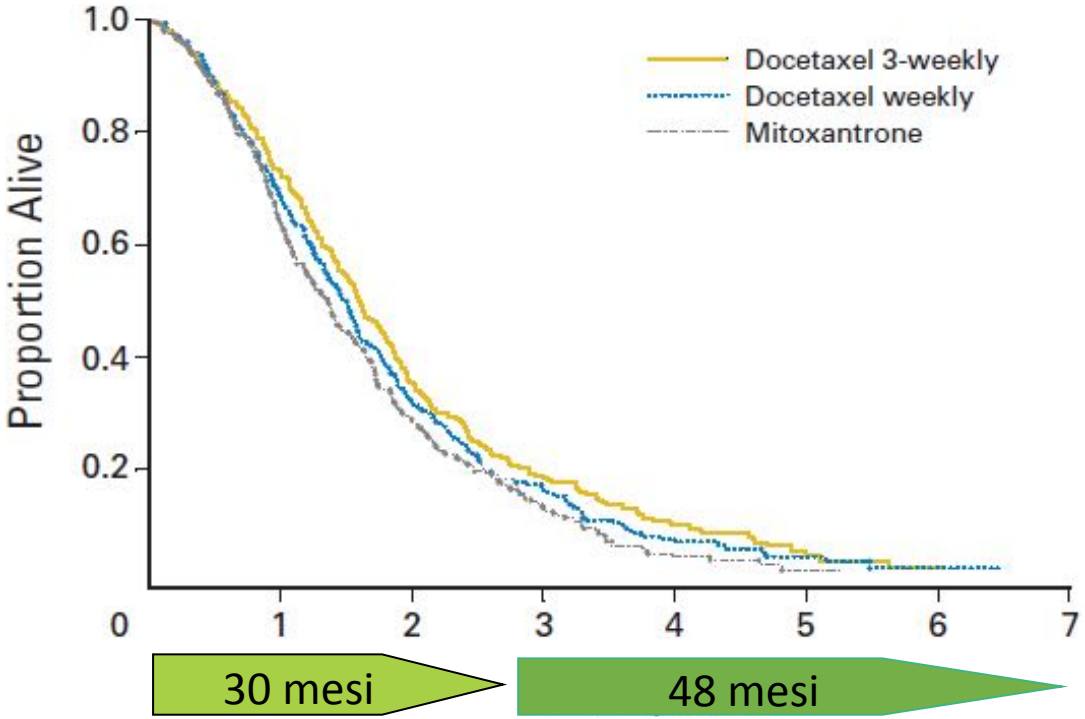
Tannock et al. N Engl J Med 2004; 351: 1502-1512

1:1

Update 2008:
OS benefit only in the 3weekly arm

	Median Survival (months)	Hazard ratio	p-value
Docetaxel q3w:	19.2	0.79	0.004
Docetaxel qw:	17.8	0.87	0.086
Mitoxantrone	16.3	–	–

Berthold DR, et al. J Clin Oncol 2008;26:242–245



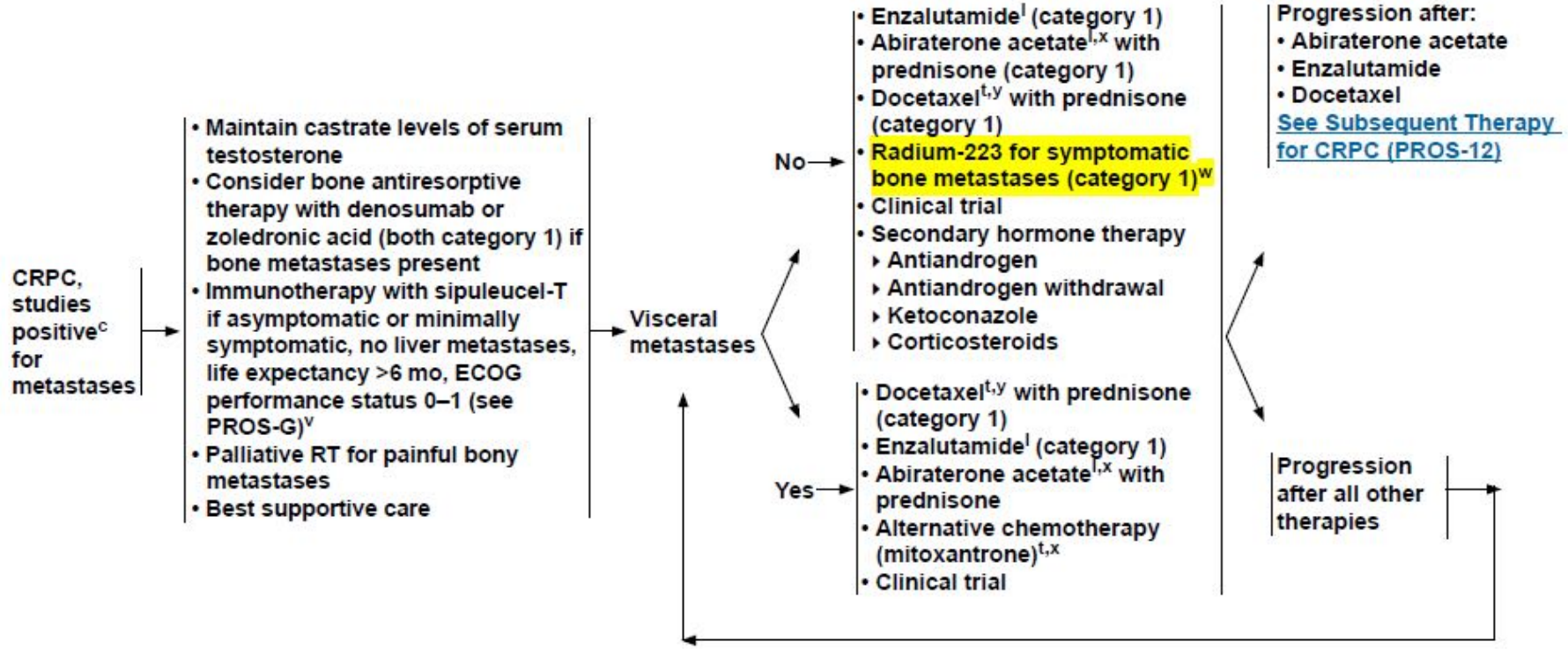
Docetaxel: TAX 327 - Dati al basale

	Docetaxel Q 3 week	Docetaxel weekly	Mitoxantrone
Randomized	335	334	337
Ineligible*(%)	12	12	12
Median age (range)	68 (42-92)	69 (36-92)	68 (43-86)
≥ 80 Karnofsky PS (%)	88	87	86
Pain level ≥ PPI 2 or AS ≥ 10 (%)	45	45	46
Prior treatment (%)			
Prostatectomy	19	24	21
Radiotherapy	52	44	51
Estramustine	19	18	21
Hormonal Manipulations (%)			
1	9	8	6
2	68	72	69
> 2	23	21	25
Median PSA (ng/ml)	114	108	123
Gleason Score (%)			
≤ 7	42	40	42
8-10	31	31	28
Not available	26	29	30
Extent of Disease (%)			
Bone Metastases	90	91	92
Visceral Disease	22	24	22

*All included in the intent to treat analysis

Tannock et al, N Engl J Med 2004; 351: 1502-1512

ADVANCED DISEASE: FIRST-LINE SYSTEMIC THERAPY FOR CRPC



[c] See Principles of Imaging (PROS-B).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[t] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[v] Sipuleucel-T has not been studied in patients with visceral metastases.
[w] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).

[x] For patients who are not candidates for docetaxel-based regimens.
[y] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ADVANCED DISEASE: SUBSEQUENT SYSTEMIC THERAPY FOR CRPC

No visceral metastases →

Prior therapy enzalutamide/abiraterone:	Prior therapy docetaxel:
• Docetaxel with prednisone (category 1)[t] • Abiraterone acetate[l] or enzalutamide • Radium-223 (category 1) if bone-predominant disease • Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1 • Clinical trial • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care	• Enzalutamide (category 1) • Abiraterone acetate[l] with prednisone (category 1) • Radium-223 (category 1) if bone-predominant disease • Cabazitaxel with prednisone (category 1)[t] • Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1 • Clinical trial • Docetaxel rechallenge[t] • Alternative chemotherapy (mitoxantrone)[t] • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care

Visceral metastases →

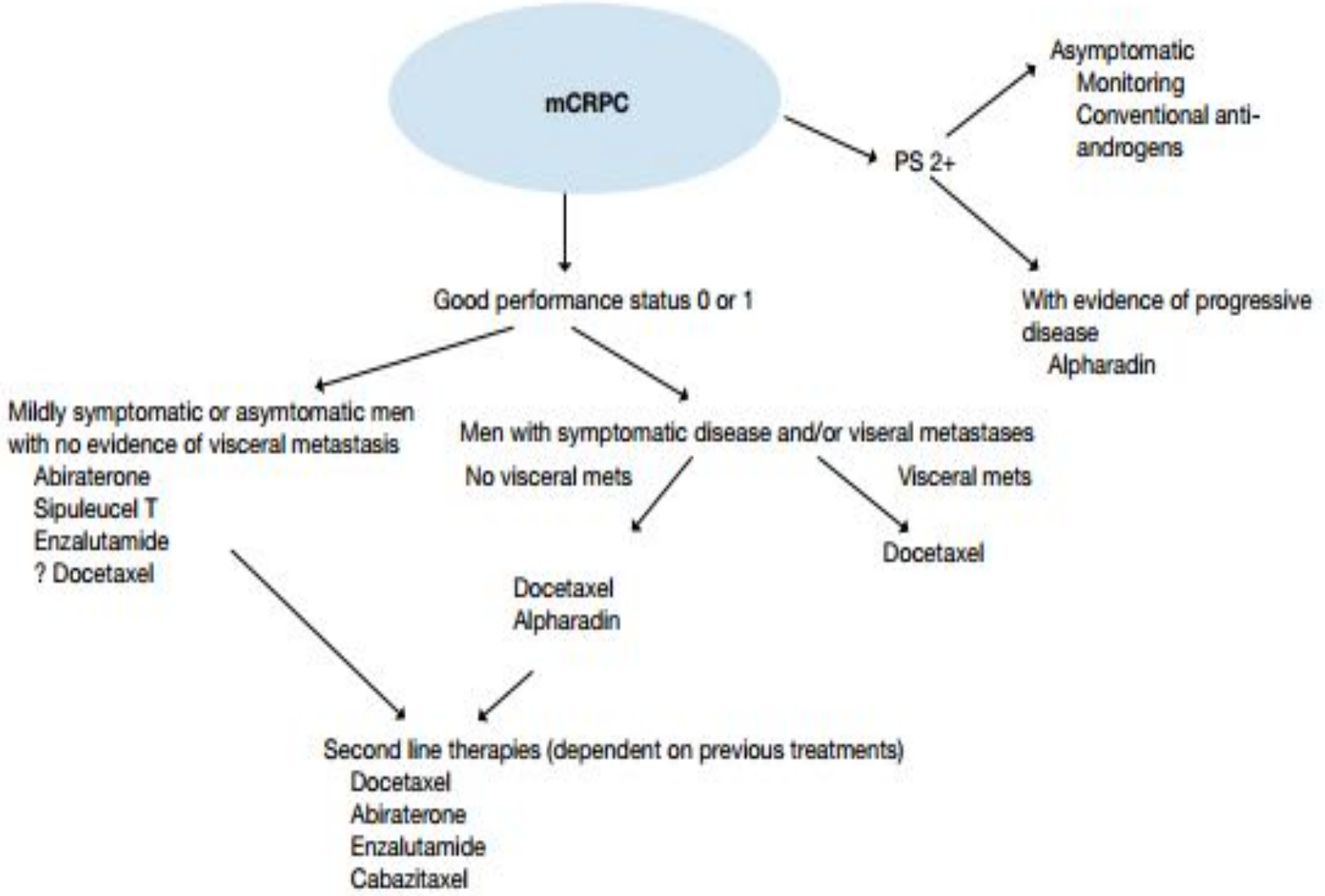
Prior therapy enzalutamide/abiraterone:	Prior therapy docetaxel:
• Docetaxel with prednisone (category 1)[t] • Clinical trial • Abiraterone acetate[l] or enzalutamide • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care	• Enzalutamide (category 1) • Abiraterone acetate[l] with prednisone (category 1) • Cabazitaxel with prednisone (category 1)[t] • Clinical trial • Docetaxel rechallenge[t] • Alternative chemotherapy (mitoxantrone)[t] • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care

[l]See Principles of Androgen Deprivation Therapy (PROS-F).

[t]See Principles of Immunotherapy and Chemotherapy (PROS-G).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Figure 6.11.1: Flowchart of the potential therapeutic options after PSA progression following initial hormonal therapy



EAU guidelines 2015

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

F13

Bracarda Sergio[1], Procopio Giuseppe[2], Parker Chris[3], Tombal Bertrand[4], Miller Kurt[5], Saad Fred[6], Fang Fang[7], Zhang Amily[8], Kornacker Martin[9], Higano Celestia[10], Smith Matthew Raymond[11]

(Previously presented at ESMO 2014, M.R.Smith, et al.).

[1] Department of Oncology, Istituto Toscano Tumori (ITT) S. Donato Hospital, Arezzo, ITALY - Arezzo, [2] Department of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, ITALY - Milano, [3] Academic Urology, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton,UK - Sutton, [4] Division of Urology, Cliniques Universitaires Saint-Luc, Brussels, BELGIUM - Brussels, [5] Department of Urology, Charité Berlin, Berlin, GERMANY - Berlin, [6] Surgery/urology, University of Montreal Hospital Center, Montreal, QC, CANADA - Montreal, [7] Global Clinical Statistics, Bayer HealthCare, Whippany, NJ, USA - Whippany, [8] Oncology, Bayer HealthCare, Whippany, NJ, USA - Whippany, [9] Clinical Development Oncology II, Bayer Pharma AG, Berlin, GERMANY - Berlin, [10] Medical Oncology, University of Washington, Seattle, WA, USA - Seattle, [11] Hematology-oncology, Massachusetts General Hospital Cancer Center, Boston, MA, USA - Boston.

BACKGROUND

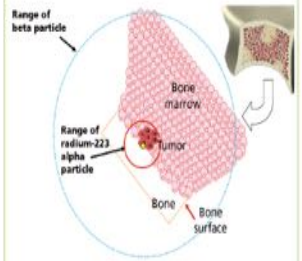
Prostate Cancer

- Prostate cancer is the second most common cancer in men and resulted in ~307,000 deaths worldwide in 2012[1]
- Most men with metastatic disease are first treated with androgen deprivation therapy; however, the majority ultimately develop castration-resistant prostate cancer (CRPC)[2]
- Approximately 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[3,4]
- > 90% of patients with metastatic CRPC have bone metastases leading to bone pain, symptomatic skeletal events (SSEs), disability, decreased quality of life, and death[5-7]

Radium-223 Dichloride (Radium-223)

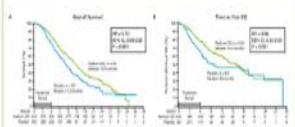
- Radium-223 is a first-in-class alpha radiopharmaceutical that selectively targets bone metastases. Radium-223 particle range is shorter than that of beta emitters (< 100 µm [< 10 cell diameters]), which limits surrounding tissue damage[8] **(Figure 1)**

Figure 1. The Target of Radium-223



- Unlike beta emitters, which are used for pain palliation, radium-223 has been shown in a large, randomized, placebo-controlled phase 3 trial (ALSYMPCA)[9] to provide a survival advantage for CRPC patients with symptomatic bone metastases when added to best standard of care (eg, local external beam radiation therapy [EBRT], corticosteroids, antiandrogens, ketoconazole, estrogens)
  - Compared with placebo, radium-223 prolonged overall survival by 3.6 months and delayed time to first SSE by 5.8 months[9] **(Figure 2)**
    - Survival was prolonged regardless of concomitant use of bisphosphonates or previous cytotoxic chemotherapy with docetaxel, which led to guidelines recommending pre- and post-docetaxel use of radium-223[3,4]
  - Radium-223 also had a favorable safety profile with low rates of myelosuppression. Lack of significant toxicity, particularly when radium-223 is administered with best standard of care, supports combining it with other agents

Figure 2. ALSYMPCA Efficacy Results



SSE = symptomatic skeletal event.

Abiraterone Acetate (Abiraterone)

- Abiraterone acetate is a prodrug rapidly converted on absorption to abiraterone, a selective irreversible steroidal inhibitor of 17α-hydroxylase/C17,20-lyase that targets androgen synthesis in testes, adrenal glands, and prostate cancer cells[10]
- In a large, randomized, placebo-controlled phase 3 trial in patients with asymptomatic or mildly symptomatic chemotherapy-naïve metastatic CRPC,[11] abiraterone 1000 mg once daily plus prednisone 5 mg twice daily, compared with placebo plus prednisone,
  - Significantly improved radiographic progression-free survival (16.5 vs 8.3 mo [HR = 0.53; 95% CI, 0.45-0.62; $P < 0.001$])
  - Showed a trend toward overall survival improvement, with a 25% decrease in the risk of death (HR = 0.75; 95% CI, 0.61-0.93; $P = 0.01$)
- 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 and mildly symptomatic patients with bone-predominant metastatic CRPC
- Given the different modes of action of radium-223 and abiraterone and their nonoverlapping safety profiles, it is expected that the combination will prolong SSE-free survival, 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-naive 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 investigative sites **(Figure 3)**
- ~800 patients will be randomized 1:1 to receive radium-223 (50 kBq/kg body weight IV) or matching placebo every 4 weeks for 6 cycles, plus oral abiraterone (1000 mg once daily) and oral prednisone (5 mg twice daily)
  - Randomization will be stratified by region, concurrent use of denosumab or bisphosphonates, and total alkaline phosphatase (< 90 U/L vs ≥ 90 U/L)
  - After completion of radium-223 treatment, all patients will continue on abiraterone plus prednisone until on-study SSE or death

END POINTS

Primary

- Symptomatic skeletal event–free survival (SSE-FS)—time from randomization to occurrence of
  - On-study SSE defined as
    - EBRT for skeletal symptoms
    - New symptomatic pathologic (non)vertebral bone fracture
    - Spinal cord compression
    - Tumor-related orthopedic surgical intervention
  - Death from any cause

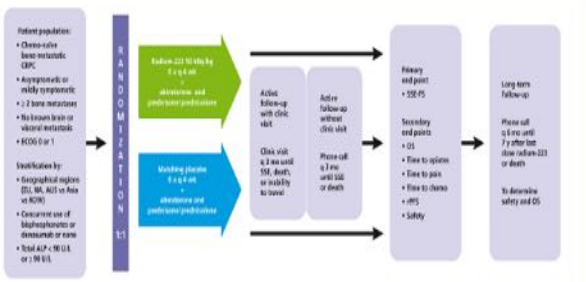
Secondary

- Overall survival
- 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) progression, prostate-specific antigen (PSA) 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 (FPSI-DRS-P) score

Figure 3. Study Design



ALP = alkaline phosphatase; AUS = Australia; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; EU = Europe; NA = North America; OS = overall survival; ROW = rest of world; rPFS = radiographic progression-free survival; SSE = symptomatic skeletal event; SSE-FS = SSE-free survival.

KEY ELIGIBILITY CRITERIA

Inclusion Criteria

- Age ≥ 18 years with life expectancy ≥ 6 months
- Histologically or cytologically confirmed prostate adenocarcinoma
- Known castration-resistant disease, 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 Index-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 Criteria

- Prior treatment with 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 Phase

- Patients will be assessed at each treatment visit for efficacy, safety, and health-related quality of life
- Clinic visits to be made 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 doses of abiraterone and prednisone alone or 6 mo post last radium-223/placebo injection, whichever occurs later)

Follow-up Phase

- Active follow-up period
  - *With* clinic visits
    - For patients discontinuing treatment without on-study SSE
    - Evaluations to occur every 3 months, extending until an SSE or the patient is unable to travel, is lost to follow-up, withdraws consent, or dies
  - *Without* clinic visits
    - For patients unable to travel, evaluations to occur by phone as above
- Long-term follow-up period
  - For patients experiencing an SSE at any point
  - Monitoring by phone to occur every 6 months and extend 7 years after the last radium-223 dose or until loss to follow-up, withdrawal of consent, or death

STATISTICAL METHODS

- The intent-to-treat population (all randomized patients) will be used in all efficacy analyses
- The safety population (all randomized patients receiving ≥ 1 study drug dose) will be used in all safety analyses
- The 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 expected to provide 389 SSE-FS events are needed to detect a 39% increase in SSE-FS; ie, an overall 0.05 level 2-sided log-rank test has approximately 90% power to detect a difference between the 2 SSE-FS curves if the alternative hypothesis HR is 0.72, assuming the median SSE-FS is 29.2 months for radium-223 versus 21.0 months for control
- The primary and secondary time-to-event end points will be analyzed using a stratified log-rank test with the randomization stratification factors
- No formal interim analysis is planned for the primary end point; one interim (at same time as final primary end point analysis) and one final analysis are planned for overall survival
- Safety variables will be analyzed using frequency tables and descriptive statistics

STUDY STATUS

- This study is currently recruiting patients
- As of September 5, 2014, 74 patients have been screened, 43 have been enrolled; first patient first visit occurred on March 31, 2014

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Morris, MJ et al (Abstract 5012)
Effects of Radium-223 dichloride (Ra-223) with docetaxel on prostate-specific antigen (PSA) and bone metastases: A Phase 1/2A Clinical Trial

EFFECTS OF RADIUM-223 DICHLORIDE (RA-223) WITH DOCETAXEL (D) VS D ON PROSTATE-SPECIFIC ANTIGEN (PSA) AND BONE ALKALINE PHOSPHATASE (BALP) IN PATIENTS (PTS) WITH CASTRATION-RESISTANT PROSTATE CANCER (CRPC) AND BONE METASTASES (METS): A PHASE 1/2A CLINICAL TRIAL. (MORRIS ET AL. ABSTRACT 5012)

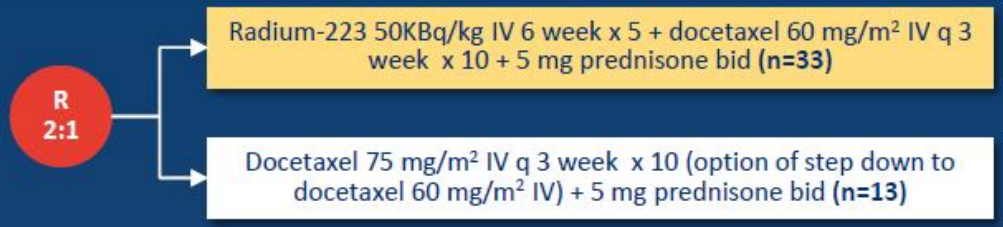
STUDY DESIGN AND RESULTS

- A follow-up presentation to Morris et al ASCO GU 2015 (Abstract 202) on the same endpoints.

PATIENTS N=46

- Progressive metastatic CRPC
- ≥2 bone metastases
- >2 lung and/or liver (>2 cm) metastases were not permitted
- No symptomatic nodal disease or other primary tumors

OBJECTIVES: Safety, PSA, and bALP dynamics



- NOTE: Only 2/13 patients who received docetaxel alone completed the approved dose of 75 mg/m². A higher percentage of patients who received docetaxel alone (54%) compared with radium-223 + docetaxel (27%), discontinued treatment.

RESULTS	PSA		bALP*	
	Ra-223 + DOC (n=33)	DOC (n=13)	Ra-223 + DOC (n=23)	DOC (n=11)
Any increase, n (%)	3 (9)	4 (31)	0	0
Decrease, n (%)				
<30%	4 912)	1 (8)	0	0
≥30%	26 (70)	8 (62)	23 (100)	11 (100)
>50%	20 (61)	7 (54)	22 (96)	9 (82)
>80%	10 (30)	4 (31)	9 (39)	2(18)
Normalization , n (%)	N/A	N/A	21 (91)	7 (64)
Median percentage change from baseline	-75	-55	-77	-59

KEY TAKE AWAY: Radium-223 + docetaxel was well tolerated as confirmed by the preliminary safety findings in the phase 2a expansion cohort. PSA and bALP declines were seen in both treatment arms. A higher percentage of patients who received radium-223 + docetaxel ––versus docetaxel alone had normalized bALP levels.

*Patients with baseline bALP > upper limit of normal (> 21 µg/L).