Third session: mCRPC first line

Clinical case and evidences from literature

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Clinical case:

L.A. 61 yo

Medical History:
Arterial hypertension
Smoking (15/day from 25 years)
Weight 71 Kg, H 168 cm.

Oncology History:
Apr 2003 PSA=8.1
Apr 2003 **Prostate biopsy.**
Histology: prostate adenocarcinoma, Gleason score 7 (4+3).

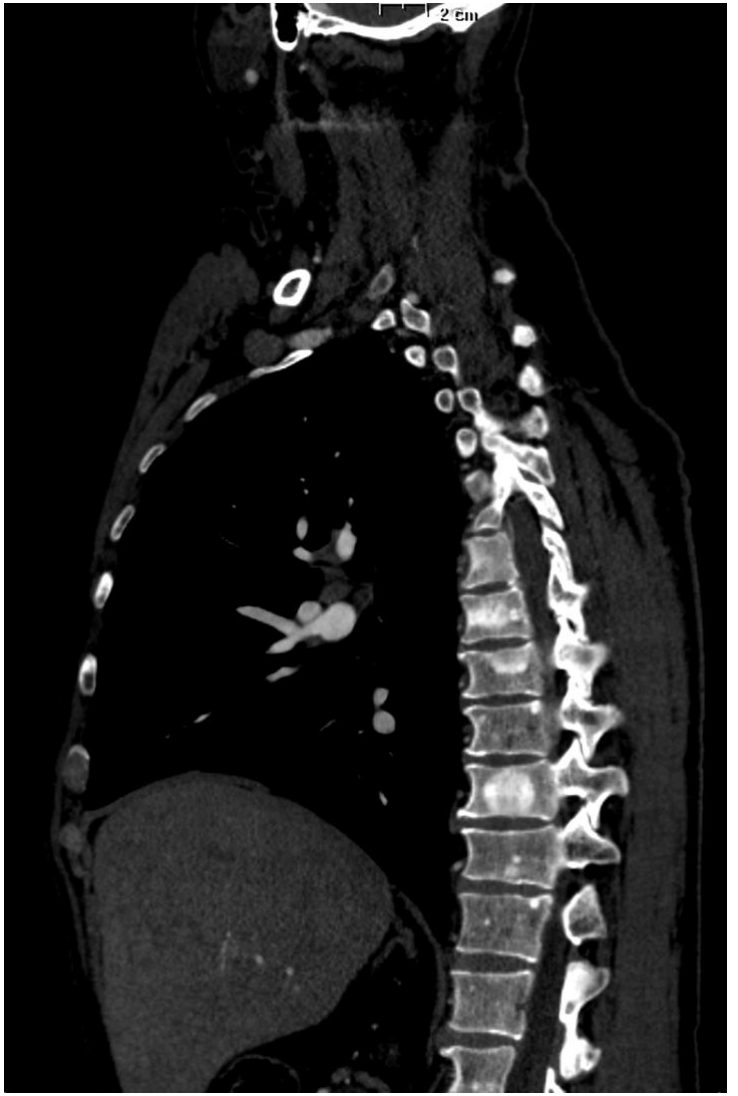
May 2003 **Radical prostatectomy and lymph node dissection**
Histology: Prostate adk Gleason score 8 (4+4) with the focal extension to right seminal vesicles. No lymph node spread (0/29). pT3b, N0 (High risk d'Amico)

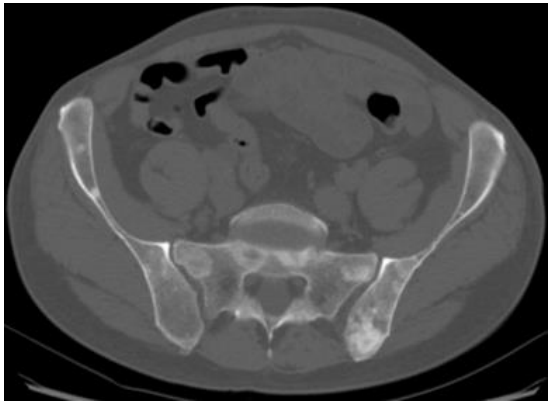
June 2003 PSA<0.008 Patient starts follow up.

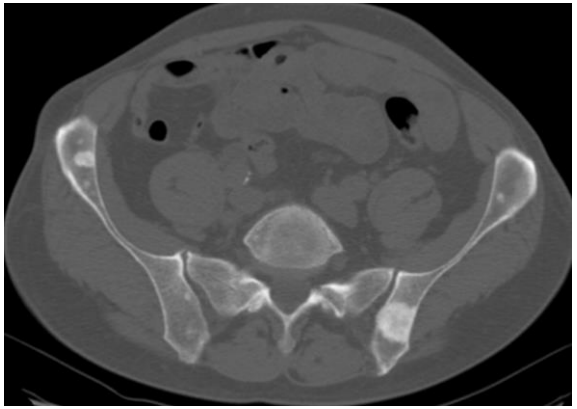
Jan 2006 PSA=0.27
Feb 2006 Salvage RT (64 Gy)
Patient restarts follow up until 2013.

Clinical case:

Oncology History:
26 Mar 2013 Hospitalization to the ER due to back pain
26 March 2013 **CT scan:** Bone lesion in the pelvis and spine. Mediastinal and retroperitoneal lymph-nodes (about 1 cm). Small solid noncalcified pulmonary node in inferior right lobe (12 mm).





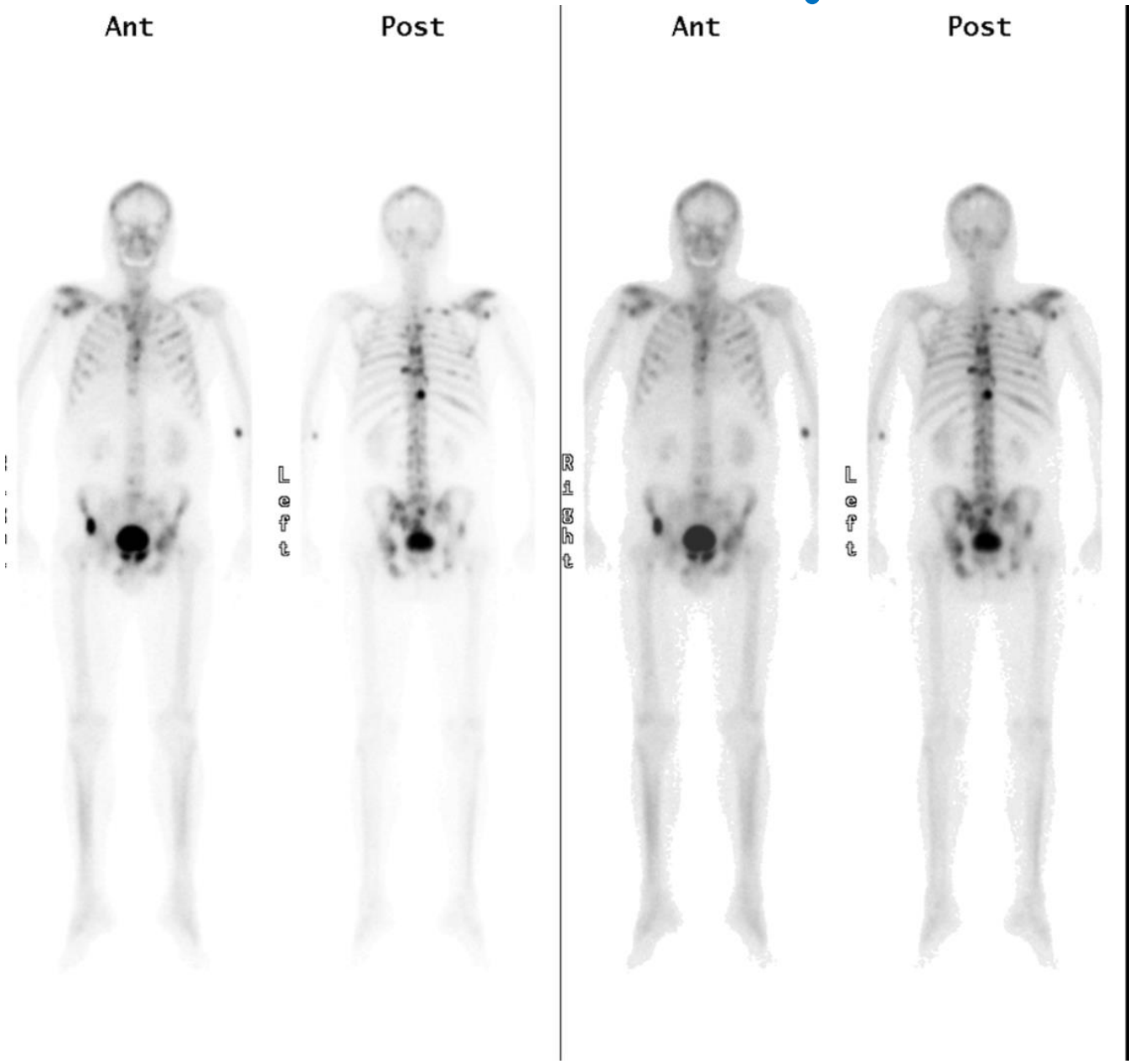


Clinical case:

27 Mar 2013 **PSA=64**

02 Apr 2013 **Starting ADT** (Bicalutamide + Triptoreline)

11 Apr 2013 **Bone Scan:** Bone lesions in the cranium, dorsal to lumbar spine, pelvis, ribs, humerus.



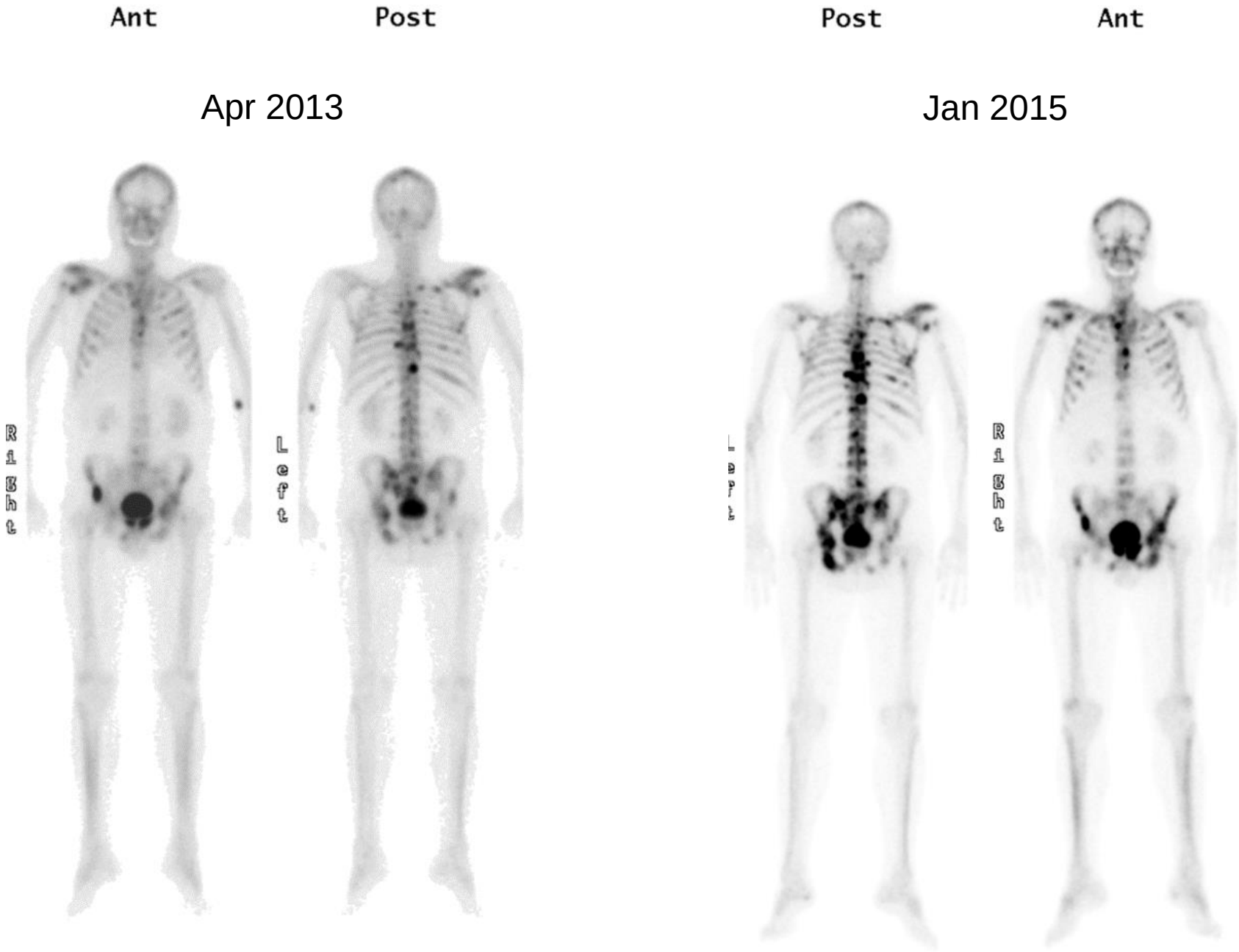
Clinical case:

07 Oct 2013 PSA=0.7
27 Mar 2014 PSA=1.1
22 Oct 2014 PSA=1.8
21 Dec 2014 PSA=3.6
07 Jan 2015 PSA=6.8; Testosterone 16 ng/dl;

Patients status: 73 yo, ECOG=1 due to back pain NRS=3/10, W 76 Kg,

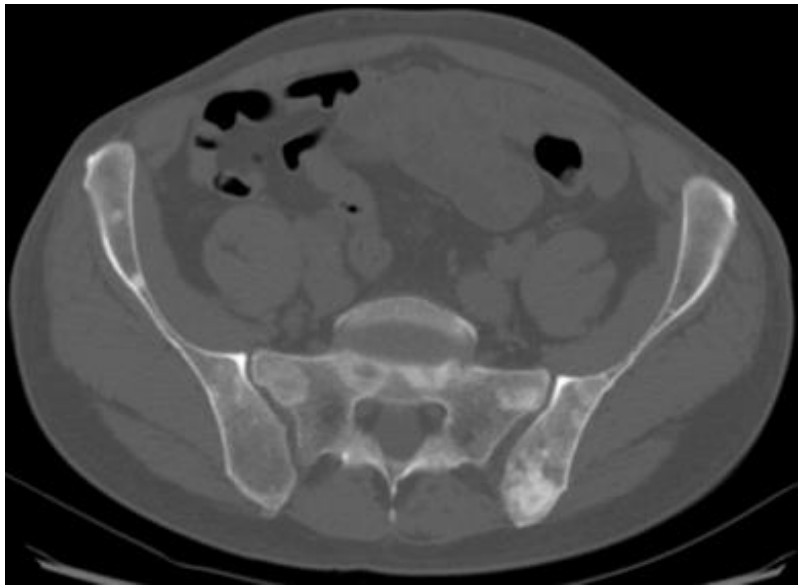
Blood test	Value	Normal rage
Hemoglobin	12.3	13.5 – 17.5
PLT	367	150 - 400
Ca	9.3	8.4 – 10.4
ALP	278	50 - 130
PSA	6.8	

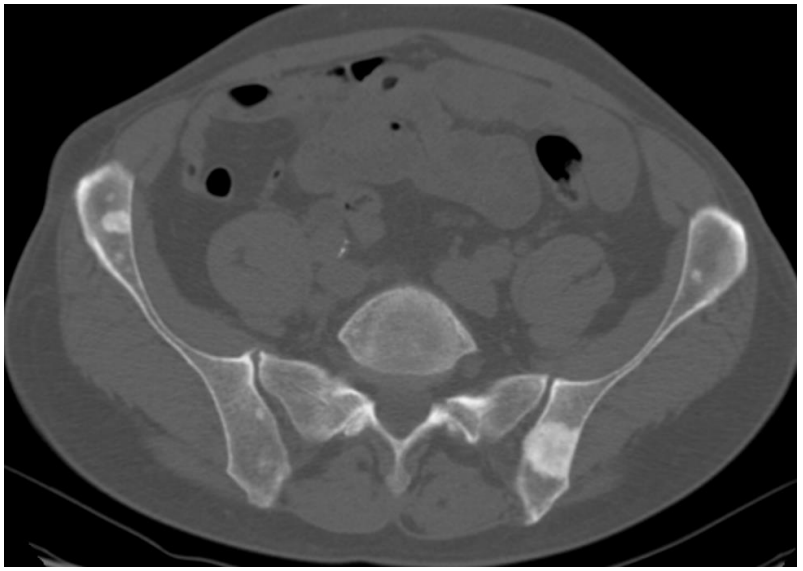
Clinical case:



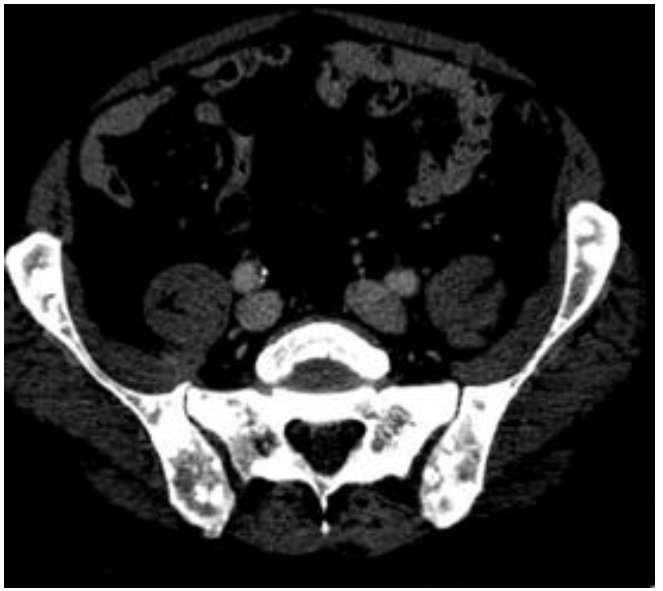
Clinical case:

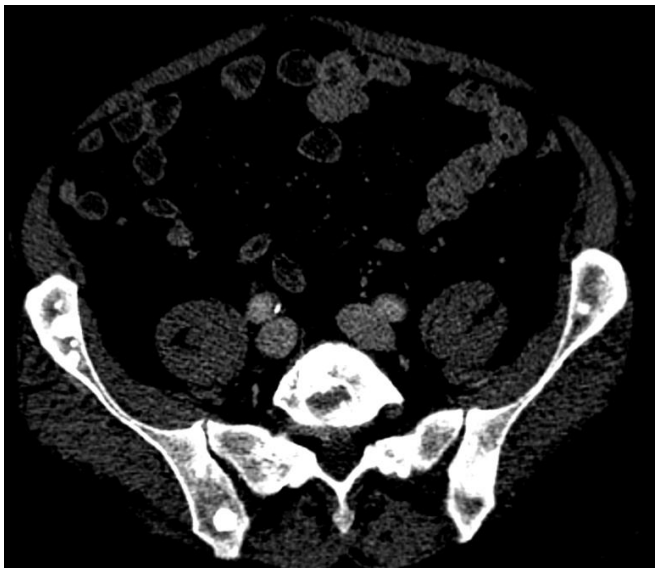
Apr 2013





Jan 2015





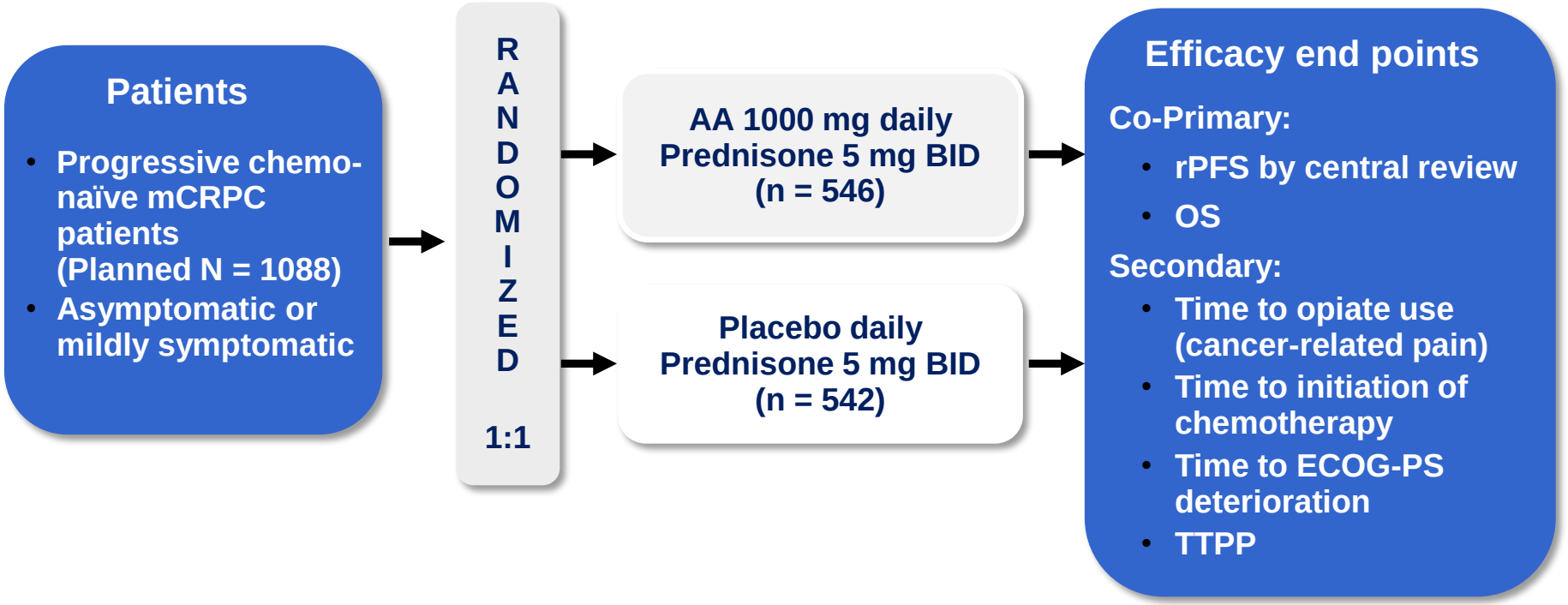
Clinical case:

What is the best treatment for this patients?

- Abiraterone
- Docetaxel 75 mg/m2, 3 weekly
- Docetaxel 50 mg/m2, 2 weekly
- Enzalutamide
- Radium 223

First-line mCRPC, *Evidences from the literature*: Abiraterone

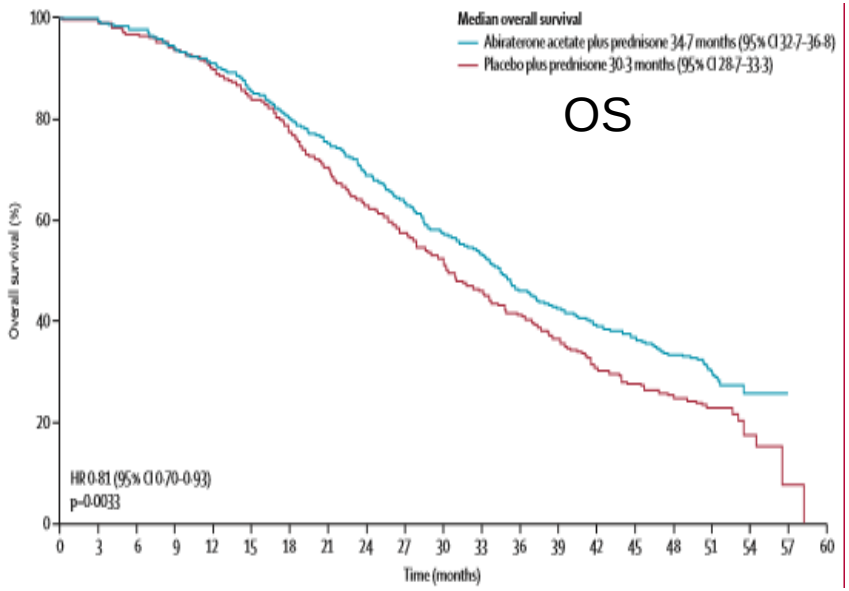
The COU-302 Trial: Study design

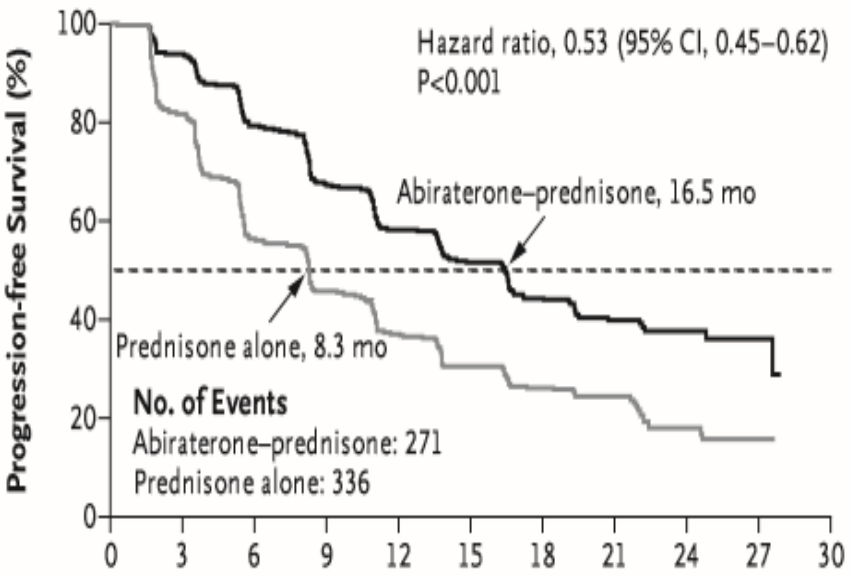


Ryan C et al. N Engl J Med 2013;368:138-48.

First-line mCRPC, *Evidences from the literature*: Abiraterone

The COU-302 Trial: results





	Pbo	ABI
Median OS, mos	30.3	34.7
HR	0.81	
95% CI	0.70-0.93	
P value	.033	

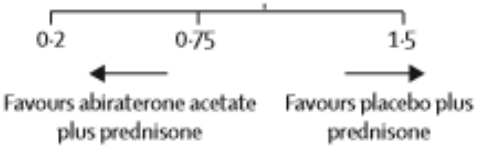
	Pbo	ABI
Median PFS, mos	8.3	16.5
HR	0.53	
95% CI	0.45-0.62	
P value	< .001	

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

First-line mCRPC, *Evidences from the literature*: Abiraterone

The COU-302 Trial: Population

	Median (months)		Hazard ratio (95% CI)	Events/N	
	Abiraterone acetate plus prednisone	Placebo plus prednisone		Abiraterone acetate plus prednisone	Placebo plus prednisone
All patients	**34·7 (32·7–36·8)**	**30·3 (28·7–33·3)**	**0·81 (0·70–0·93)**	**354/546**	**387/542**
Baseline ECOG					
0	35·4 (33·7–39·0)	32·0 (29·9–35·0)	0·79 (0·66–0·93)	261/416	292/414
1	27·9 (24·6–34·4)	26·4 (22·3–30·5)	0·87 (0·65–1·16)	93/130	95/128
Baseline BPI-SF					
0–1	38·1 (35·0–41·9)	33·4 (30·1–37·3)	0·77 (0·64–0·93)	223/370	233/346
2–3	26·4 (24·4–28·8)	27·4 (22·8–30·9)	0·97 (0·75–1·27)	100/129	120/147
Bone metastasis only at entry					
Yes	38·9 (34·9–45·2)	34·1 (30·1–39·1)	0·78 (0·62–0·97)	147/238	162/241
No	31·6 (27·8–34·5)	29·0 (26·0–30·9)	0·83 (0·69–1·00)	207/308	225/301
Age (years)					
<65	34·5 (31·5–41·7)	30·2 (27·9–36·9)	0·78 (0·59–1·03)	89/135	111/155
≥65	34·7 (31·2–36·8)	30·8 (27·3–33·6)	0·81 (0·69–0·96)	265/411	276/387
≥75	29·3 (26·1–34·5)	25·9 (21·4–30·0)	0·79 (0·61–1·10)	125/185	125/165
Baseline PSA above median					
Yes	28·5 (26·4–32·5)	25·8 (23·1–28·4)	0·86 (0·71–1·04)	208/282	206/260
No	43·1 (36·7–50·0)	34·4 (31·2–38·4)	0·72 (0·58–0·90)	146/264	181/282
Baseline LDH above median					
Yes	31·2 (27·3–34·3)	24·8 (21·5–28·6)	0·74 (0·61–0·90)	192/278	203/259
No	38·3 (34·5–44·2)	35·8 (32·7–38·8)	0·85 (0·69–1·05)	162/268	184/283
Baseline ALK-P above median					
Yes	28·6 (26·4–32·3)	26·8 (23·2–31·7)	0·92 (0·76–1·11)	211/279	201/256
No	44·5 (37·4–50·4)	33·2 (30·0–37·6)	0·68 (0·55–0·85)	143/267	186/286
Region					
North America	37·0 (33·5–40·6)	31·2 (28·7–34·9)	0·74 (0·61–0·91)	184/297	198/275
Other	33·2 (28·5–35·4)	30·1 (27·2–33·6)	0·90 (0·73–1·11)	170/249	189/267

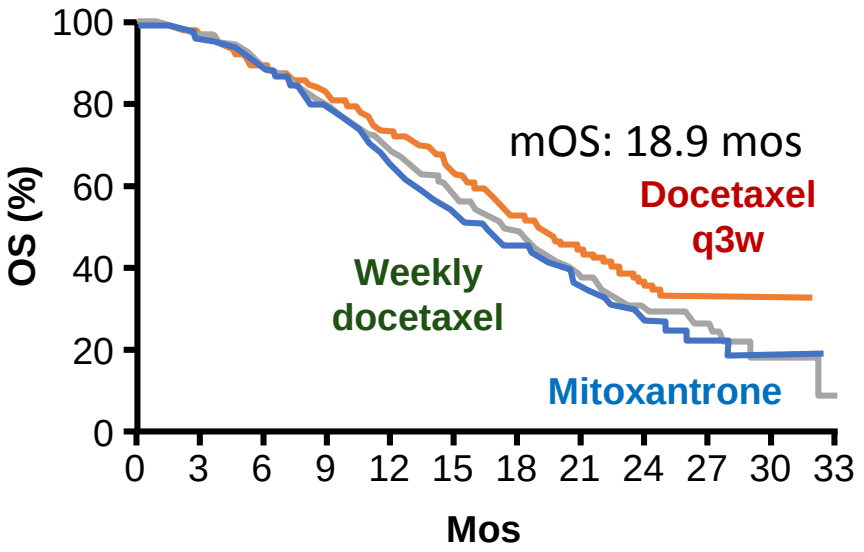


Ryan CJ et al. Lancet Oncol 2015; 16: 152–60

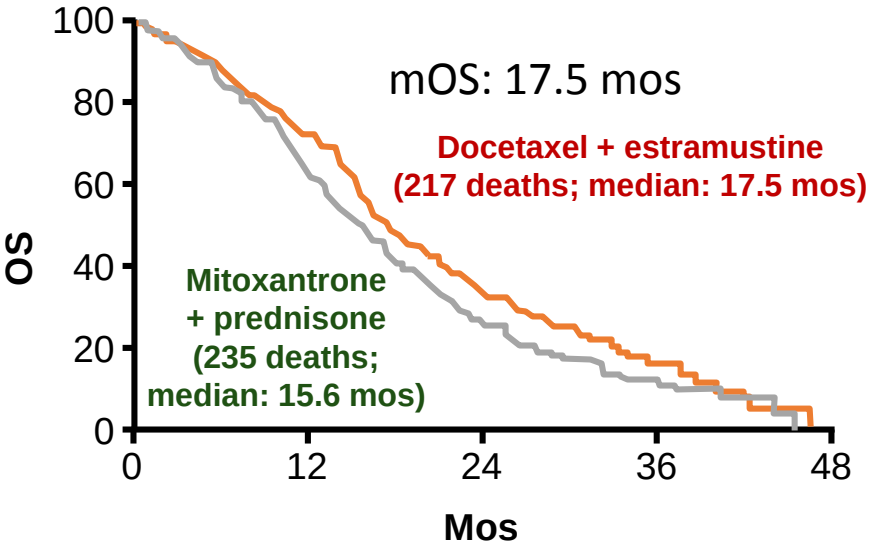
First-line mCRPC, *Evidences from the literature*: Docetaxel

The TAX 327 and SWOG 99-16 Trials: results

TAX-327: Docetaxel improved survival and rates of response in terms of pain, PSA level, and quality of life vs mitoxantrone/prednisone[1]



SWOG 99-16: Docetaxel/estramustine improved median survival by 2 mos vs mitoxantrone/prednisone[2]



	Aflibercept		Placebo		p value
	Number assessable	Median (95% CI)	Number assessable	Median (95% CI)	
Median overall survival (months)	612 patients (428 deaths)	22·1 (95·6% CI 20·3–24·1)	612 patients (445 deaths)	21·2 (95·6% CI 19·6–23·8)	0·38
Time to first skeletal-related event (months)	612 patients (497 events)	15·3 (14·1–16·7)	612 patients (516 events)	15·0 (13·7–16·4)	0·31
PFS (months)	612 patients (592 events)	6·9 (6·2–7·4)	612 patients (592 events)	6·2 (5·6–6·9)	0·31
PSA-PFS (months)	608 patients (567 events)	8·3 (7·8–8·8)	606 patients (571 events)	8·1 (7·6–8·6)	0·42
Pain-PFS (months)	287 patients (244 events)	9·2 (8·2–10·4)	301 patients (263 events)	9·7 (8·5–11·5)	0·87

Unless otherwise indicated figures in parentheses represent 95% confidence intervals. Except for the primary endpoint of overall survival, p values are descriptive and exploratory; they are not corrected for multiplicity. PFS=progression-free survival. PSA=prostate-specific antigen.

Table 3: Time to event efficacy outcomes, by treatment group

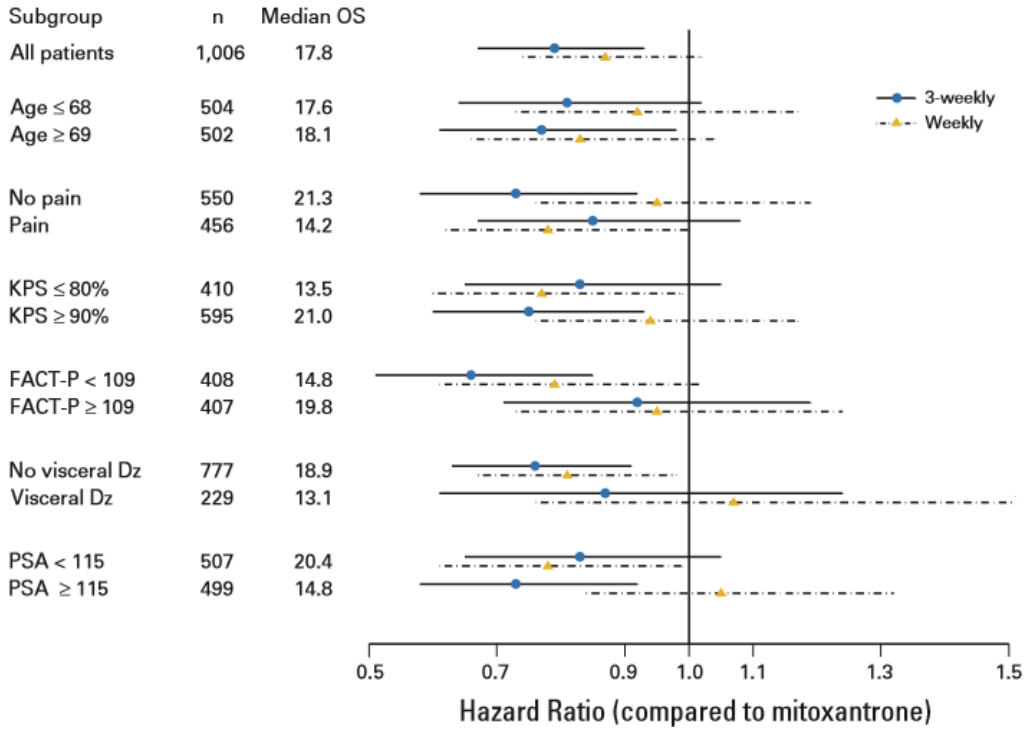
Tannock TF, et al. N Engl J Med. 2004;351:1502-1512.
Petrylak DP, et al. N Engl J Med. 2004;351:1513-1520.
Tannock TF, et al. Lancet Oncol 2013; 14: 760–68

First-line mCRPC, *Evidences from the literature*: Docetaxel

The TAX 327 Trial: population

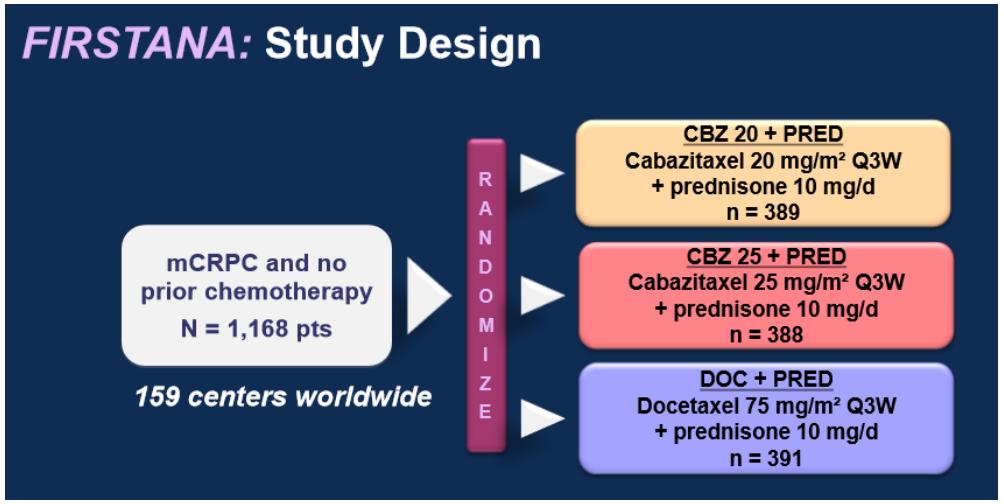
Table 1. Baseline Characteristics of the Patients.*

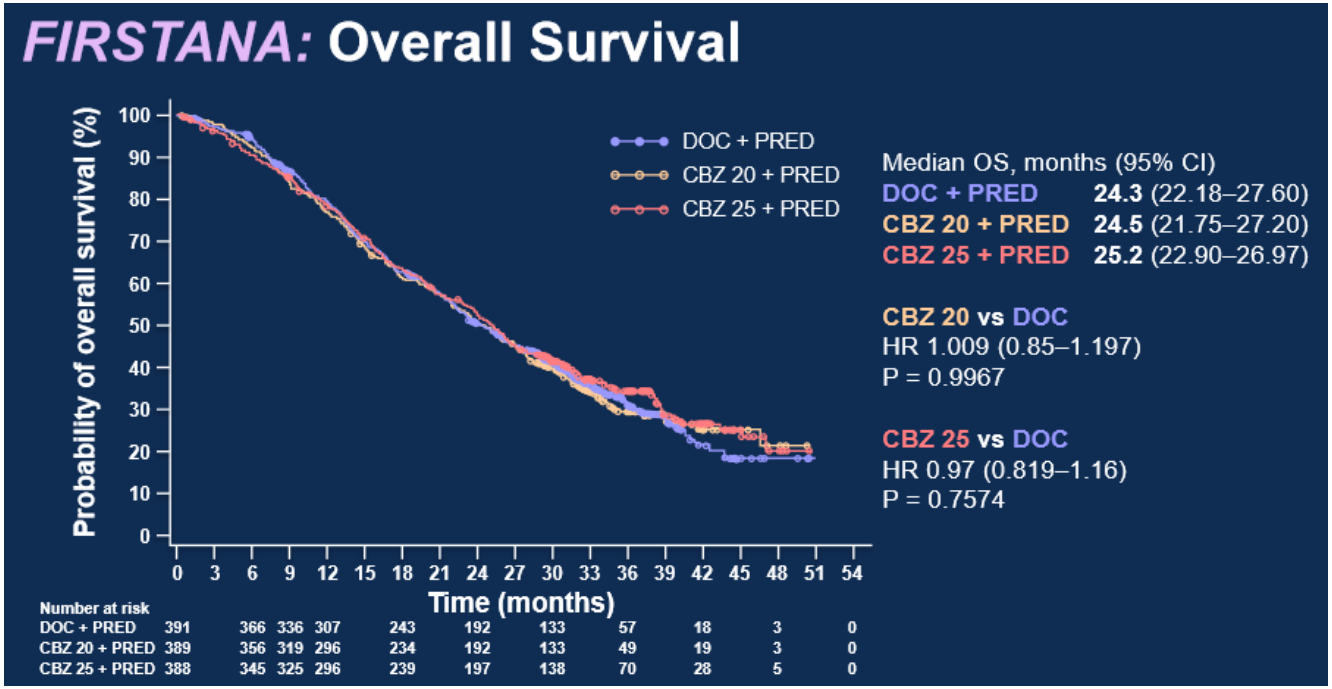
Characteristic	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
No. randomized	335	334	337
Ineligible (%)	12	12	12
Age			
Median (yr)	68	69	68
Range (yr)	42–92	36–92	43–86
≥75 Yr (%)	20	21	20
Gleason score (%)			
≤7	42	40	42
8–10	31	31	28
Not available	26	29	30
Prior treatment (%)			
Prostatectomy	19	24	21
Radiotherapy	52	44	51
Estramustine	19	18	20
Hormonal manipulations (%)†			
1	9	8	6
2	68	72	69
>2	23	21	25
Karnofsky performance-status score ≤70% (%)	13	12	14
Pain (%)‡	45	45	46
Serum PSA			
Median (ng/ml)	114	108	123
≥20 ng/ml (%)	87	84	89
Extent of disease (%)			
Bone metastases	90	91	92
Visceral disease	22	24	22
Measurable lesions	40	39	40
Evidence of progression at entry (%)§			
Bone scan	71	69	69
Increase in measurable lesions	28	30	28
Increase in nonmeasurable lesions	13	16	15
Increased PSA	72	66	68



First-line mCRPC, *Evidences from the literature*: Docetaxel

The Firstana Trials: study design and results





Oudard S et al. J Clin Oncol. 2017;35:3189-3197.

First-line mCRPC, *Evidences from the literature*: Docetaxel

The Firstana Trials: Population

Table 1. Patient Characteristics

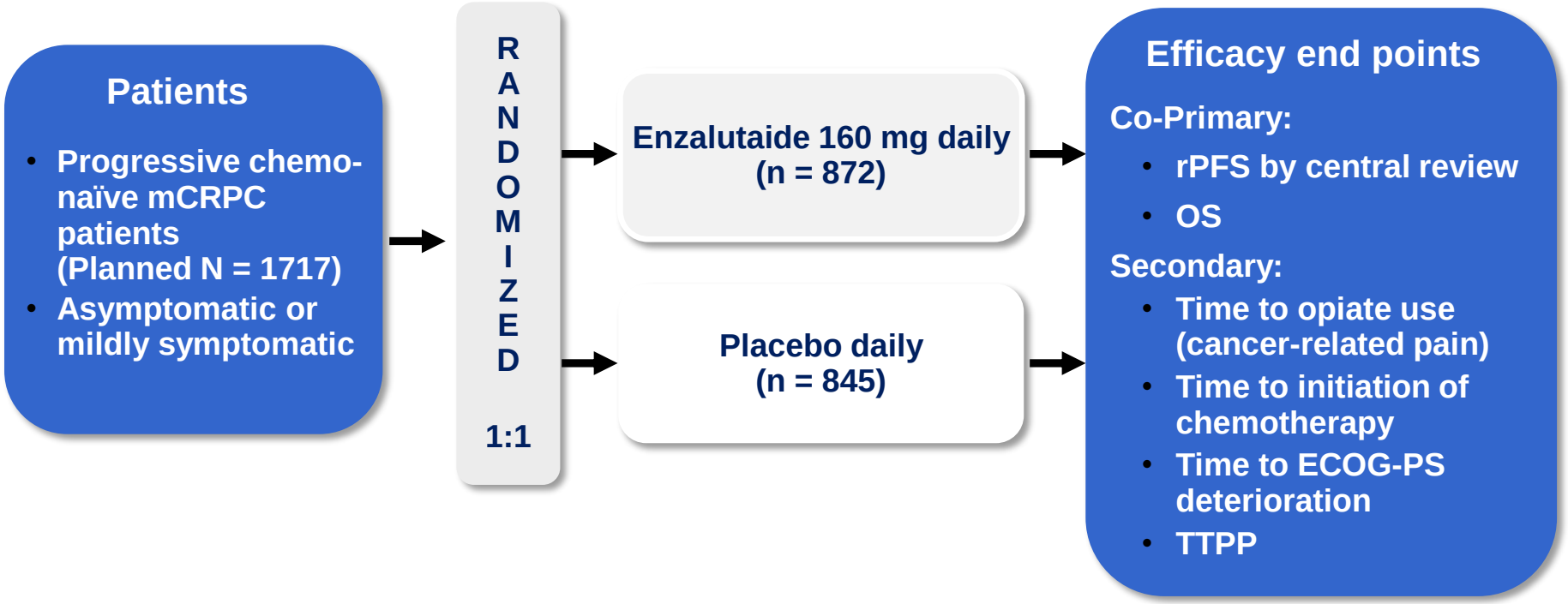
Characteristic	C20 (n = 389)	C25 (n = 388)	D75 (n = 391)
Age, years			
Mean (SD)	67.7 (7.8)	67.8 (7.6)	68.2 (7.7)
Median (range)	68.0 (44-90)	68.5 (42-85)	69.0 (41-87)
Age group, years, No. (%)			
< 65	128 (32.9)	125 (32.2)	123 (31.5)
65-74	187 (48.1)	182 (46.9)	181 (46.3)
≥ 75	74 (19.0)	81 (20.9)	87 (22.3)
Race, No. (%)			
White	365 (93.8)	360 (92.8)	363 (92.8)
Black	8 (2.1)	6 (1.5)	9 (2.3)
Asian	13 (3.3)	17 (4.4)	17 (4.3)
Other	3 (0.8)	5 (1.3)	2 (0.5)
ECOG performance status, No. (%)			
0 or 1	370 (95.1)	376 (96.9)	374 (95.7)
2	19 (4.9)	12 (3.1)	17 (4.3)
Gleason score, No. (%)			
≤ 6	54 (13.9)	52 (13.4)	42 (10.7)
≥ 7	299 (76.9)	312 (80.4)	309 (79)
PSA, ng/mL			
Mean (SD)	213.21 (434.24)	257.89 (578.78)	252.81 (625.20)
Median (range)	76.00 (0.0-3,289.3)	80.04 (0.1-6,312.7)	73.92 (2.4-6,862.0)
Quartile 1	29.58	28.25	30.00
Quartile 3	176.10	235.30	195.80
LDH levels, No./total No.* (%)			
Normal	211/360 (58.6)	240/380 (63.2)	214/385 (55.6)
> ULN	149/360 (41.4)	140/380 (36.8)	171/385 (44.4)
Elevated alkaline phosphatase, No./total No.* (%)	173/369 (46.9)	181/389 (46.5)	191/386 (49.5)
Hemoglobin < LLN, No./total No.* (%)	254/368 (69.0)	271/391 (69.3)	270/387 (69.8)
Metastases, No. (%)			
Bone	345 (88.7)	345 (88.9)	356 (91.0)
Lymph nodes	207 (53.2)	208 (53.6)	211 (54.0)
Lungs	58 (14.9)	50 (12.9)	47 (12.0)
Liver	32 (8.2)	39 (10.1)	35 (9.0)
Disease progression before study, No. (%)	385 (99.0)	386 (99.5)	390 (99.7)
Increasing PSA only	216 (55.5)	222 (57.2)	224 (57.3)
Radiologic only	48 (12.3)	44 (11.3)	48 (12.3)
Prior hormonal therapy, No. (%)	379 (97.4)	383 (98.7)	382 (97.7)
1 regimen	147 (37.8)	143 (36.9)	150 (38.4)
2 regimens	87 (22.4)	108 (27.8)	105 (26.9)
≥ 3 regimens	145 (37.3)	132 (34.0)	127 (32.5)

60% of patients had pain at baseline

Oudard S et al. J Clin Oncol. 2017;35:3189-3197.

First-line mCRPC, *Evidences from the literature*: Enzalutamide

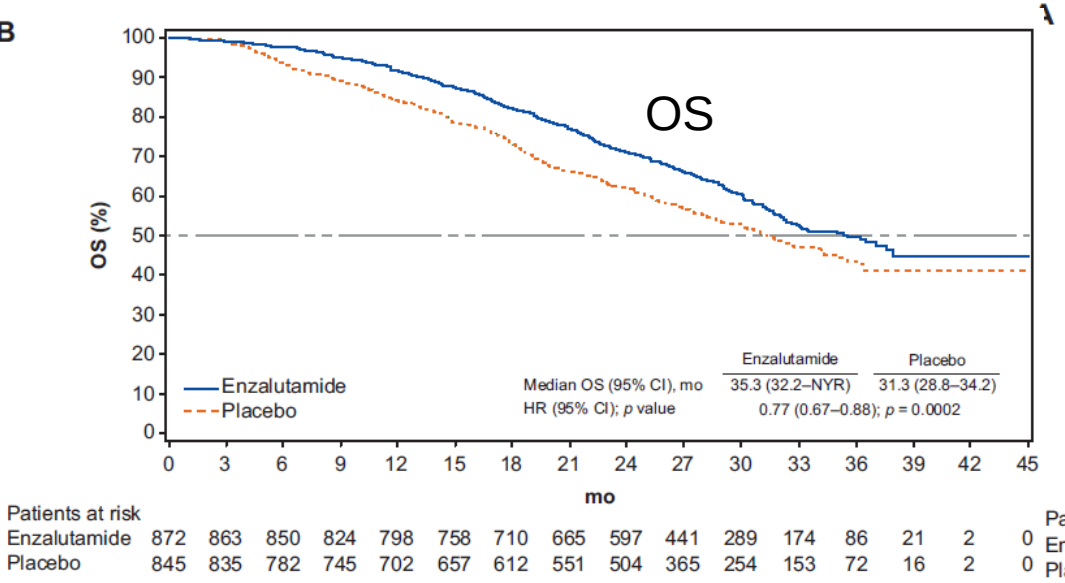
The PREVAIL Trial: Study design

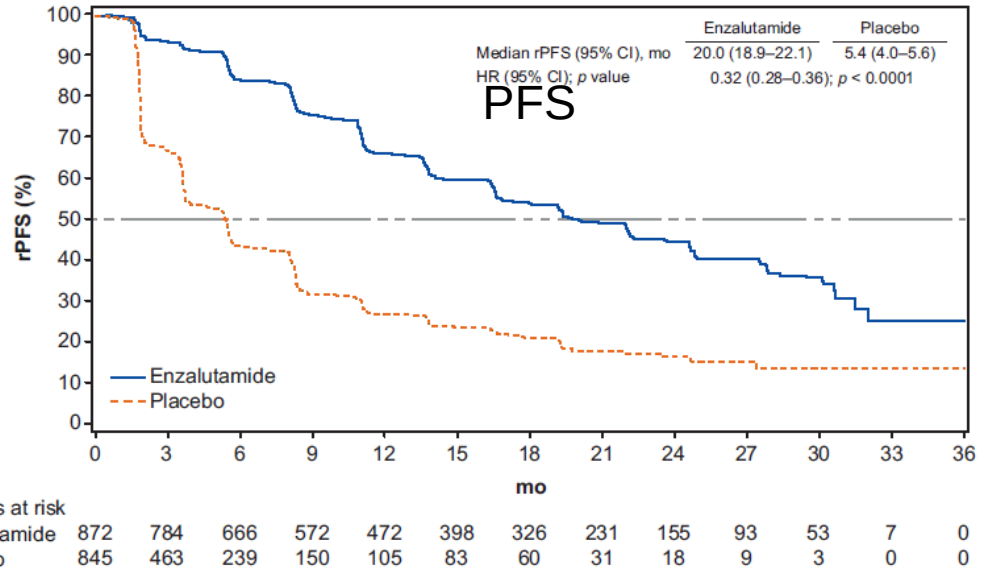


Beer TM et al. N Engl J Med. 2014;371:424-33

First-line mCRPC, *Evidences from the literature*: Enzalutamide

The PREVAIL Trial: results





	Pbo	ENZ
Median OS, mos	31.3	35.3
HR	0.77	
95% CI	0.47-0.88	
P value	<.001	

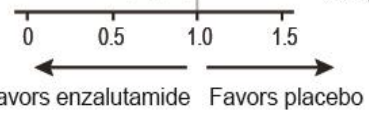
	Pbo	ENZ
Median PFS, mos	5.4	20.0
HR	0.32	
95% CI	0.28-0.36	
P value	<.001	

Beer TM et al. Eur Urol. 2017;71:151-154.

First-line mCRPC, *Evidences from the literature*: Enzalutamide

The PREVAIL Trial: population

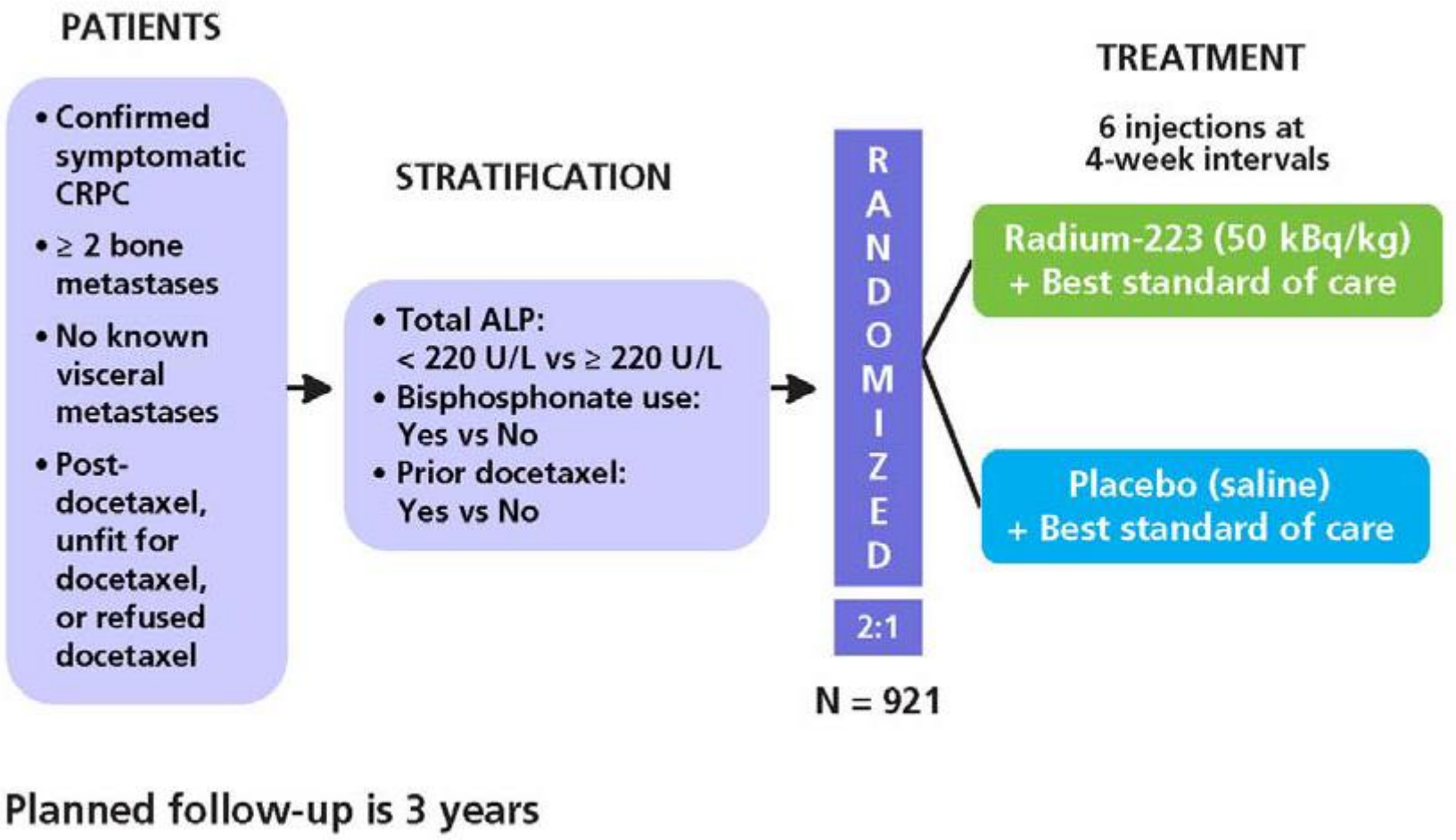
Subgroup	No. of patients, enzalutamide/ placebo	Overall survival median (mo) enzalutamide/ placebo	Hazard ratio for death (95% CI) (unstratified)
All patients	872/845	35.3/31.3	0.77 (0.67–0.88)
ECOG Performance Status at baseline = 0	584/585	37.1/35.3	0.80 (0.67–0.96)
ECOG Performance Status at baseline = 1	288/260	31.7/25.4	0.68 (0.54–0.86)
Age <75 yr	555/553	35.5/35.0	0.87 (0.72–1.04)
Age ≥75 yr	317/292	32.6/24.6	0.62 (0.50–0.78)
Geographic region, North America	218/208	37.9/35.3	0.88 (0.66–1.17)
Geographic region, Europe	465/446	33.5/30.0	0.74 (0.61–0.90)
Geographic region, Rest of world	189/191	NYR/31.8	0.71 (0.52–0.97)
Total Gleason Score at diagnosis ≤7	414/385	36.5/31.8	0.75 (0.61–0.93)
Total Gleason Score at diagnosis ≥8	424/423	32.4/31.3	0.80 (0.66–0.98)
Type of progression at study entry, PSA progression only	375/369	NYR/NYR	0.69 (0.54–0.88)
Type of progression at study entry, radiographic progression with or without PSA progression	475/451	31.2/27.3	0.80 (0.67–0.95)
Visceral disease (lung and/or liver) at screening, yes	98/106	30.0/21.3	0.69 (0.48–1.01)
Visceral disease (lung and/or liver) at screening, no	774/739	35.5/31.8	0.78 (0.67–0.91)
Baseline PSA value ≤median (49.60), ng/ml	420/440	NYR/NYR	0.86 (0.68–1.09)
Baseline PSA value >median (49.60), ng/ml	452/404	30.1/22.5	0.65 (0.55–0.77)
Baseline LDH value ≤median (185), U/l	443/423	37.9/NYR	0.74 (0.60–0.93)
Baseline LDH value >median (185), U/l	428/421	29.5/25.3	0.80 (0.67–0.96)
Baseline hemoglobin value ≤median (130), g/l	455/416	30.9/25.5	0.75 (0.63–0.90)
Baseline hemoglobin value >median (130), g/l	417/429	37.9/36.4	0.75 (0.60–0.94)



Beer TM et al. Eur Urol. 2017;71:151-154.

First-line mCRPC, *Evidences from the literature*: RAD-223

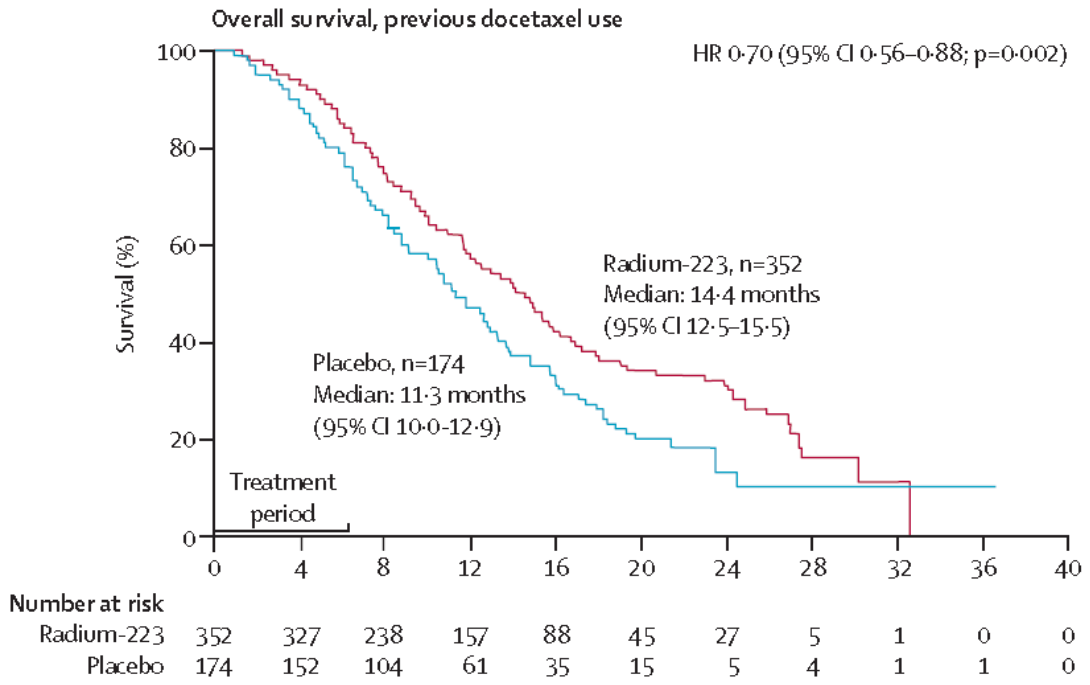
The ALSYMPCA Trial: Study design

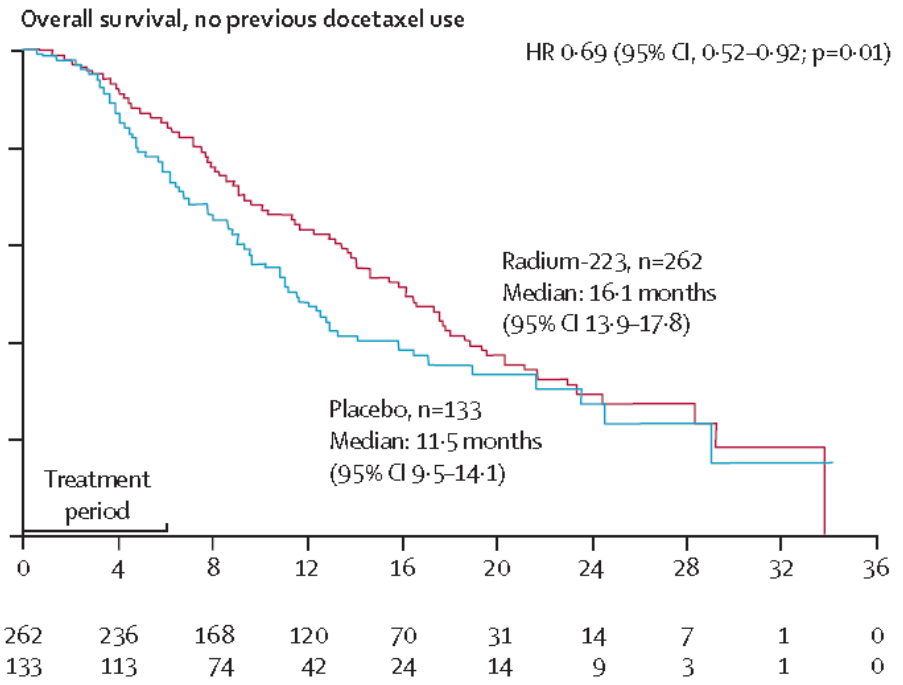


Parker C, et al. N Engl J Med. 2013; 369: 213-23.

First-line mCRPC, *Evidences from the literature*: RAD-223

The ALSYMPCA Trial: Results





	Ra223	Pbo
Median **OS**, mos	14.4	11.3
HR	0.70	
95% CI	0.56-0.88	
P value	.002	

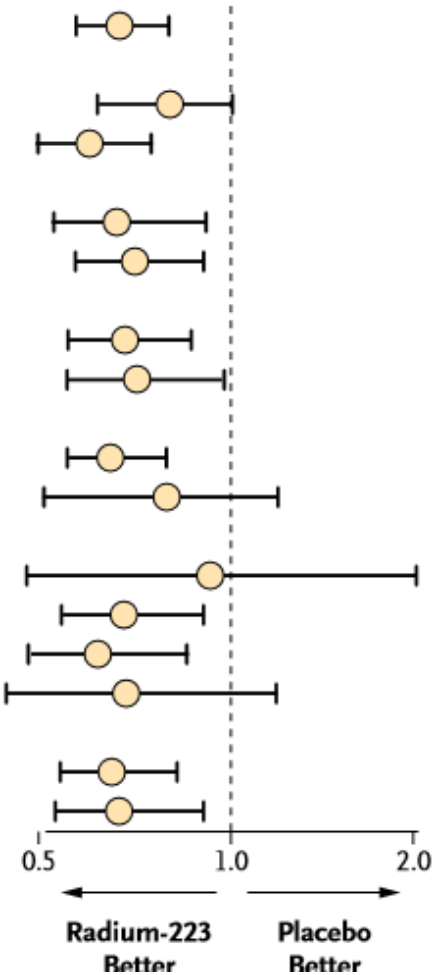
	Ra223	Pbo
Median **PFS**, mos	16.1	11.5
HR	0.69	
95% CI	0.52-0.92	
P value	.01	

Hoskin P, et al. Lancet Oncol 2014; 15: 1397–406

First-line mCRPC, *Evidences from the literature*: RAD-223

The ALSYMPCA Trial: Population

Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
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)
Previous docetaxel use					
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 performance-status score					
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)



Thank you

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