The Management and treatment options for secondary bone disease

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07 December 2012

Congratulations

Please tell me how you would rate the honesty and ethical standards of people in these different fields -- very high, high, average, low, or very low? How about -- [RANDOM ORDER]?

Sorted by % very high/high

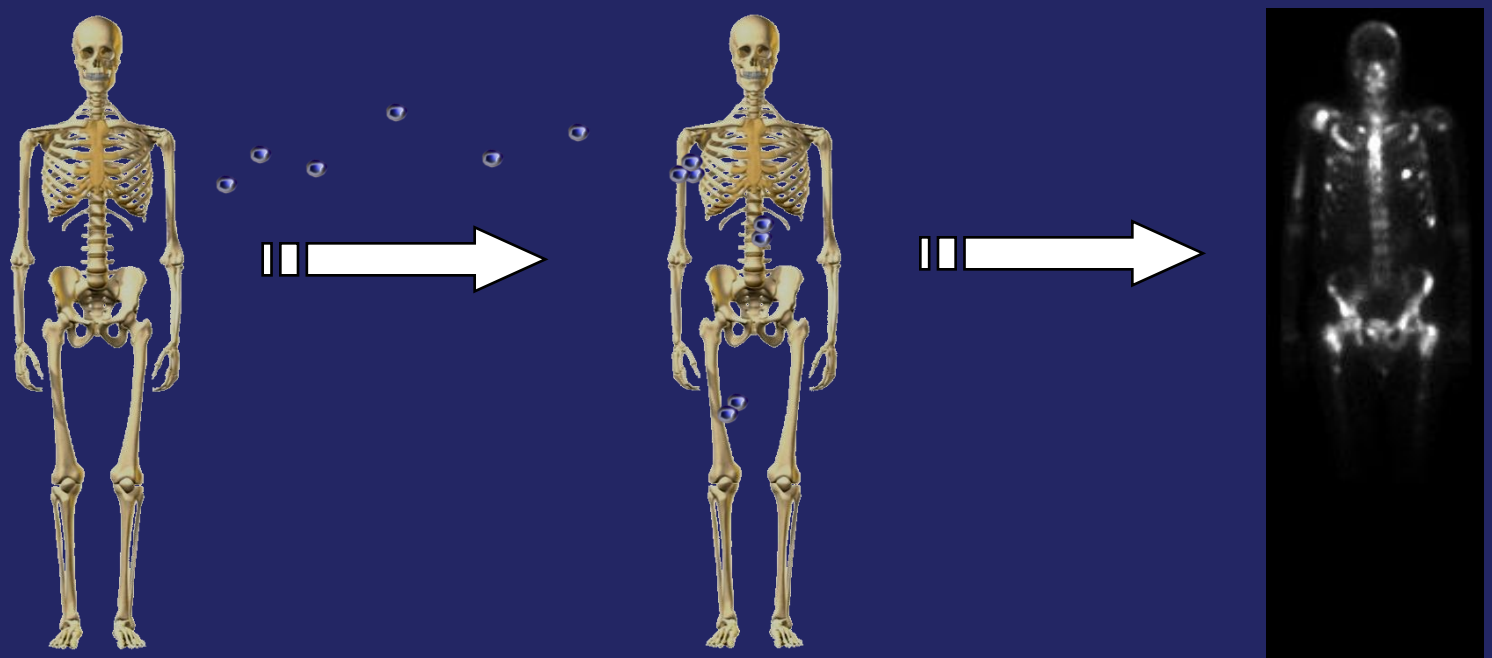
	% Very high/ High	% Average	% Very low/ Low
Nurses	85	12	3
Pharmacists	75	21	3
Medical doctors	70	26	4
Engineers	70	25	3
Dentists	62	33	4
Police officers	58	32	10
College teachers	53	34	10
Clergy	52	33	9
Psychiatrists	41	43	11
Chiropractors	38	46	11
Bankers	28	48	24
Journalists	24	45	30
Business executives	21	50	27
State governors	20	48	31
Lawyers	19	42	38
Insurance salespeople	15	49	36
Senators	14	39	45
HMO Managers	12	52	27
Stockbrokers	11	48	39
Advertising practitioners	11	50	36
Members of Congress	10	34	54
Car salespeople	8	43	49

Gallup, Nov. 26-29, 2012

GALLUP

Spectrum of Bone Disease in Prostate Cancer

Treatment-related fractures — New bone metastases — Disease-related skeletal complications

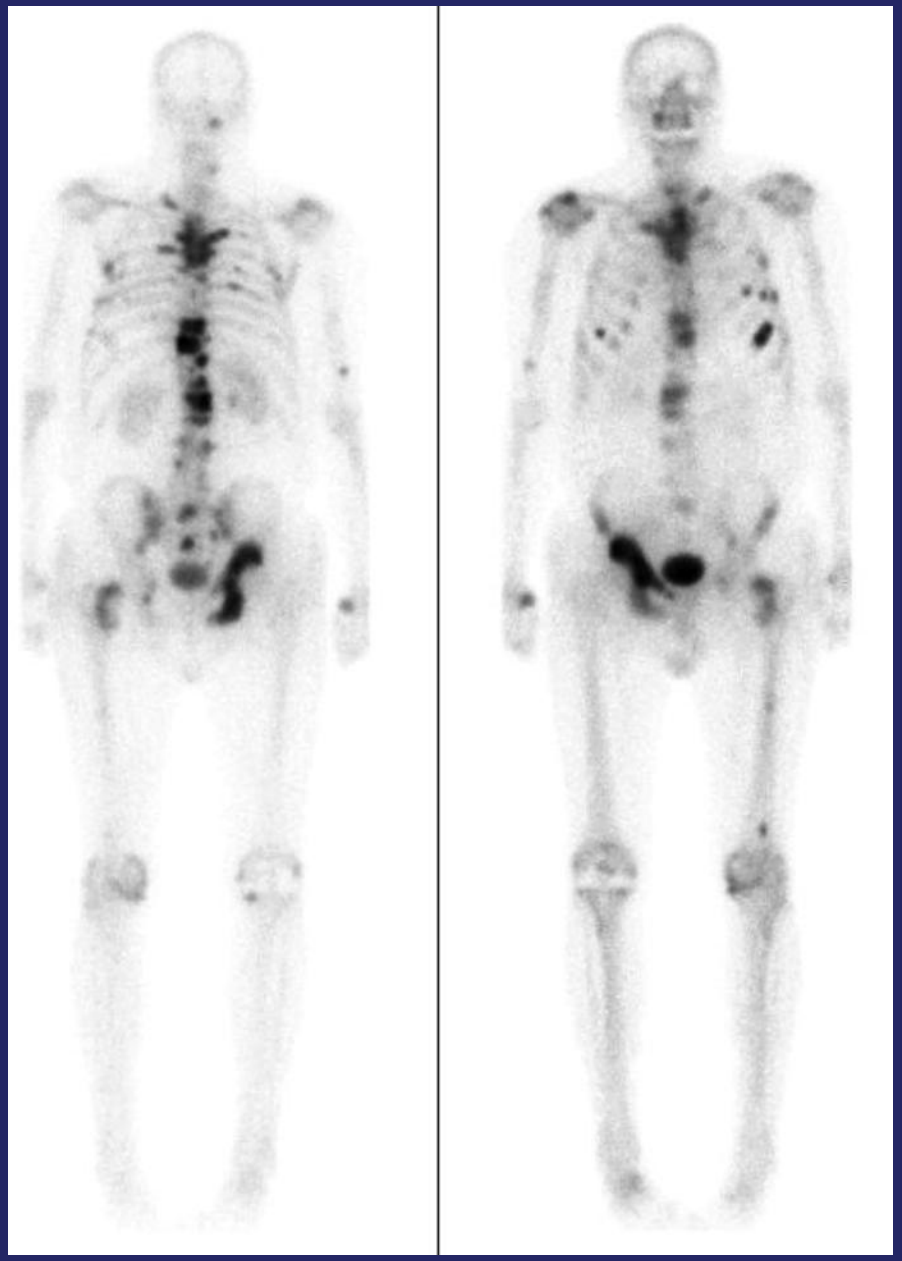


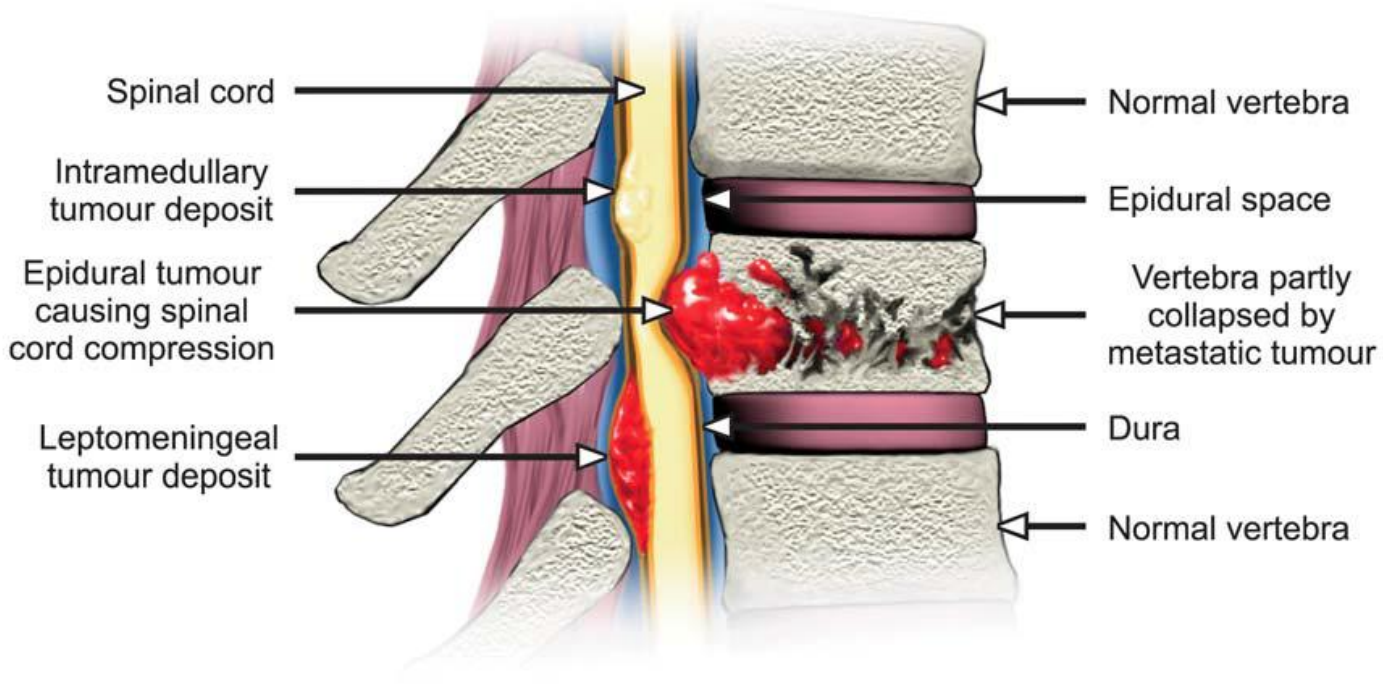
Castrate sensitive , nonmetastatic

Castrate resistant , nonmetastatic

Castrate resistant , metastatic

Prostate cancer bone metastases are typically widely disseminated





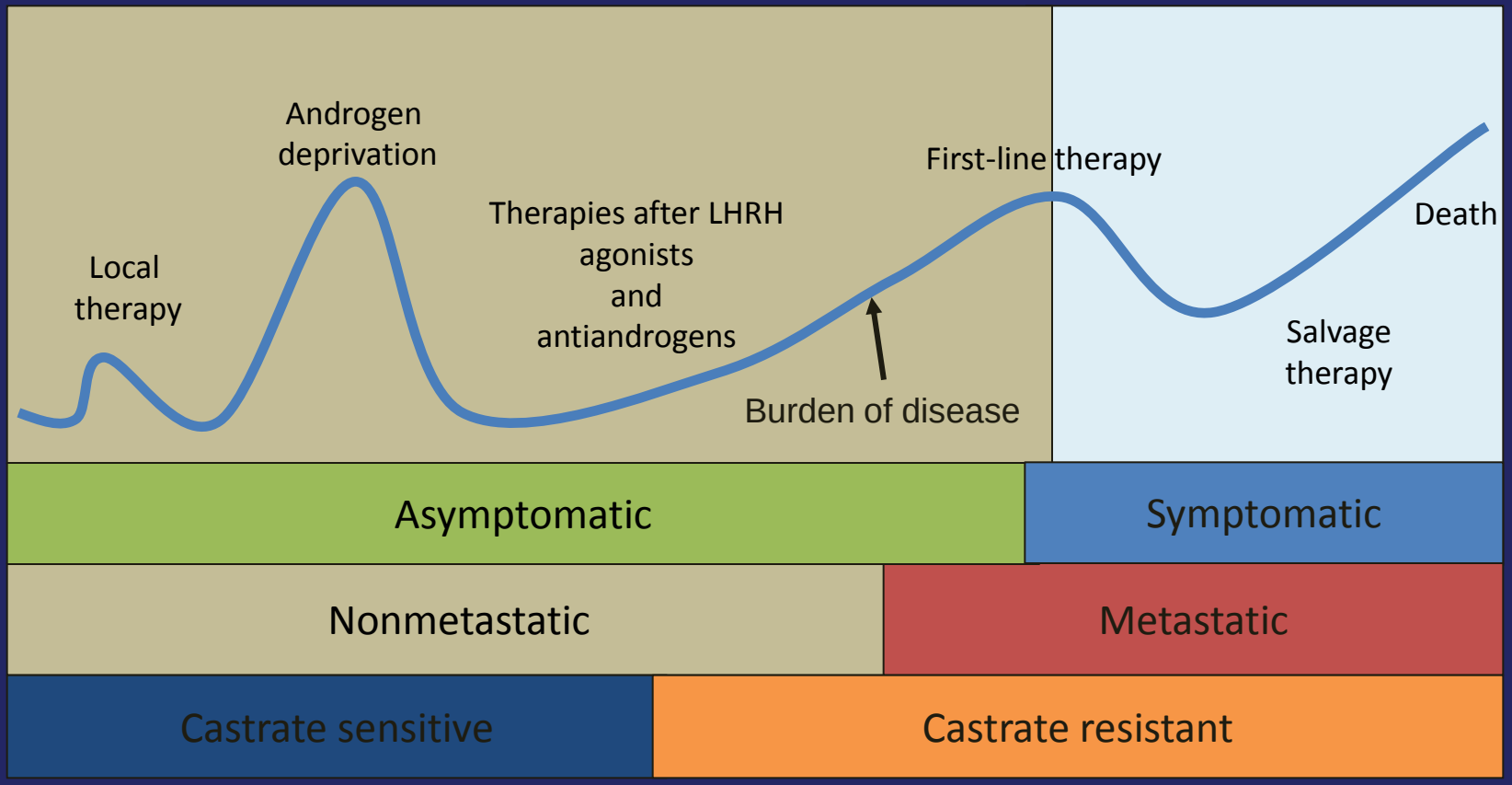
Clinical evaluation

- Early detection and assessment of symptoms
- History
- Clinical examination
- FBC, Biochemical profile, PSA
- Imaging as clinically indicated / appropriate
- Immediate management:

1. Analgesic: Simple / NSAID / Morphine based / specialised input
2. PCT input and support / GP
3. Awareness / understanding of the problem

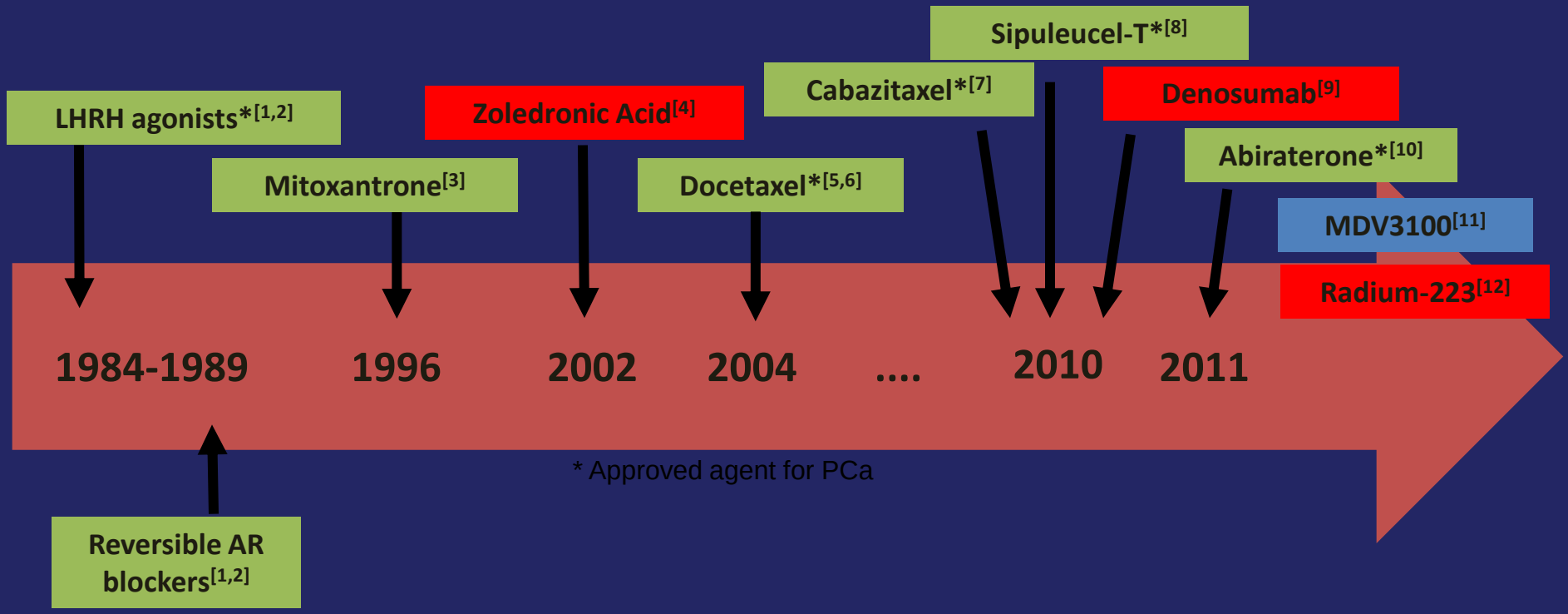
Natural History of Prostate Cancer

- Typical patient presentation as they move through different stages



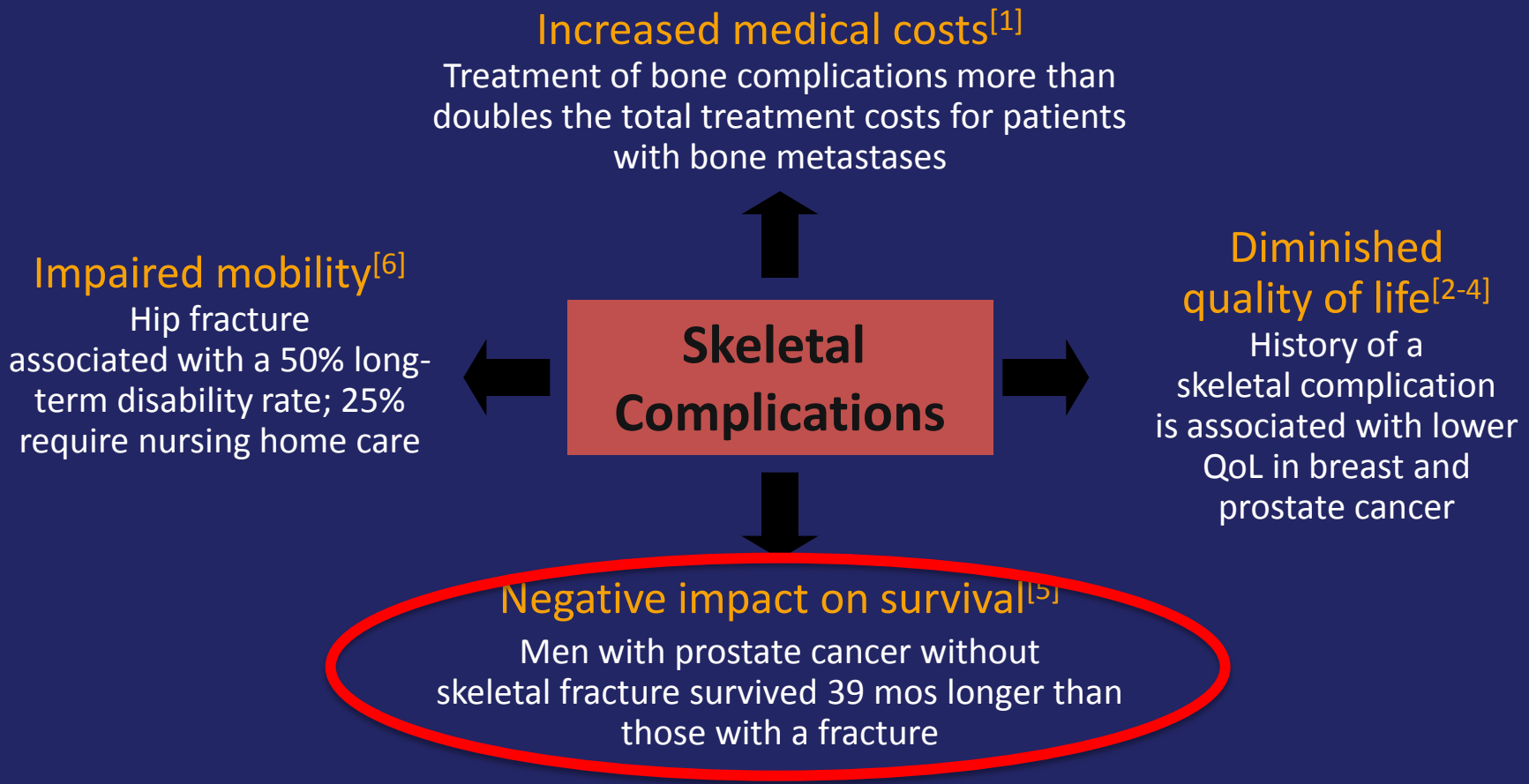
Higano C, et al. In: Figg WD, et al. Drug management of prostate cancer; 2010.

Treatment Options for Prostate Cancer



1. The Leuprolide Study Group. N Engl J Med. 1984;311:1281-1286. 2. Crawford ED, et al. N Engl J Med. 1989;321:419-424. 3. Tannock IF, et al. J Clin Oncol. 1996;14:1756-1764. 4. Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468. 5. Petrylak DP, et al. N Engl J Med. 2004;351:1513-1520. 6. Tannock IF, et al. N Engl J Med. 2004;351:1502-1512. 7. de Bono JS, et al. Lancet. 2010;376:1147-1154. 8. Kantoff PW, et al. N Engl J Med. 2010;363:411-422. 9. Fizazi K, et al. Lancet. 2011;377:813-822. 10. de Bono JS, et al. N Engl J Med. 2011;364:1995-2005. 11. Scher HI, et al. ASCO GU 2012. Abstract LBA1.
12. Parker C, et al. ASCO GU 2012. Abstract 8.

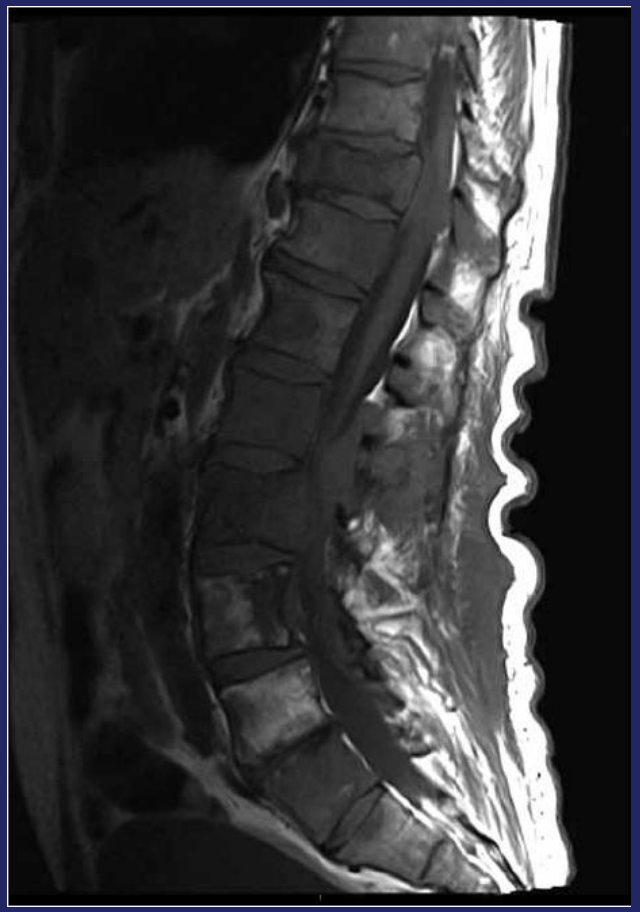
Negative Impact of Bone Complications



1. Groot MT, et al. Eur Urol. 2003;43:226-232. 2. Weinfurt KP, et al. Ann Oncol. 2005;16:579-584.
3. Weinfurt KP, et al. Med Care. 2004;42:164-175. 4. Saad F, et al. Eur Urol. 2004;46:731-740.
5. Oefelein MG, et al. J Urol. 2002;168:1005-1007. 6. Riggs BL, et al. Bone. 1995;17:505S-511S.

Skeletal-Related Events (SREs)

1) Radiation for bone pain
2) Pathological fracture
3) Spinal cord compression
4) Surgery to bone



Implications

- Mobility:

1) 50% have impairment
2) 25% require nursing home care

- Health care economics

1) Care of SREs doubles treatment costs

- Impacts upon QOL
- Impacts upon survival

Surgical intervention

- Surgery aims to relieve pain and restore function and prevent the need for emergency intervention for an unexpected pathological fracture
- The surgery must be planned to allow immediate weight bearing and aim to last the lifetime of the patient. Surgery for spinal metastases should aim for decompression and stabilisation.
- Radiotherapy can help control symptoms, but it will not relieve pain which is mechanical in nature

Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.

	Surgery + XRT	XRT	
Able to walk	42/50 (84%)	29/51 (57%)	p=0.001
Duration (walking)/median)	122 days	13 days	p=0.003

Direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.

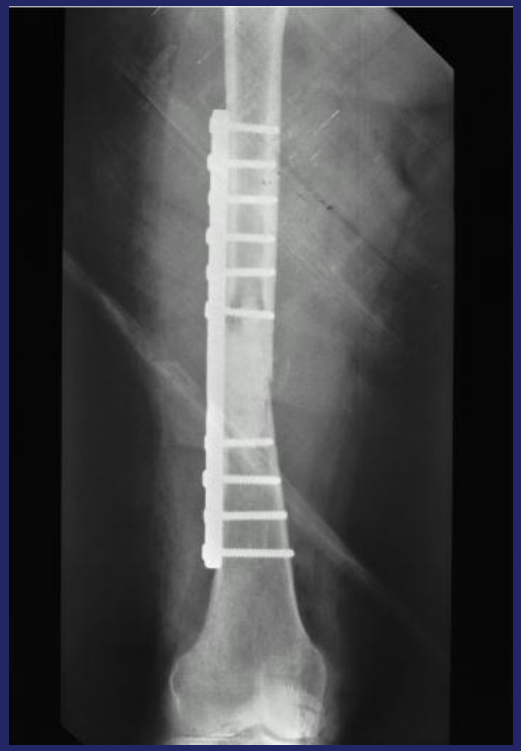
Lancet. 2005 Aug 20-26;366(9486):643-8.

Advantages of surgical decompression

- Improved rates of continence
- Improved muscle strength
- Improved 30 day mortality rates
- Thought to be due to the immediate reversal of vascular compromise to the cord
- Did NOT lead to longer hospital admission
- Surgical complications were rare

In Mirel's scoring system

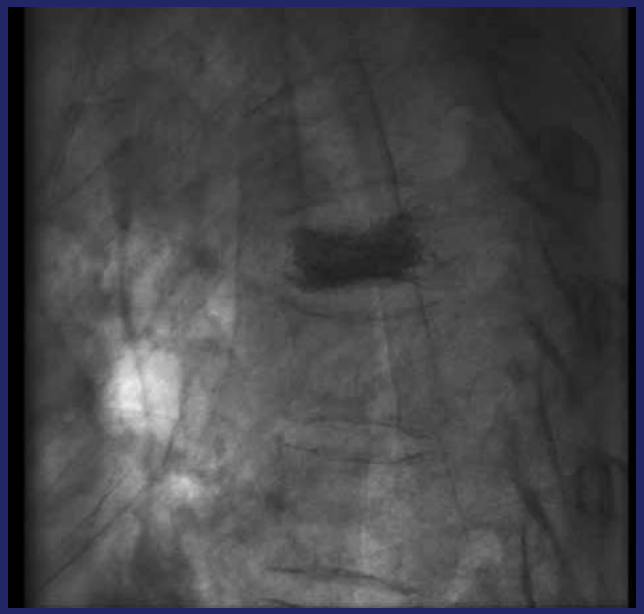
Variable	1 point	2 points	3 points
Site	Upper limb	Lower limb	Peritro-chanteric
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Lesion size/diameter of bone involved on any plain X-ray view	<1/3	1/3–2/3	>2/3



Clinical Orthopaedics 1989; 249: 256-64

Percutaneous cementoplasty/vertebroplasty

- Painful bony metastases refractory to analgesia in the axial skeleton can be treated effectively with image-guided injection of acrylic bone cement



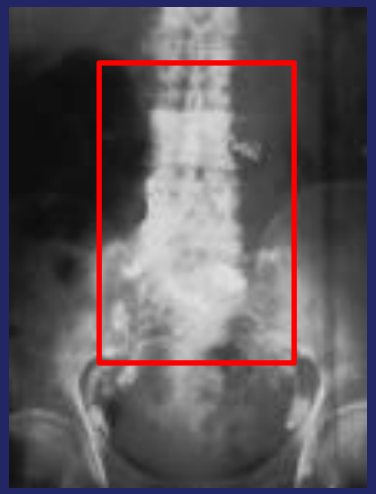
Radiation therapy

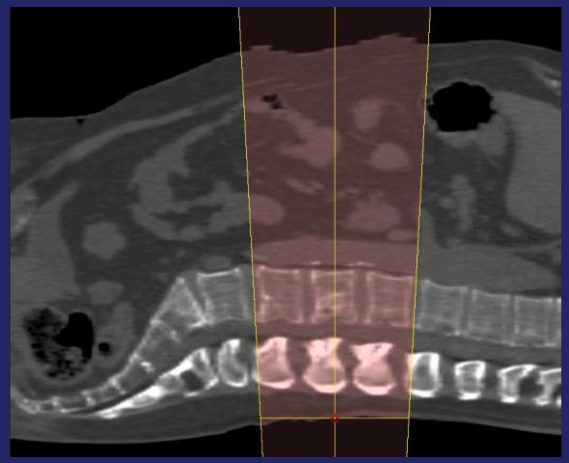
Palliative radiotherapy trials for bone metastases: a systematic review.

8 Gy / 1 fraction

20 Gy / 5 Fractions

30 Gy / 10 Fractions





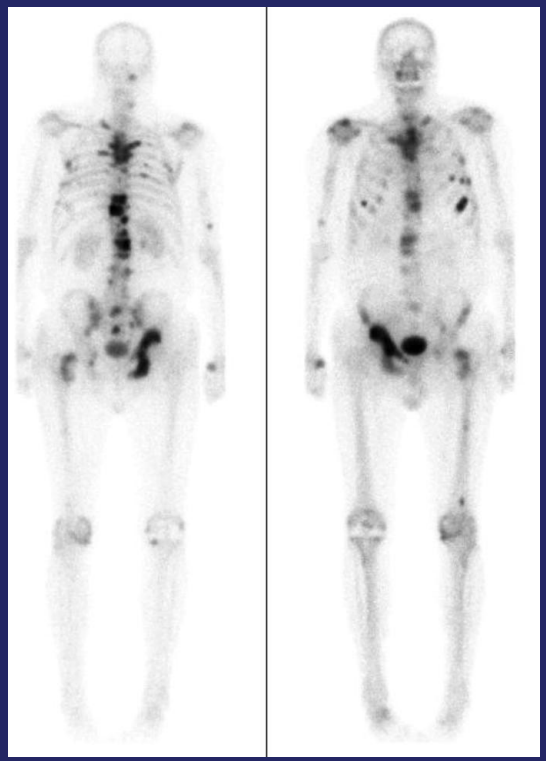
J Clin Oncol. 2007 Apr 10;25(11):1423-3 Chow E, Harris K, Fan G, Tsao M, Sze WM.

Strontium 89

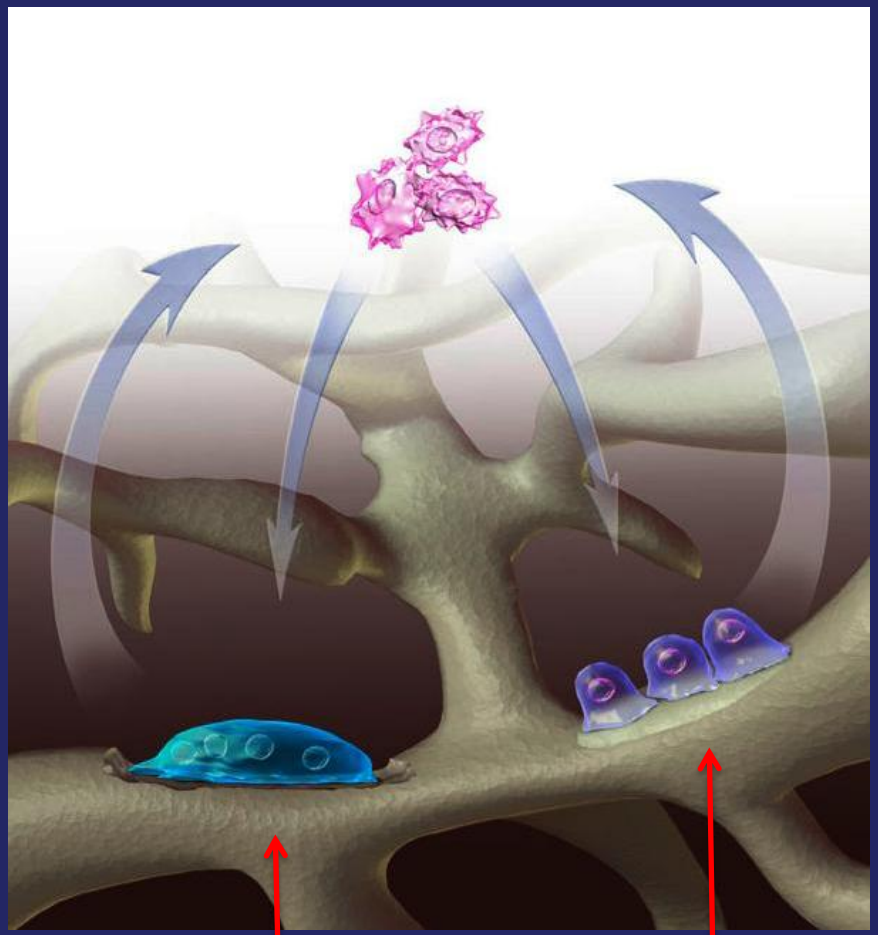
- Randomized phase III trial to evaluate strontium-89 in the management of HRPC
- 126 patients requiring palliative EBRT for bone mets from HRPC + Sr-89/placebo
- Benefit for Sr-89 at 3 months in terms of:

1) Analgesic free: 17.1% vs 2.4% ($p < 0.05$)
2) New site of pain: 0.59 vs 1.21 ($p < 0.002$)
3) Freedom from further EBRT ($p = 0.03$)
4) Quality of life: ($p = 0.006$)

- ***Porter et al. IJROBP 1993; 25(5): 805-13***

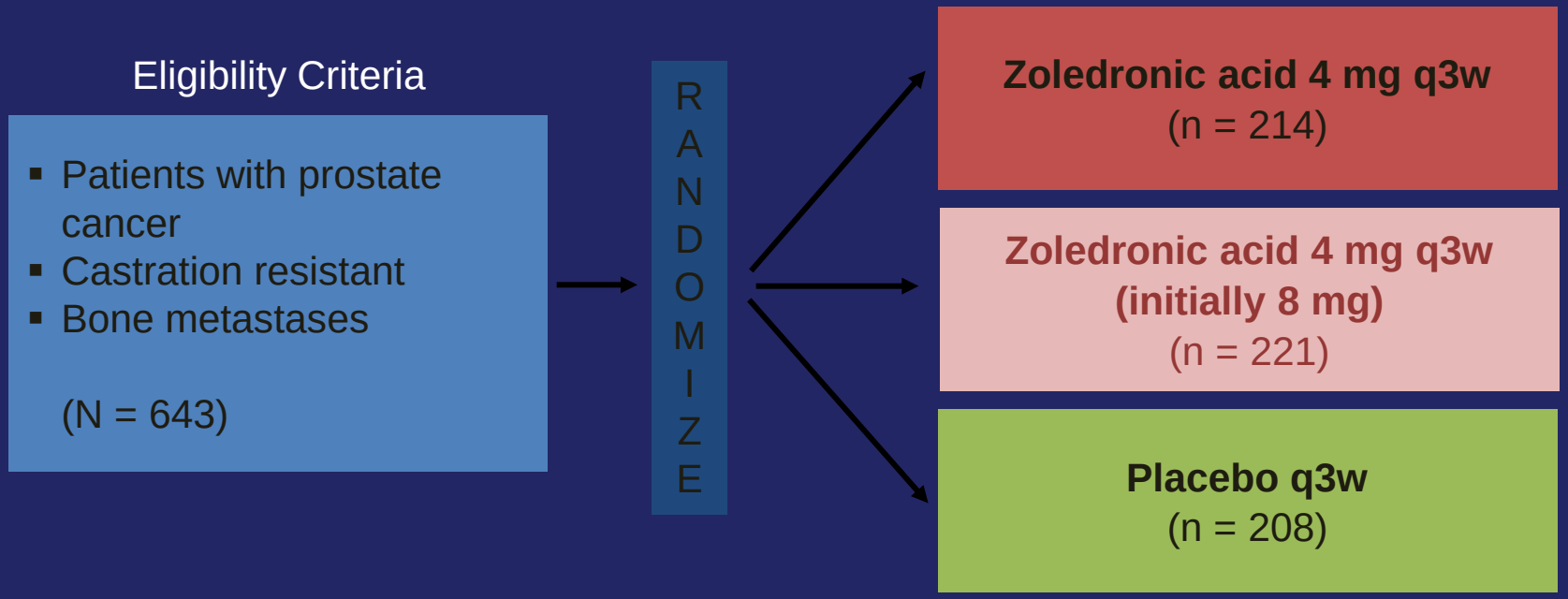


Bisphosphonates



- Increased bone mineral density(BMD)
- Reduction in new and recurrent SREs
- Palliate bone pain

Zoledronic Acid in Castration-Resistant Prostate Cancer

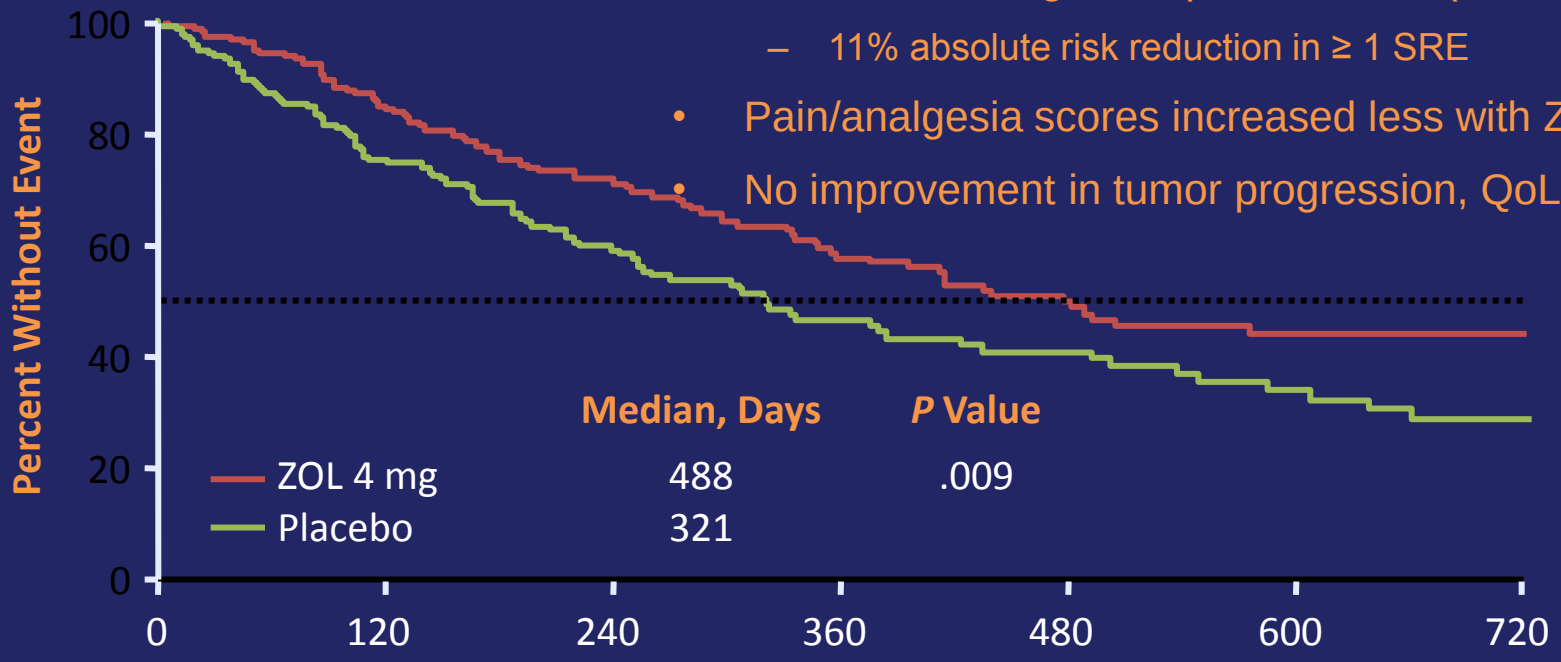


- Patients in 8-mg arm reduced to 4 mg owing to renal toxicity
- Primary outcome: proportion of patients having ≥ 1 SRE
- Secondary outcomes: time to first on-study SRE, proportion of patients with SREs, and time to disease progression

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468.

Time to First SRE

- SREs: ZOL 4 mg 38%; placebo 49% (*P* = .028)
  - 11% absolute risk reduction in ≥ 1 SRE
- Pain/analgesia scores increased less with ZOL
- No improvement in tumor progression, QoL, OS



Pts at Risk, n

ZOL 4 mg	214	149	97	70	47	35	3
Placebo	208	128	78	44	32	20	3

Saad F, et al. J Natl Cancer Inst. 2002;94:1458-1468. Saad F, et al. ASCO 2003. Abstract 1523.
Saad F, et al. J Natl Cancer Inst. 2004;96:879-882.

Study Design: International, Randomized, Double-Blind, Active-Controlled Study

Key Inclusion

- Hormone-refractory (castration-resistant) prostate cancer and bone metastases

Key Exclusion

- Current or previous IV bisphosphonate treatment

Denosumab 120 mg SC and **Placebo IV*** q4w (n = 950)

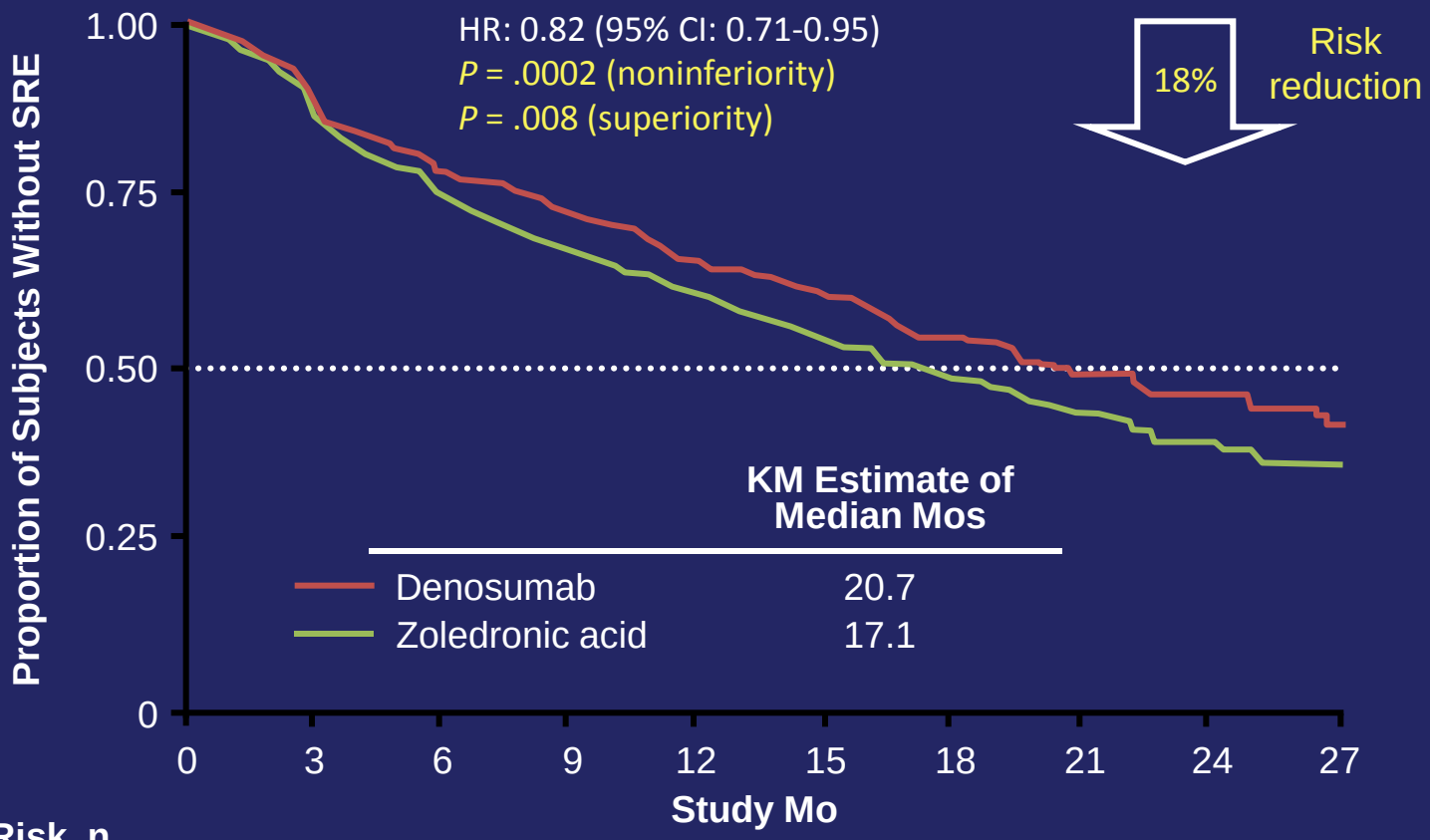
Zoledronic acid 4 mg IV* and **Placebo SC** q4w (n = 951)

- Calcium and vitamin D supplemented in both treatment groups
- Accrual period from May 2006 to December 2008
- Analysis cutoff date: October 2009

*Per protocol and zoledronic acid label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.
No SC dose adjustments made due to increased serum creatinine.

Fizazi K, et al. Lancet. 2011;377:813-822.

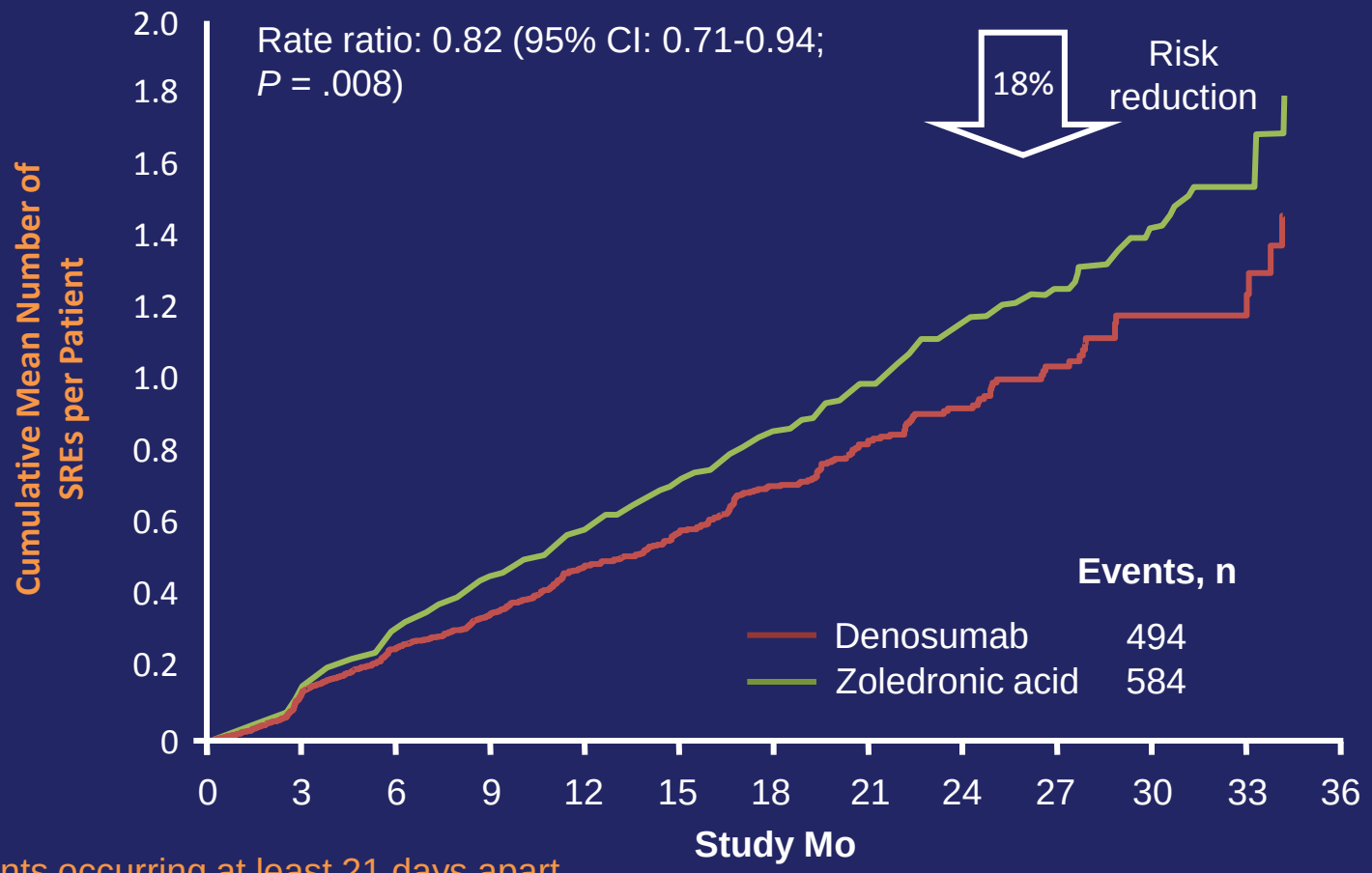
Time to First On-Study SRE



Pts at Risk, n										
Zoledronic acid	951	733	544	407	299	207	140	93	64	47
Denosumab	950	758	582	472	361	259	168	115	70	39

Fizazi K, et al. Lancet. 2011;377:813-822.

Time to First and Subsequent On-Study SRE* (Multiple Event Analysis)



*Events occurring at least 21 days apart.

Fizazi K, et al. Lancet. 2011;377:813-822.

Denosumab vs Zoledronic Acid: Safety

Adverse Event, %	Zoledronic Acid (n = 945)	Denosumab (n = 943)
Serious adverse events	60	63
Adverse events causing treatment discontinuation	15	17
Most common adverse events		
▪ Anemia	36	36
▪ Back pain	30	32
▪ Decreased appetite	29	28
▪ Nausea	26	29
▪ Fatigue	23	27
Acute-phase reactions (first 3 days)	18	8
Renal adverse events	16	15
ONJ	1	2
Hypocalcemia	6	13

Fizazi K, et al. Lancet. 2011;377:813-822.

Kaplan-Meier Estimates of OS and TTP

Endpoint, Mos	Denosumab	Zoledronic Acid	HR (95% CI)	*P* Value
Median OS	19.4	19.8	1.03 (0.91-1.17)	.65
Median TTP	8.4	8.4	1.06 (0.95-1.18)	.30

Fizazi K, et al. Lancet. 2011;377:813-822.

SRE Prevention in CRPC

Current Status of Antiresorptive Agents

Agent	Study Duration (mo)	# Pts with SREs (%)	Median Time to 1st SRE (mo)	HR/RR
ZOL (n = 214) vs placebo (n = 208)[a]	24	81 (38%) vs 101 (49%) *P* = .028	16.0 vs 10.5 *P* = .009	HR 0.64 *P* = .002
Pamidronate (n = 169) vs placebo (n = 181)[b]	6.8	42 (25%) vs 46 (25%) *P* = NA	NA	NA
Denosumab (n = 950) vs ZOL (n = 951)[c]	41	341 (36%) vs 386 (41%)	20.7 vs 17.1 *P* = .0002	RR 0.82 *P* = .008

Denosumab, a human monoclonal antibody against RANKL, proved better than zoledronic acid for SRE prevention

a. Saad F, et al. *J Natl Cancer Inst*. 2004;96:879-882.
b. Small EJ, et al. *J Clin Oncol*. 2003;21:4277-4284.
c. Fizazi K, et al. *Lancet*. 2011;377:813-822.

FDA-Approved Agents for Prevention of SREs in Metastatic Prostate Cancer

Agent	Drug Class	Recommended Dose and Schedule
Zoledronic acid	Bisphosphonate	4 mg IV q3-4w
Denosumab	RANKL-targeted MAb	120 mg SQ q4w

- NCCN recommends either zoledronic acid or denosumab for prevention/delay of SREs in men with CRPC and bone metastases[1]
- Choice between agents may be guided by
  - Underlying comorbidities
  - Adverse events: renal insufficiency, ONJ, hypocalcemia
  - Logistics: differences in administration (SQ vs IV)
  - Cost considerations

1. NCCN. Clinical practice guidelines in oncology: prostate cancer. v.2.2012.

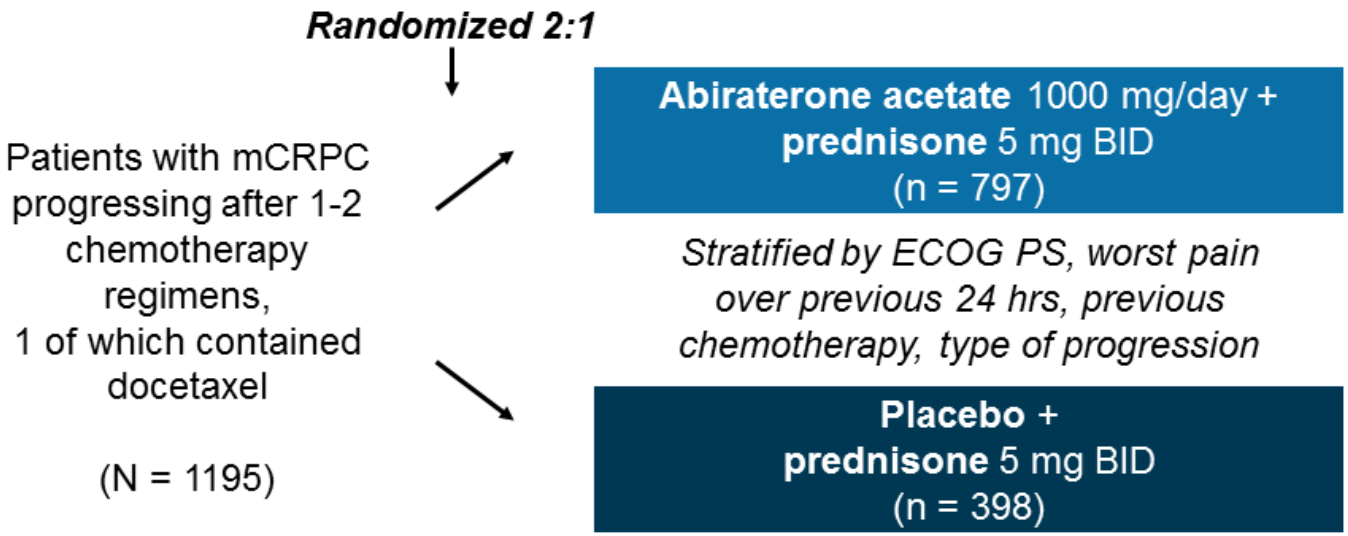
Take-Home Points

- Bone health is of critical importance for men with advanced prostate cancer
- Denosumab is approved to reduce SREs and has been shown to be superior to zoledronic acid in this setting

Impact of Systemic therapy / Abiraterone

COU-AA-301

Phase 3 Study of Abiraterone in mCRPC

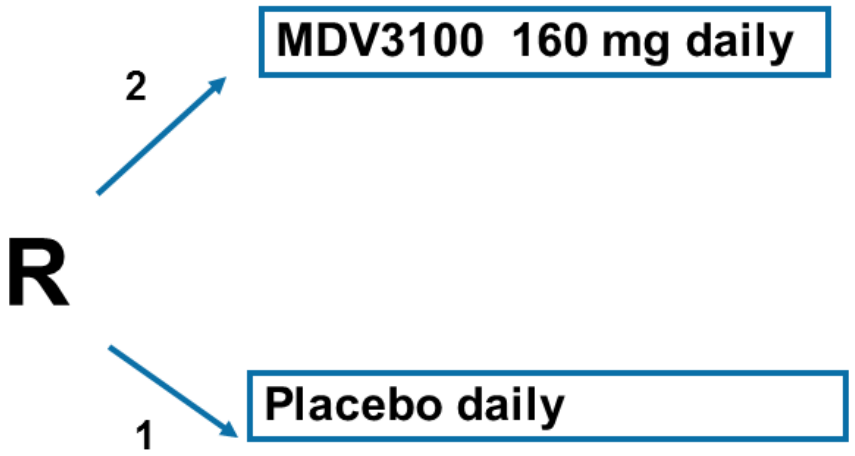


de Bono J, et al. *N Engl J Med*. 2011;364:1995-2005.

Impact of Systemic therapy / Enzalutamide

AFFIRM

Postchemotherapy Phase 3 Trial



OS primary endpoint

Interim analyses after 520 deaths

Steroid use was optional for MDV3100

ClinicalTrials.gov Identifier: NCT00974311.

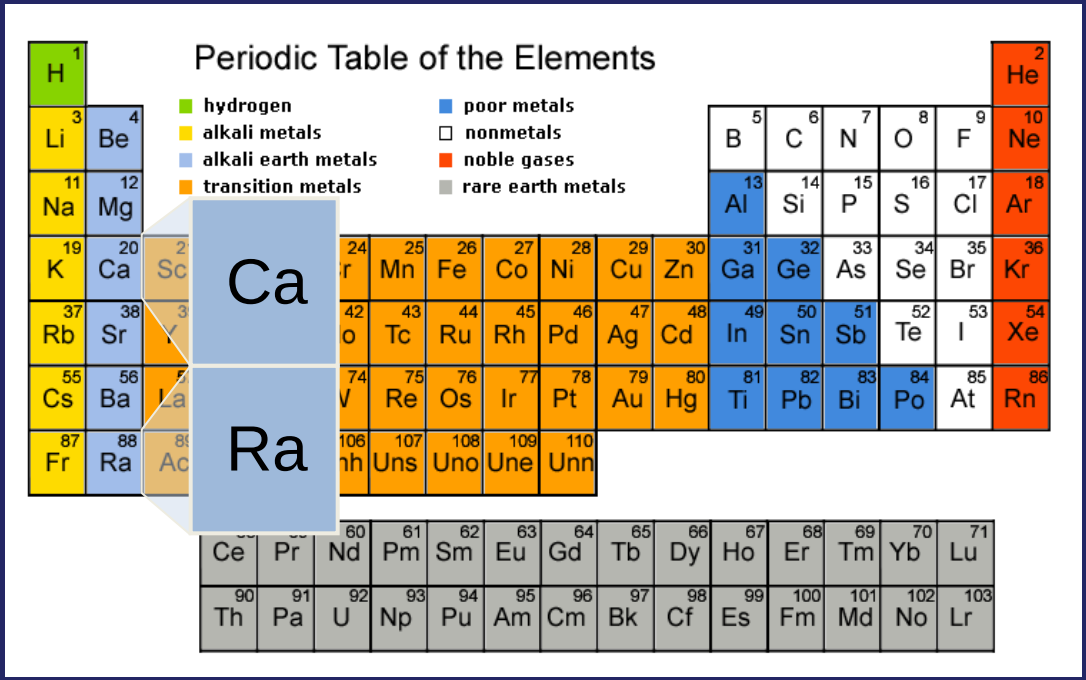
Impact of Systemic therapy / Enzalutamide

Table 2. Secondary End Points Related to Response and Disease Progression.*

End Point	Enzalutamide (N=800)	Placebo (N=399)	Hazard Ratio (95% CI)	P Value
Confirmed PSA decline†				
Patients with ≥1 postbaseline PSA assessment — no. (%)	731 (91)	330 (83)		
PSA response — no./total no. (%)				
Decline ≥50% from baseline	395/731 (54)	5/330 (2)		<0.001
Decline ≥90% from baseline	181/731 (25)	3/330 (1)		<0.001
Soft-tissue objective response				
Patients with measurable disease — no. (%)	446 (56)	208 (52)		
Complete or partial objective response — no./total no. (%)	129/446 (29)	8/208 (4)		<0.001
FACT-P quality-of-life response†				
Patients with ≥1 postbaseline assessment — no. (%)	651 (81)	257 (64)		
Quality-of-life response — no./total no. (%)‡	281/651 (43)	47/257 (18)		<0.001
Progression indicators				
Time to PSA progression — mo			0.25 (0.20–0.30)	<0.001
Median	8.3	3.0		
95% CI	5.8–8.3	2.9–3.7		
Radiographic progression-free survival — mo			0.40 (0.35–0.47)	<0.001
Median	8.3	2.9		
95% CI	8.2–9.4	2.8–3.4		
Time to first skeletal-related event — mo			0.69 (0.57–0.84)	<0.001
Median	16.7	13.3		
95% CI	14.6–19.1	9.9–NYR		

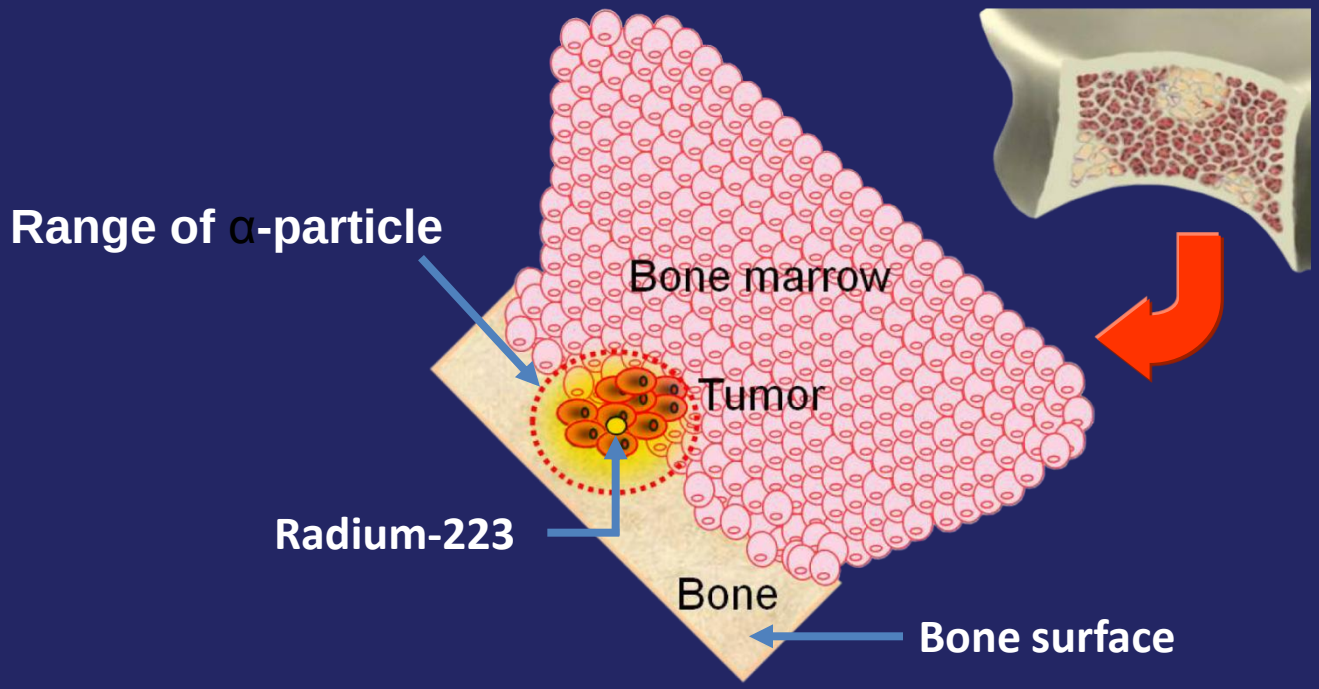
Radium-223 Targets Bone Metastases

- Radium-223 functions as a calcium mimic
- Targets sites of new bone growth within and around bone metastases
- Excreted by the small intestine



Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

Radium-223 Targets Bone Metastases



- α-particles cause double-strand DNA breaks in nearby tumour cells
  - Limited penetration of α emitters (~ 2-10 cell diameters) results in highly localized killing of tumor cells with minimal collateral damage to normal tissue in surrounding area

Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8. Perez CA, et al. Principles and practice of radiation oncology. 5th ed. 2007.

ALSYMPCA: Phase III Study Design

Randomized 2:1 and stratified by total ALP (< vs ≥ 220 U/L), bisphosphonate use (yes vs no), and previous docetaxel (yes vs no)

Patients with:
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel

(N = 921)

Radium-223 50 kBq/kg + **Best Standard of Care**

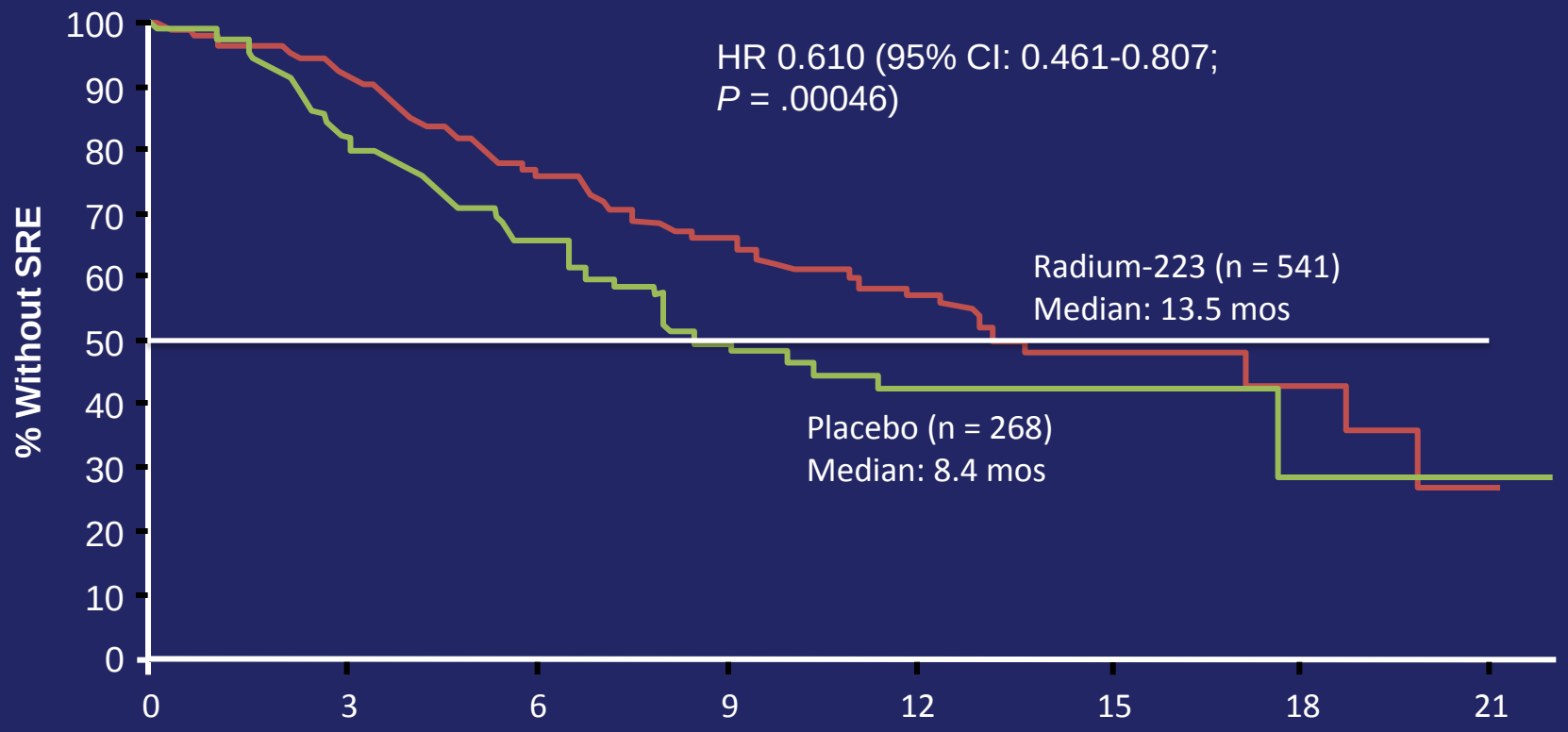
Placebo (saline) + **Best Standard of Care**

6 injections at 4-wk intervals

Planned follow-up: 3 yrs

Clinicaltrials.gov. NCT00699751. Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

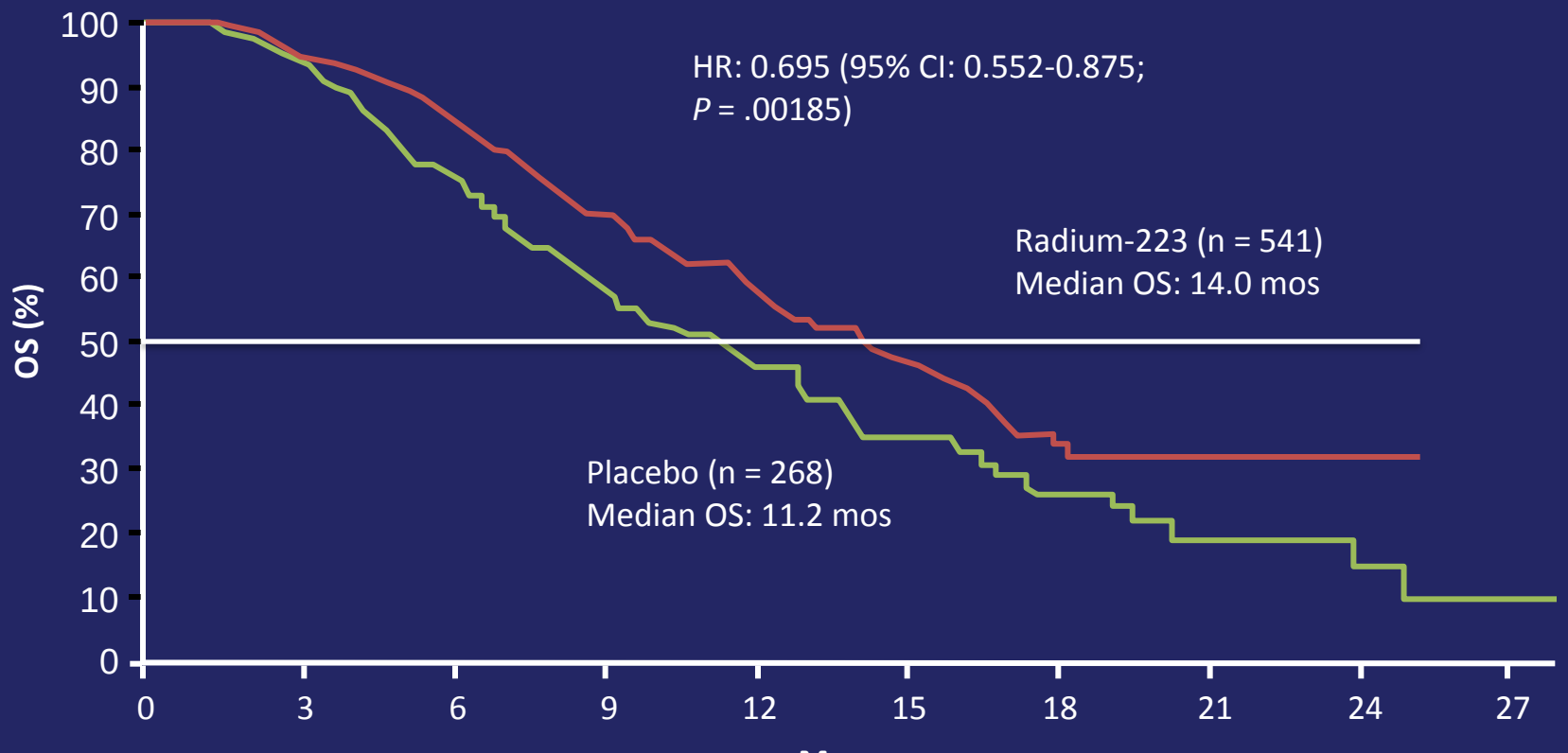
ALSYMPCA: Time to First Skeletal-Related Event



Pts at Risk, n:								
Radium-223	541	379	214	111	51	22	6	0
Placebo	268	159	74	30	15	7	2	0

Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

ALSYMPCA: Overall Survival



Pts at Risk, n										
Radium-223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

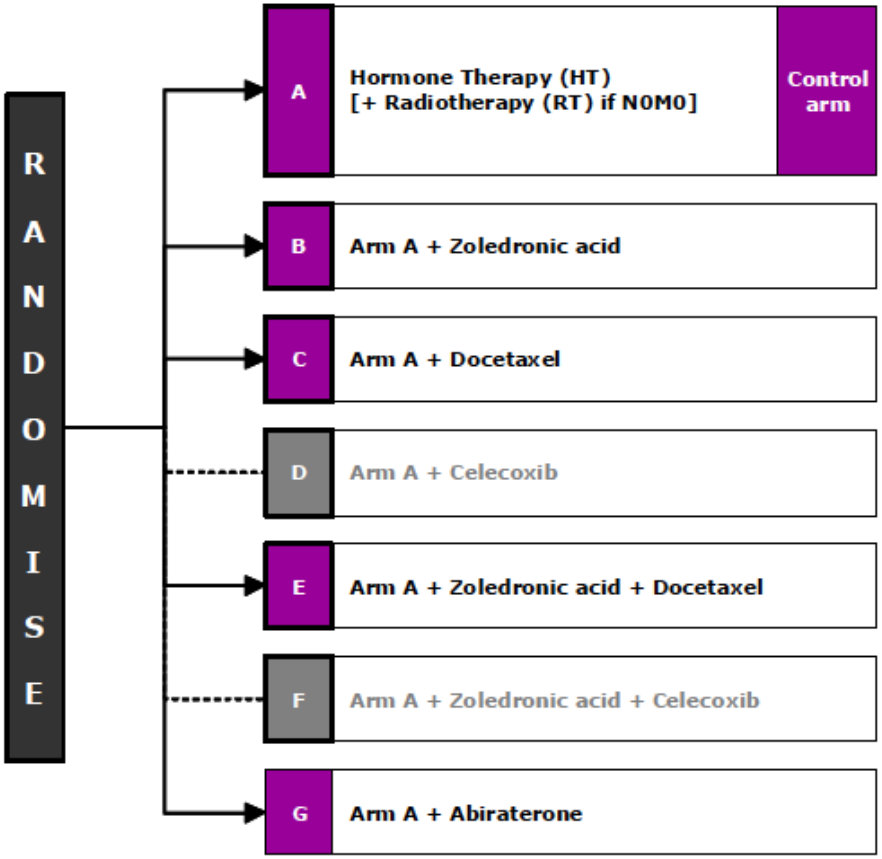
ALSYMPCA Adverse Events of Interest

Adverse Event, n (%)	All Grades		Grade 3/4	
	Radium-223 (n = 509)	Placebo (n = 253)	Radium-223 (n = 509)	Placebo (n = 253)
Hematologic				
▪ Anemia	136 (27)	69 (27)	54 (11)	29 (12)
▪ Neutropenia	20 (4)	2 (1)	9 (2)	2 (1)
▪ Thrombocytopenia	42 (8)	14 (6)	22 (4)	4 (2)
Nonhematologic				
▪ Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
▪ Diarrhea	112 (22)	34 (13)	6 (1)	3 (1)
▪ Nausea	174 (34)	80 (32)	8 (2)	4 (2)
▪ Vomiting	88 (17)	32 (13)	10 (2)	6 (2)
▪ Constipation	89 (18)	46 (18)	6 (1)	2 (1)

Parker C, et al. 2012 ASCO GU Cancers Symposium. Abstract 8.

Trials and research

Figure 1c – Arms of the STAMPEDE Trial from protocol version 8.0

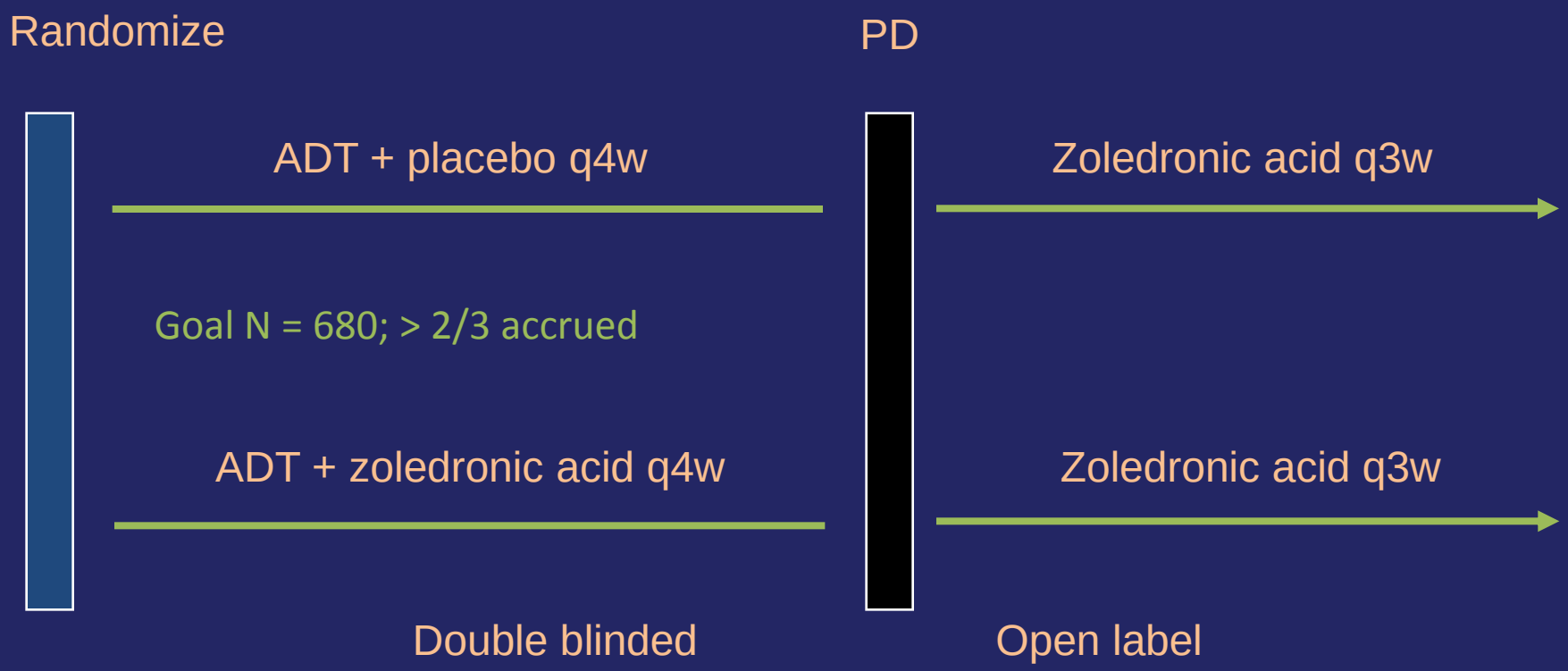


Randomized Controlled Clinical Trials in Metastatic Castrate-Sensitive PC Patients

- Zoledronic acid vs placebo
  - CALGB/CTSU 90202 trial
  - Planned enrollment of 680 men with prostate cancer and bone mets on ADT within 6 mos
  - Zoledronic acid 4 mg IV every 4 wks
  - Crossover from placebo to zoledronic acid allowed
  - Accrual complete

ClinicalTrials.gov. NCT00079001.

CALGB 90202: ZOL in Hormone-Sensitive Bone Mets PC



Primary endpoint: time to SRE; secondary endpoints: OS, toxicity

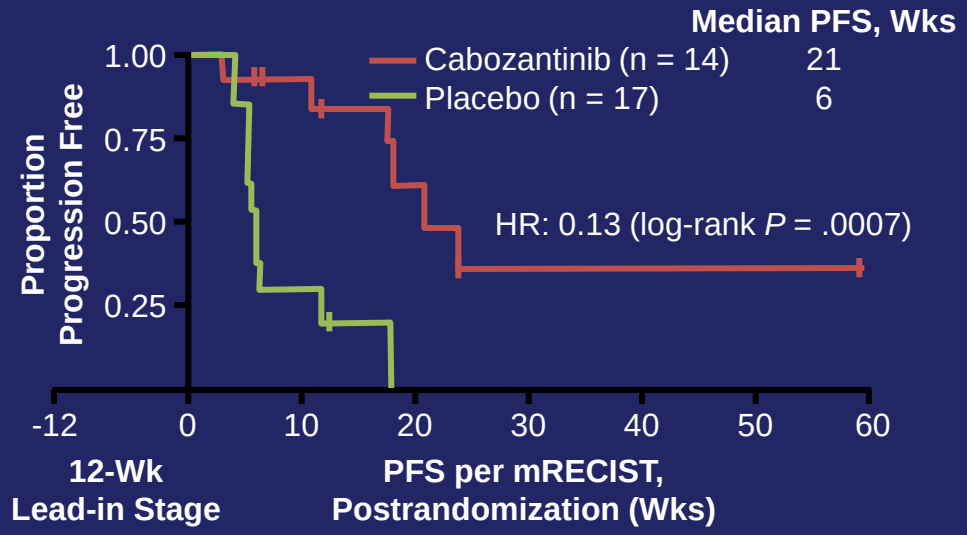
ClinicalTrials.gov. NCT00079001.

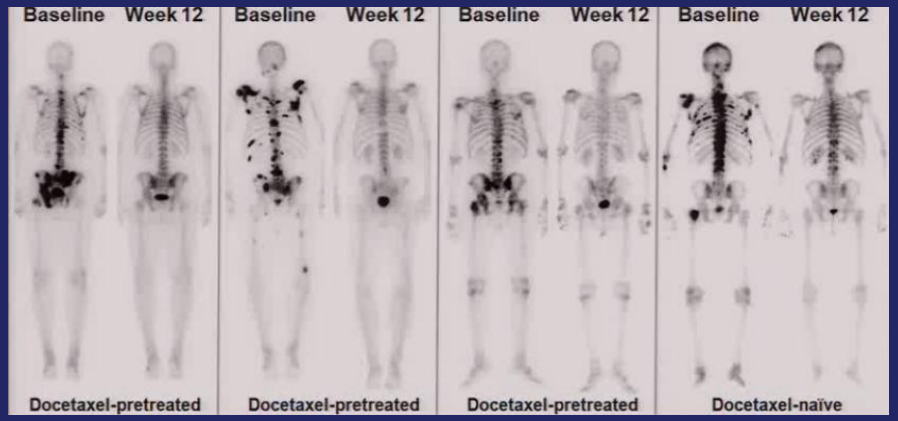
Novel Agents Targeting Bony Metastatic CRPC

- Cabozantinib
  - MET/VEGFR-targeted agent
- Dasatinib
  - Src inhibitor

Saylor PJ, et al. J Clin Oncol. 2011;29:3705-3714.

Cabozantinib vs Placebo in mCRPC: Efficacy and Safety





Hussain M, et al. ASCO 2011. Abstract 4516.

- Authors concluded cabozantinib has substantial antitumor activity in progressive mCRPC
  - Disease control at Wk 12: 68%
  - Measurable disease regression: 74%
  - Evidence of improvement on bone scan: 76%
  - Pain improvement: 67%
  - Moderate but manageable toxicity profile; similar to other TKIs

COMET-1: CabOzantinib MET Inhibition CRPC Efficacy Trial–1 (Planned Design)

Patients with:

- Confirmed mCRPC with bone metastases
- Previously treated with docetaxel
- Previously treated with either abiraterone or MDV3100
- No limit to prior treatments

Arm A
(n = 640)

Cabozantinib 60 mg QD +
Placebo

N = 960

Placebo +
Prednisone 5 mg BID

Arm B
(n = 320)

Primary endpoint: OS

Secondary endpoint: bone scan response (IRF assessed)

COMET-2: CabOzantinib MET Inhibition CRPC Efficacy Trial–2 Study Design

Patients with:
- Confirmed mCRPC with bone metastases
- Bone pain (BPI ≥ 4)
- Previously treated with docetaxel and either abiraterone or MDV3100

(N = 246)

Cabozantinib 60 mg QD +
Mitoxantrone Placebo +
Prednisone Placebo
(n = 123)

Mitoxantrone +
Prednisone +
Cabozantinib Placebo
(N = 123)

Primary endpoint: durable pain response

Secondary endpoint: bone scan response by IRF, OS

ClinicalTrials.gov. NCT01522443.

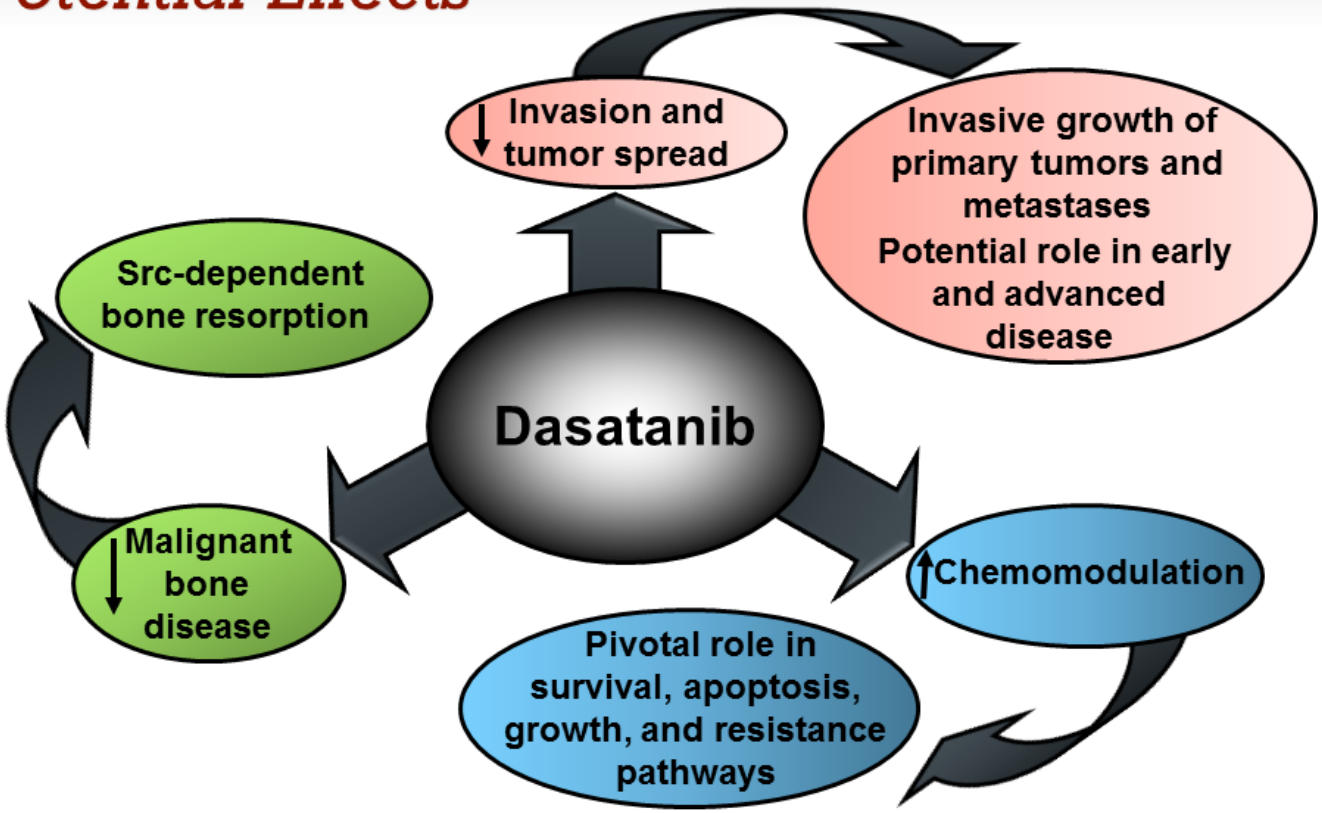
COMET-2

- Randomized, controlled, double-blinded
  - Cabozantinib 60 mg QD vs mitoxantrone/prednisone
  - N = 246 (1:1 randomization)
  - Pain and analgesic use measured similarly to NRE
- Eligibility
  - mCRPC patients who failed docetaxel and abiraterone or MDV3100
  - Moderate to severe pain (BPI ≥ 4) despite "optimized" narcotics
- Endpoints
  - Primary: pain response at Wk 6 confirmed at Wk 12
  - Secondary: bone scan response and OS
  - Goal of OS analysis: show no decrement (80% power to detect a 0.67 HR)

ClinicalTrials.gov. NCT01522443.

Dasatanib (BMS-354825)

Potential Effects



Adapted from Fizazi K. *Ann Oncol.* 2007;18:1765-1773.

Dasatinib in CRPC

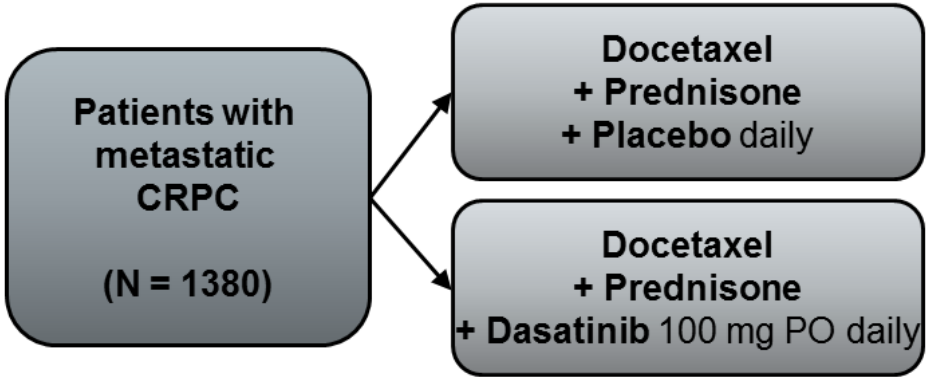
- Oral TKI approved for Ph+ CML and Ph+ ALL
- Separate mechanism: Src inhibition
- Phase I/II study of dasatinib plus docetaxel in mCRPC showed PSA responses and clinical benefit[1]
- Phase II study in chemotherapy-naive mCRPC showed disease stabilization and reduction in bone biomarkers (regardless of bisphosphonate use)[2]
  - Bone alkaline phosphatase
  - Urinary N-telopeptide
- Ongoing phase III trial of docetaxel ± dasatinib in mCRPC[3]

1. Araujo JC, et al. Cancer. 2012;118:63-71. 2. Yu EY, et al. Clin Cancer Res. 2009;15:7421-7428.
3. ClinicalTrials.gov. NCT00744497.

Dasatinib: Src Inhibition

Docetaxel ± Dasatinib in CRPC

Phase 3 Study (READY)

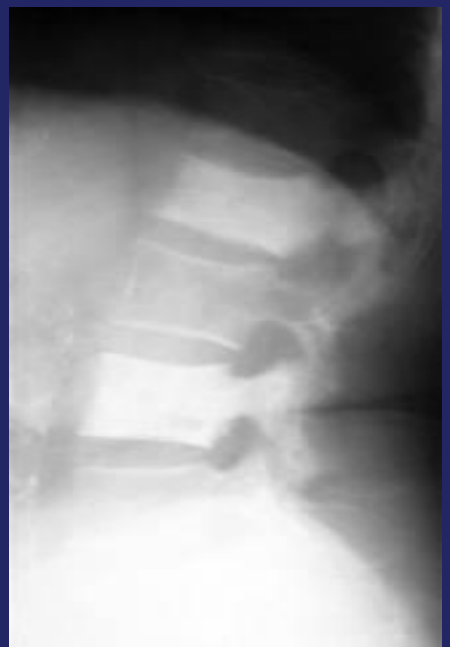


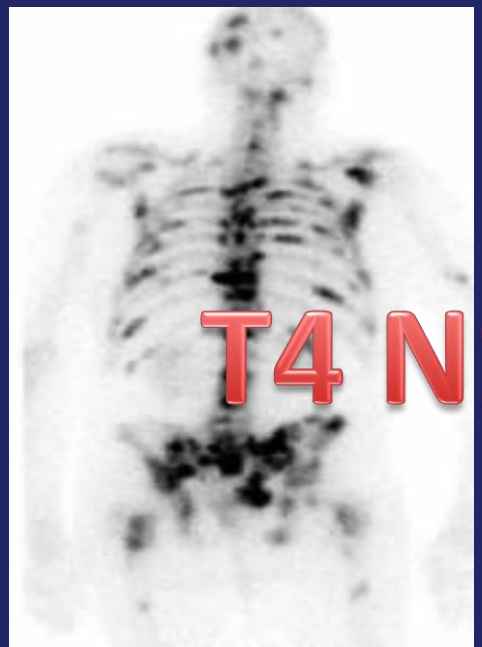
- **Primary endpoint:** OS
- **Secondary endpoints:** Change in uNTX, time to first SRE, change in pain intensity, time to PSA progression, tumor response rate, SD, safety/tolerability

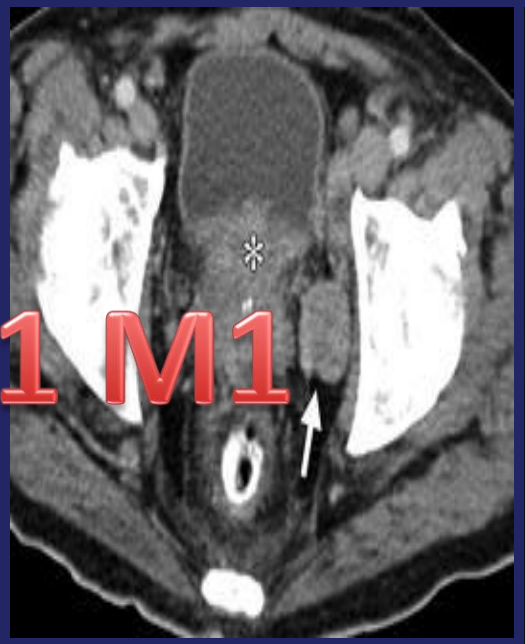
Available at: http://www.clinicaltrials.gov/ct2/show/NCT00744497

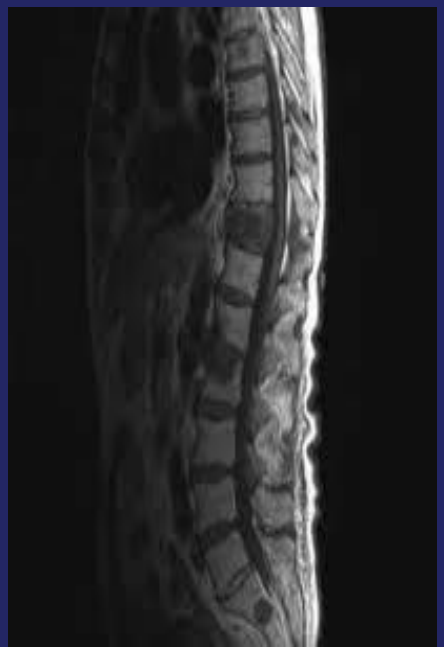
Case presentation

- 74y back pain
- PSA=132
- PS=1, cT3
- CMB: HT, OA
- Medication: BFZ / Cocodamol.









T4 N1 M1

Thank you for your attention