Uma Viagem ao Novo Mundo do Câncer de Próstata

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Centro de Oncológico Antônio Ermírio de Moraes –

Beneficência Portuguesa São Paulo

Membro do Comite Gestor Hospital Israelita Albert Einstein

Declaração de conflito de interesses

- De acordo com a Resolução 1595/2000 do Conselho Federal de Medicina e RDC 96/08 da ANVISA, declaro que:

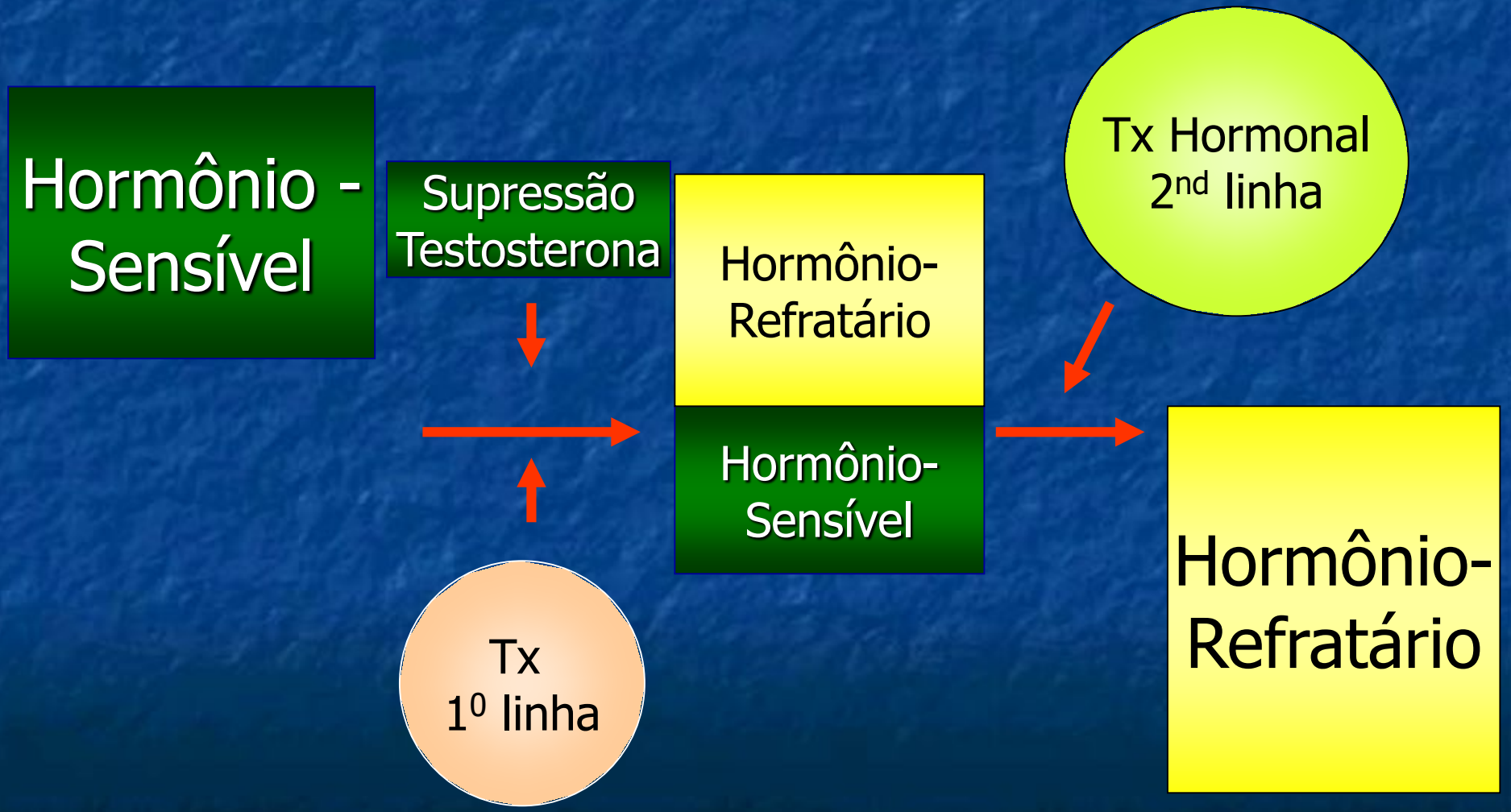
- Participo de estudos clínicos patrocinados pelas empresas: Sanofi-aventis, Janssen, Astrazeneca, Roche, Astellas, MSD, BMS, Novartis

- Participo como speaker de eventos das empresas: Sanofi-aventis, Janssen, Astrazeneca, Roche, Astellas, MSD, BMS, Novartis, Amgen, Ferring

- Participo como membro do advisoryboard das empresas: Sanofi-aventis, Janssen, Astrazeneca, Roche, Astellas, MSD, BMS, Novartis, Amgen, Ferring

Câncer de Próstata Hormone-Sensível

Progressão após Tratamento



Câncer de Próstata
Doença Androgênio "Resistente"

- Hormônioterapia
  - Segunda linha
  - Manutenção da castração
- Quimioterapia
  - Manutenção da castração
- Imunoterapia
- Bisfosfonados
- Radioterapia Paliativa
  - Externa
  - Radiofármacos

Câncer de Próstata

Doença Androgênio "Resistente": Tratamentos Hormonais de 2nd-Linha

Respostas Clínica
Manipulação Hormonal de Segunda-linha

• Retirada de Anti-androgênio	15-30%
• Bicalutamida	25%
• Nilutamida	25% (?)
• DES	30-55%
• PC-SPES	40-50%
• Ketoconazole (+ corticóide)	20-60%
• Glucocorticóide	20-80%
• Acetato Megestrol	15%

Manipulação Hormonal de Segunda-linha

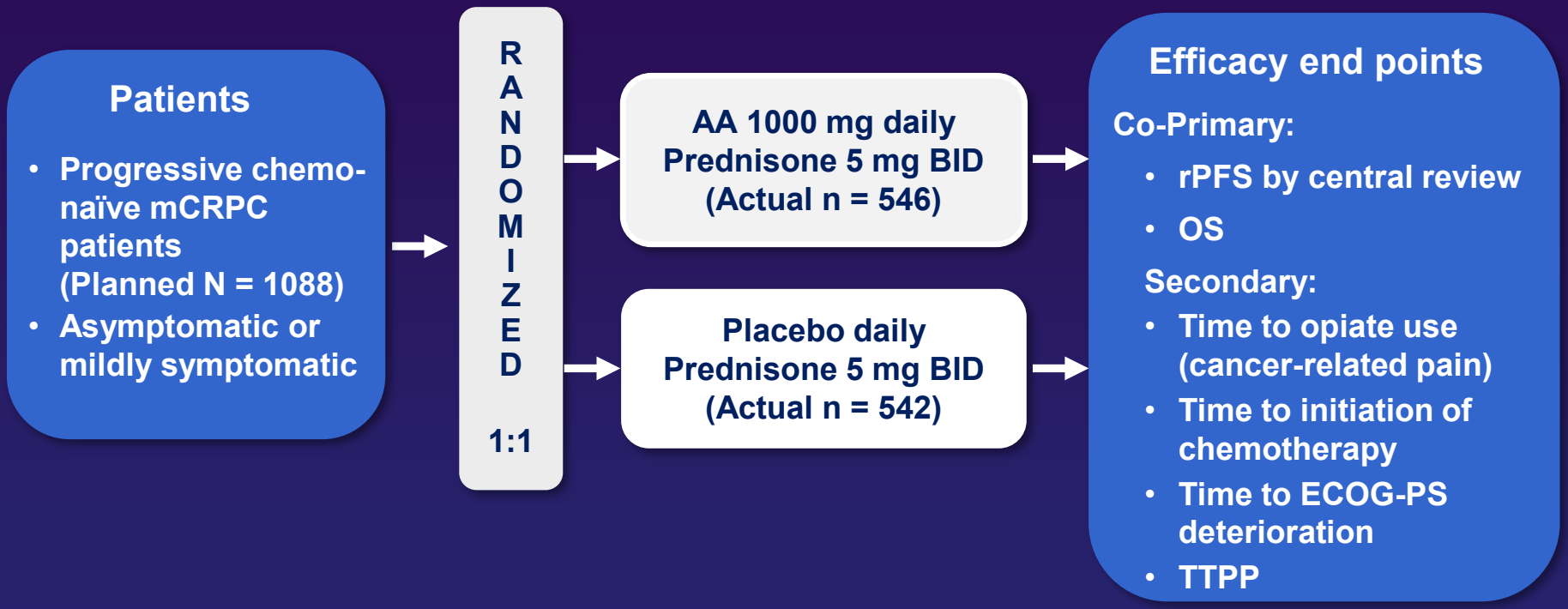
Questões / Aspectos

- Duração média é limitada (2-4 m)
- Impacto a longo prazo até 2012 ?

Câncer de Próstata

Novas Estratégias na Doença Androgênio "Resistente": Pré-Quimioterapia

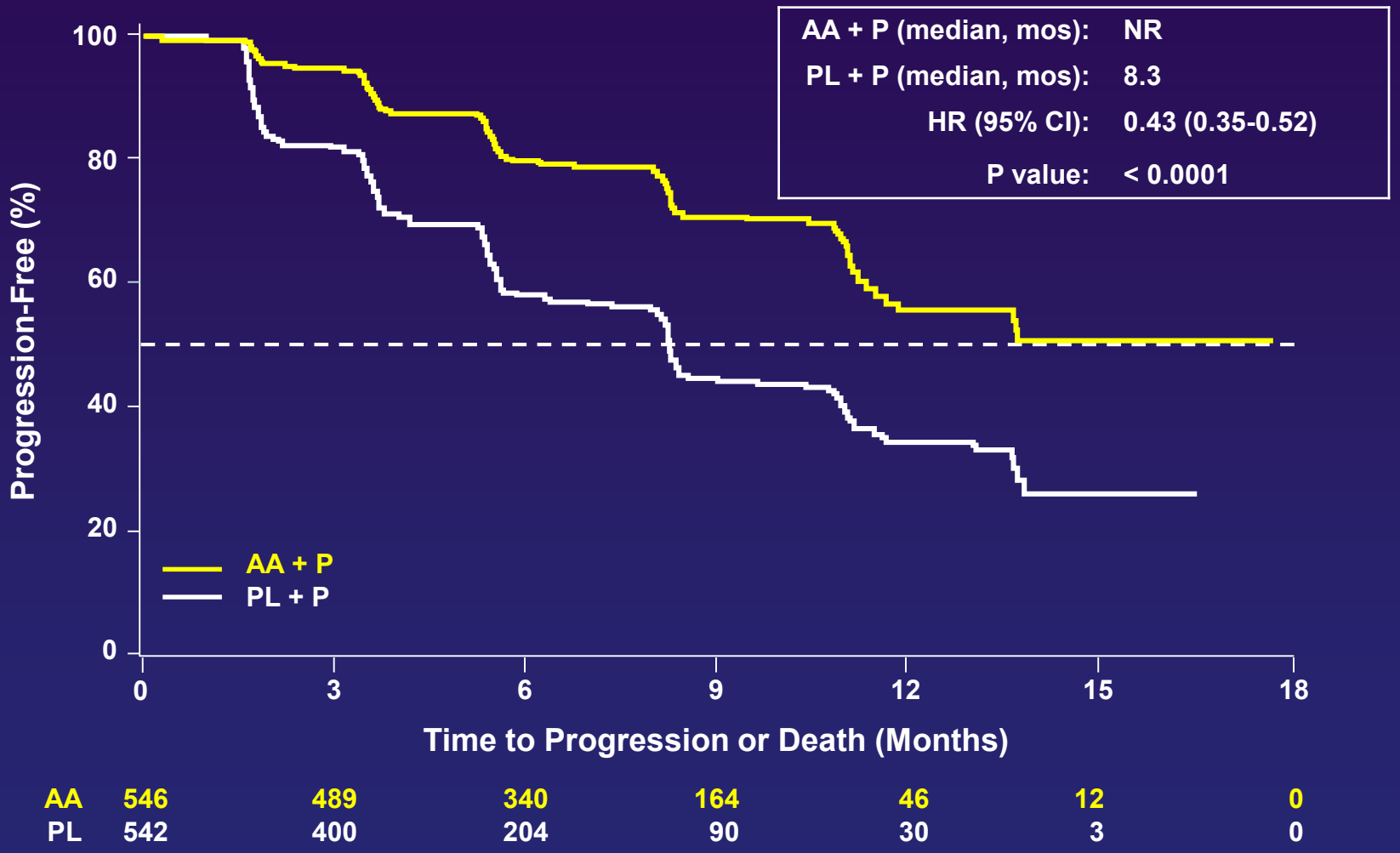
Overall Study Design of COU-AA-302



- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs. 1

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

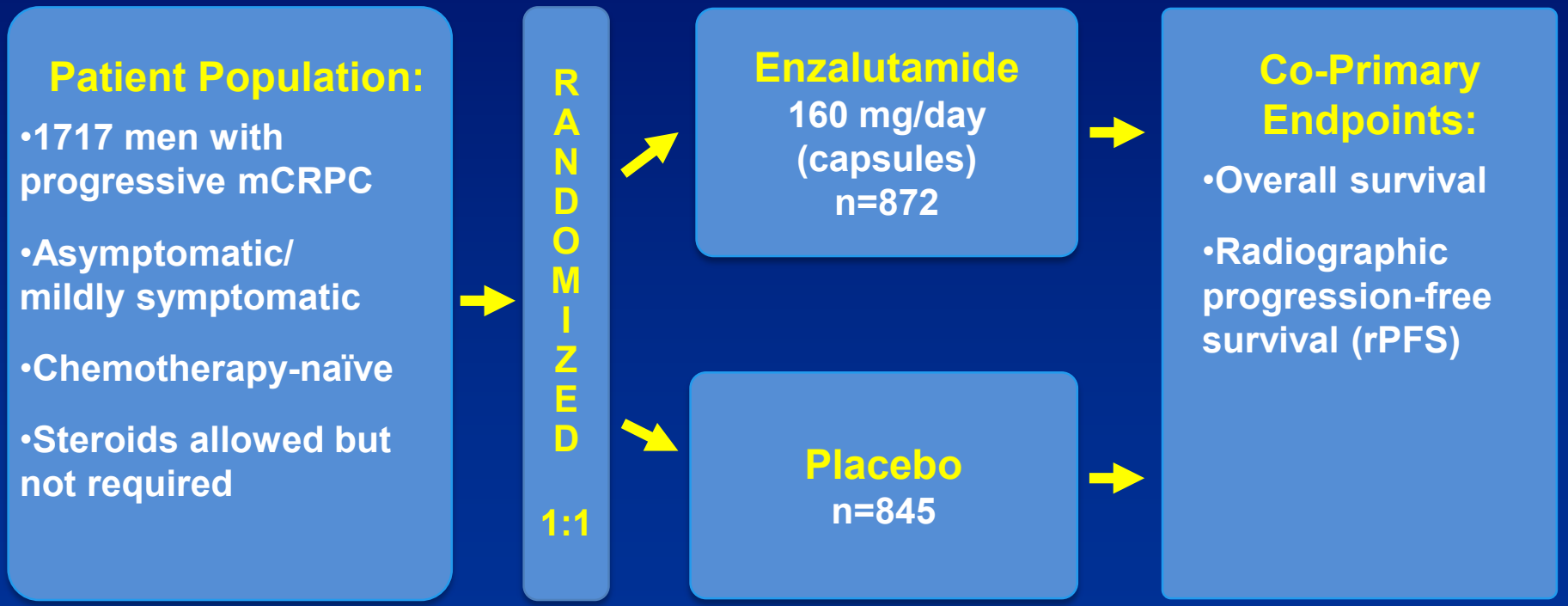
Statistically Significant Improvement in rPFS Primary End Point



Data cutoff 20/12/2010

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

PREVAIL: A Phase 3 Trial of Enzalutamide After Progression on Androgen Deprivation Therapy in Men with Metastatic Prostate Cancer

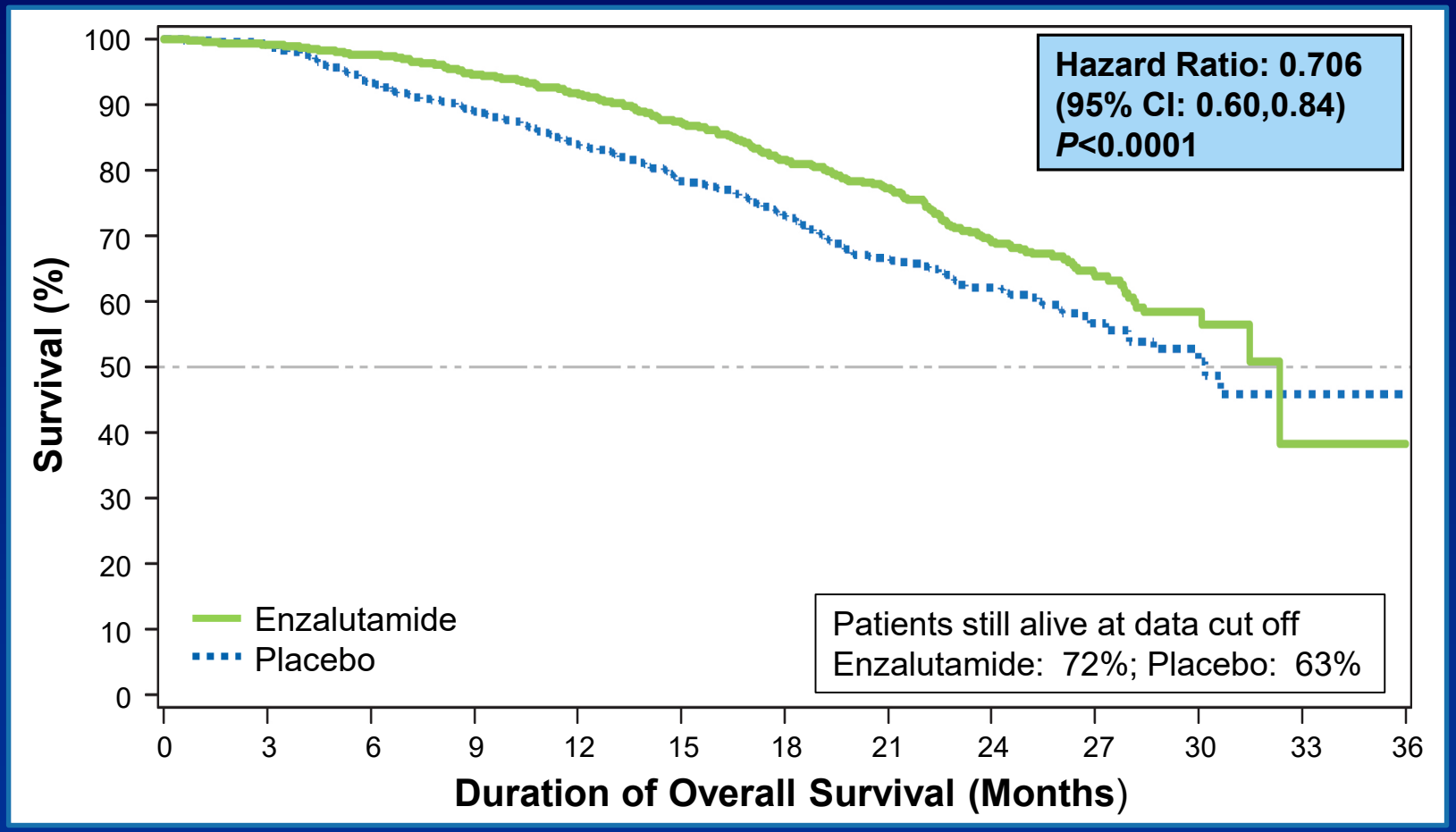


ClinicalTrials.gov identifier: NCT01212991.

Beer TM et al. ASCO GUCS; Jan. 30-Feb. 1, 2014; San Francisco, CA; Abstract LBA1^

Proprietary and Confidential; Not for Distribution or Promotional Use

PREVAIL: Overall Survival



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

Estimated median OS, months (95% CI): Enzalutamide: 32.4 (30.1, NYR); Placebo: 30.2 (28.0, NYR)

NYR = Not Yet Reached

Beer TM et al. ASCO GUCS; Jan. 30-Feb. 1, 2014; San Francisco, CA; Abstract LBA1^

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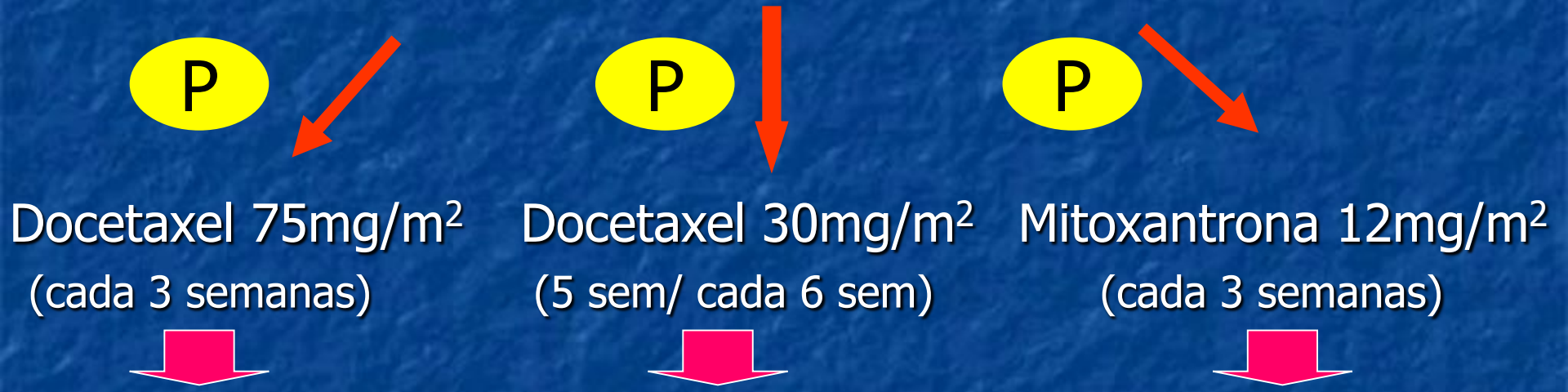
Câncer de Próstata

Docetaxel

TAX 327

1006 pts HFRT

(supressão de testosterona)

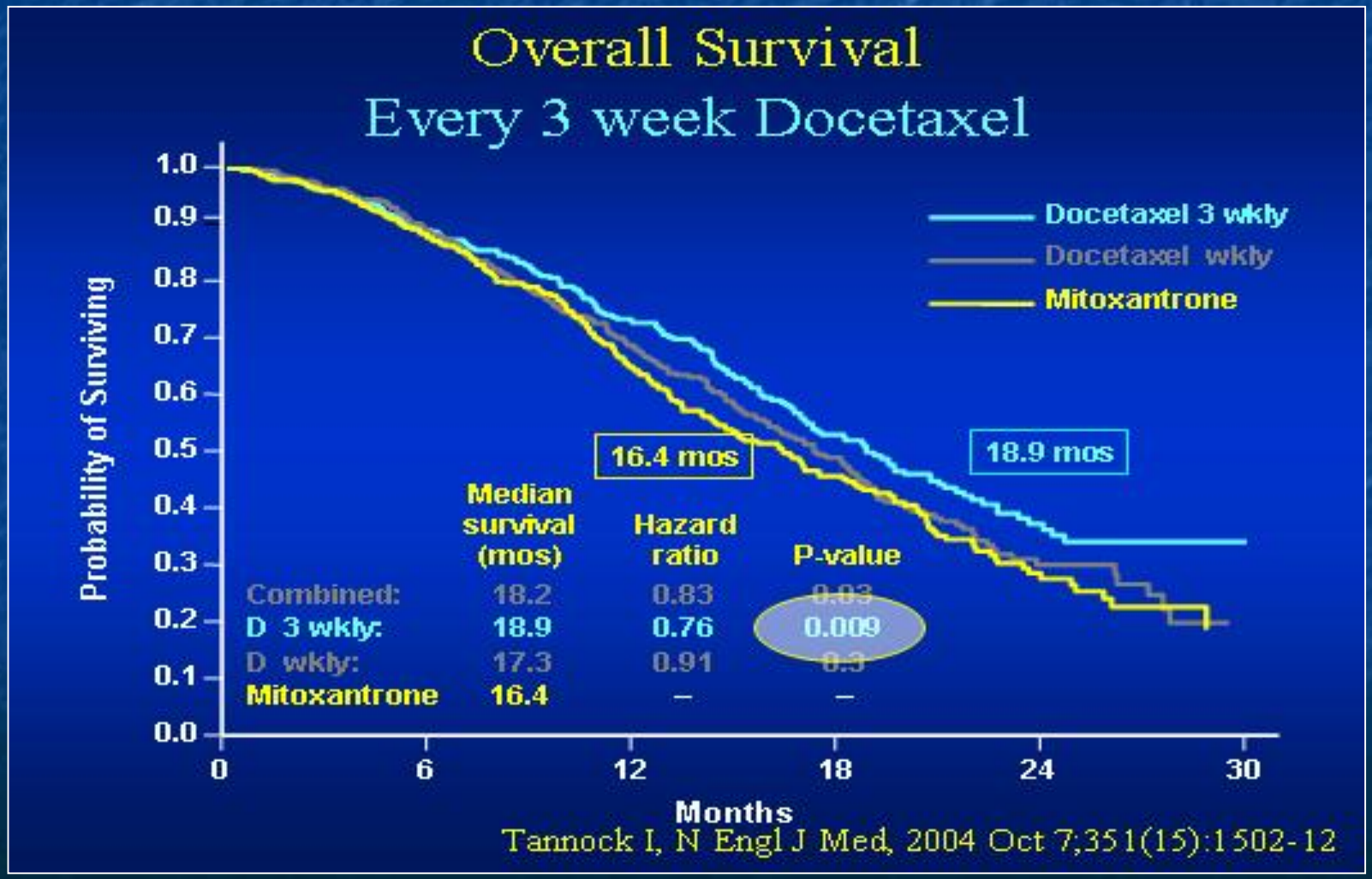


- Estratificação:
  - KPS: ≤ 70 vs > 80
  - Grau de dor: PPI ≥ 2 ou AS ≥ 10 vs PPI < 2 ou AS < 10
- Objetivos:
  - * SVG (força estatística 90%, HR: 0,75, two-sided, 0.05)
  - Resposta PSA, melhora de dor óssea, QOL, toxicidade

TAX 327

Eficácia

Sobrevida Global



Câncer de Próstata

Novas Estratégias na Doença Androgênio "Resistente": Pós-Quimioterapia

TROPIC: Phase III Registration Study
146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen
(N=755)

Stratification factors
ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles
(n=378)

mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles
(n=377)

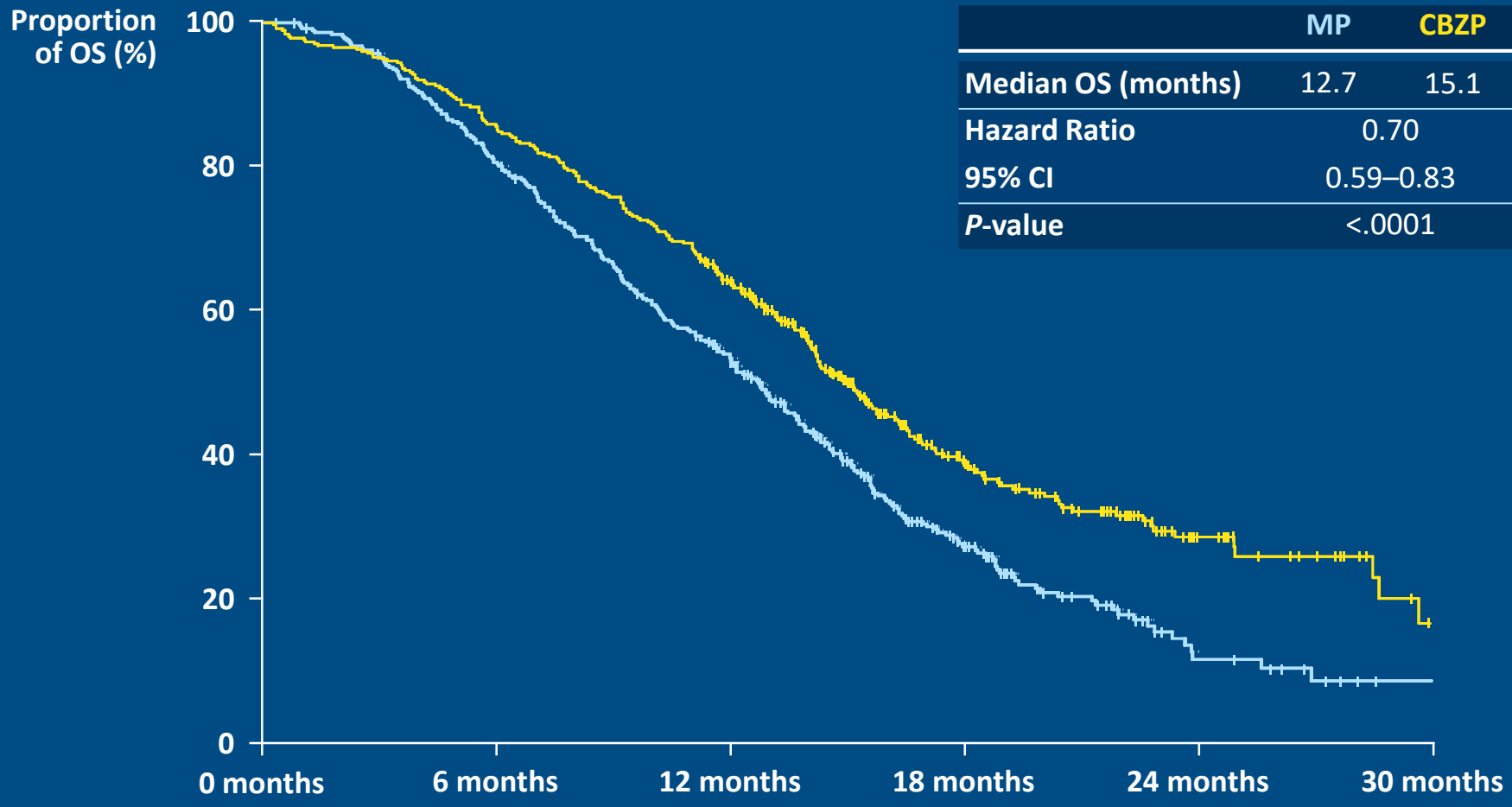
*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

Primary Endpoint: Overall Survival (ITT Analysis)



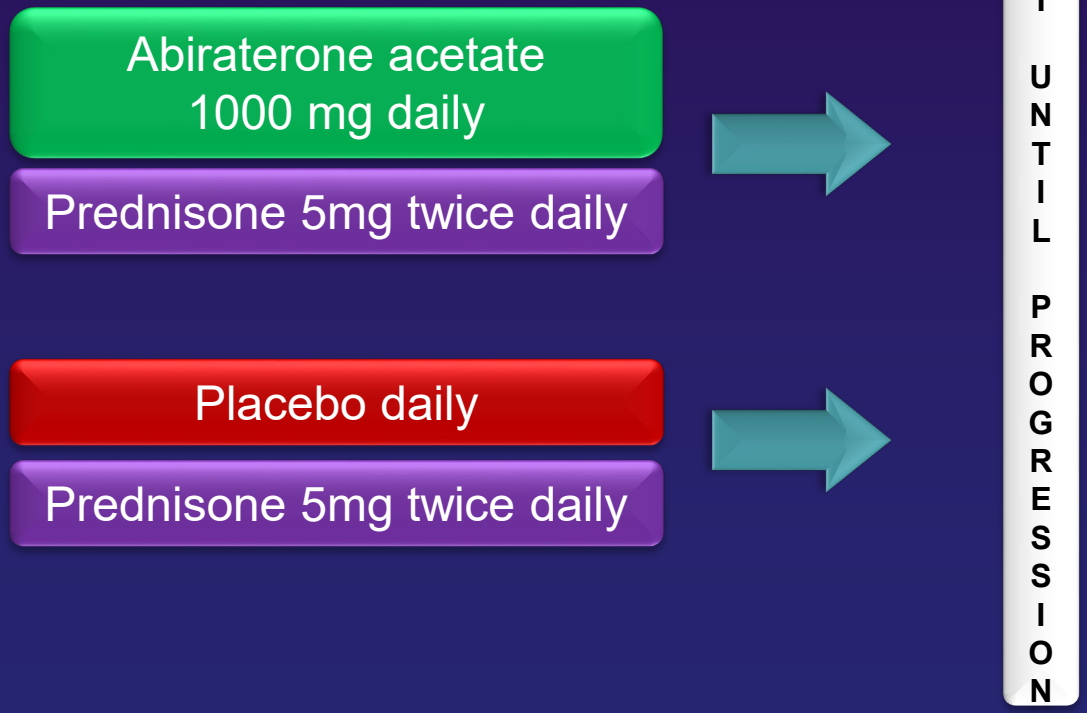
	MP	CBZP
Median OS (months)	12.7	15.1
Hazard Ratio	0.70	
95% CI	0.59–0.83	
P-value	<.0001	

Number at risk	0 months	6 months	12 months	18 months	24 months	30 months
MP	377	300	188	67	11	1
CBZP	378	321	231	90	28	4

COU-AA-301 Study Design

Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study (147 sites in 13 countries; USA, Europe, Australia, Canada)

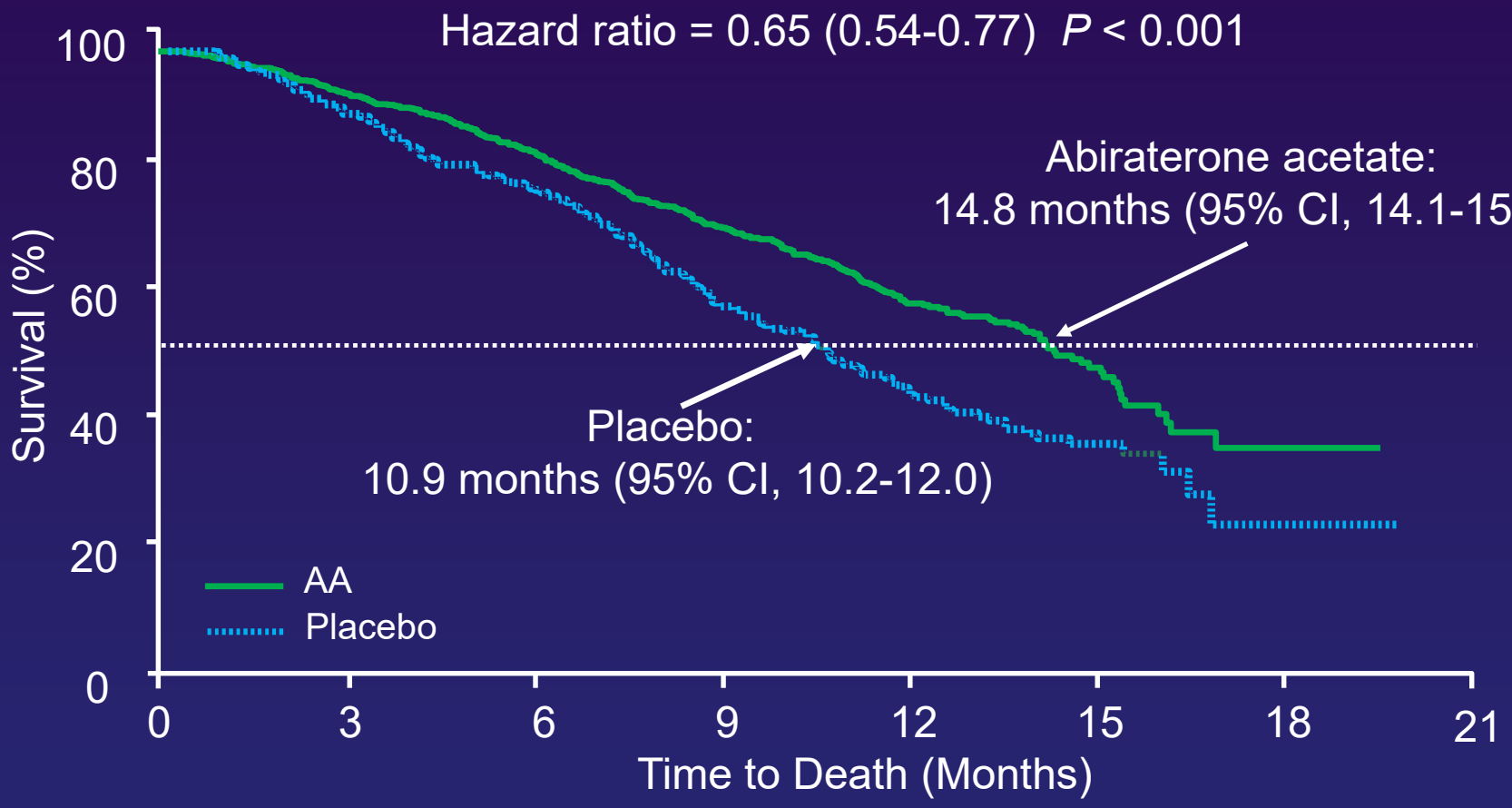
- 1195 patients with progressive, mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel
- Randomised 2:1
- Stratification by:
  - ECOG performance status (0-1 vs. 2)
  - Worst pain over previous 24 hours (BPI short form; 0-3 [absent] vs. 4-10 [present])
  - Prior chemotherapy (1 vs. 2)
  - Type of progression (PSA only vs. radiographic progression with or without PSA progression)



Primary endpoint: OS (25% improvement; HR 0.8)

de Bono et al. N Engl J Med 2011; 346(21): 1995-2005

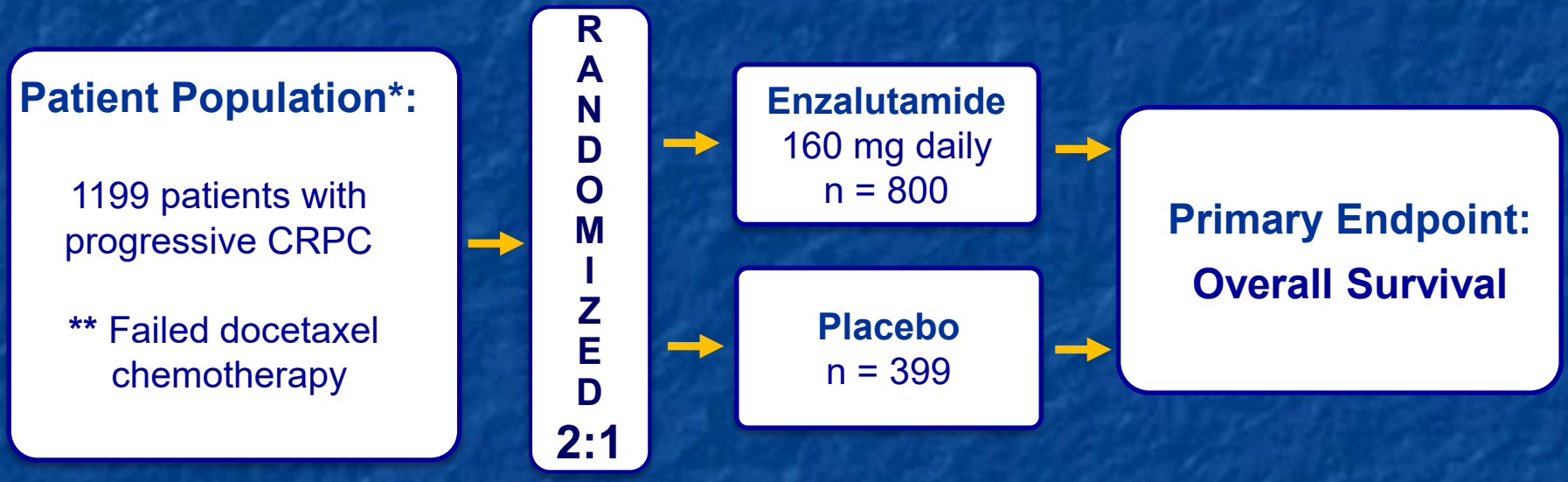
Overall Survival – Interim Analysis



AA	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

de Bono et al. N Engl J Med 2011; 346(21): 1995-2005

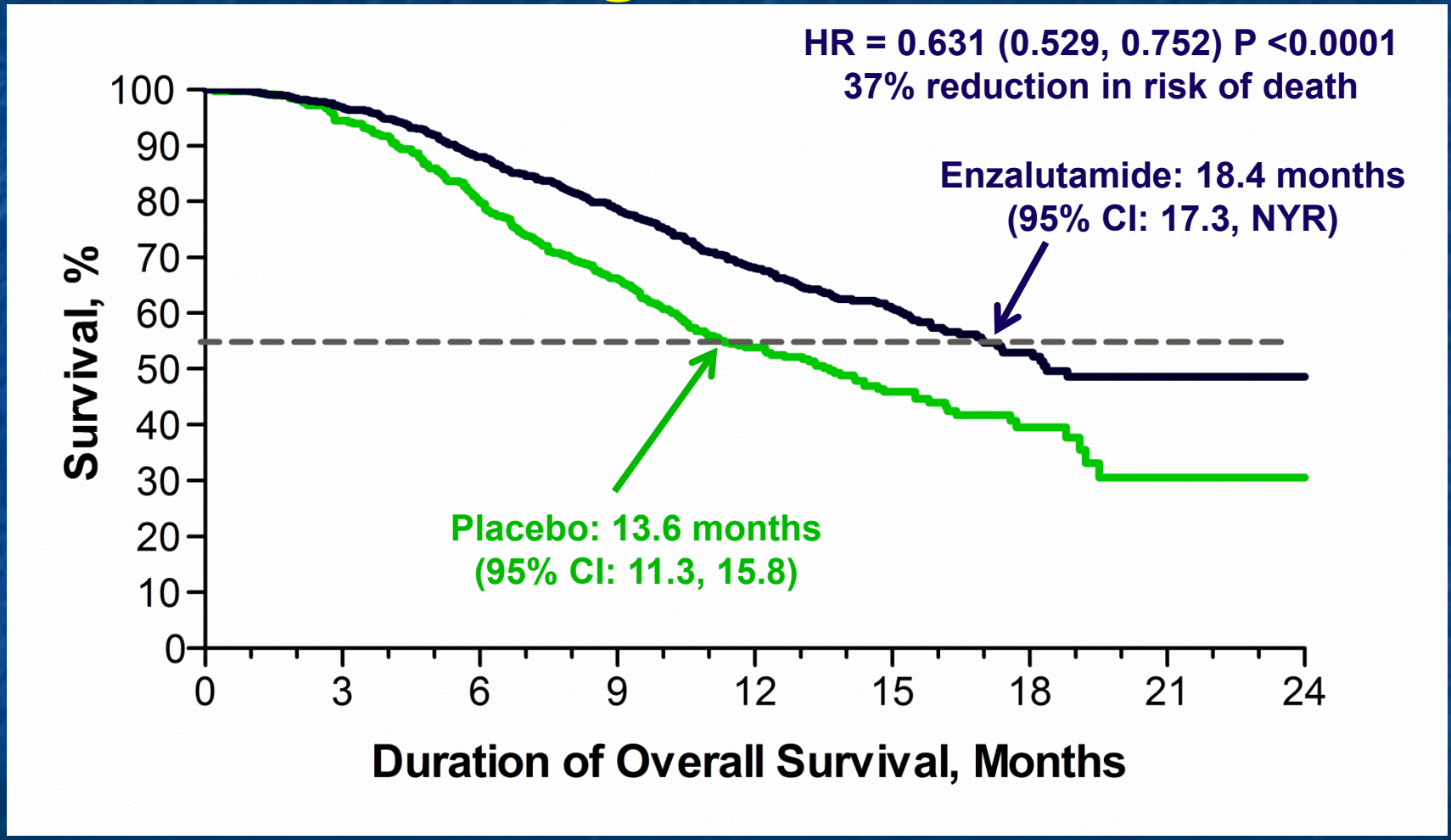
AFFIRM: Enzalutamide vs Placebo in Post-Chemotherapy Castration-Resistant Prostate Cancer (CRPC)



*Stratification variables:
ECOG Performance Status (0-1, 2)
Mean Brief Pain Inventory Q#3 Score (<4, ≥ 4)

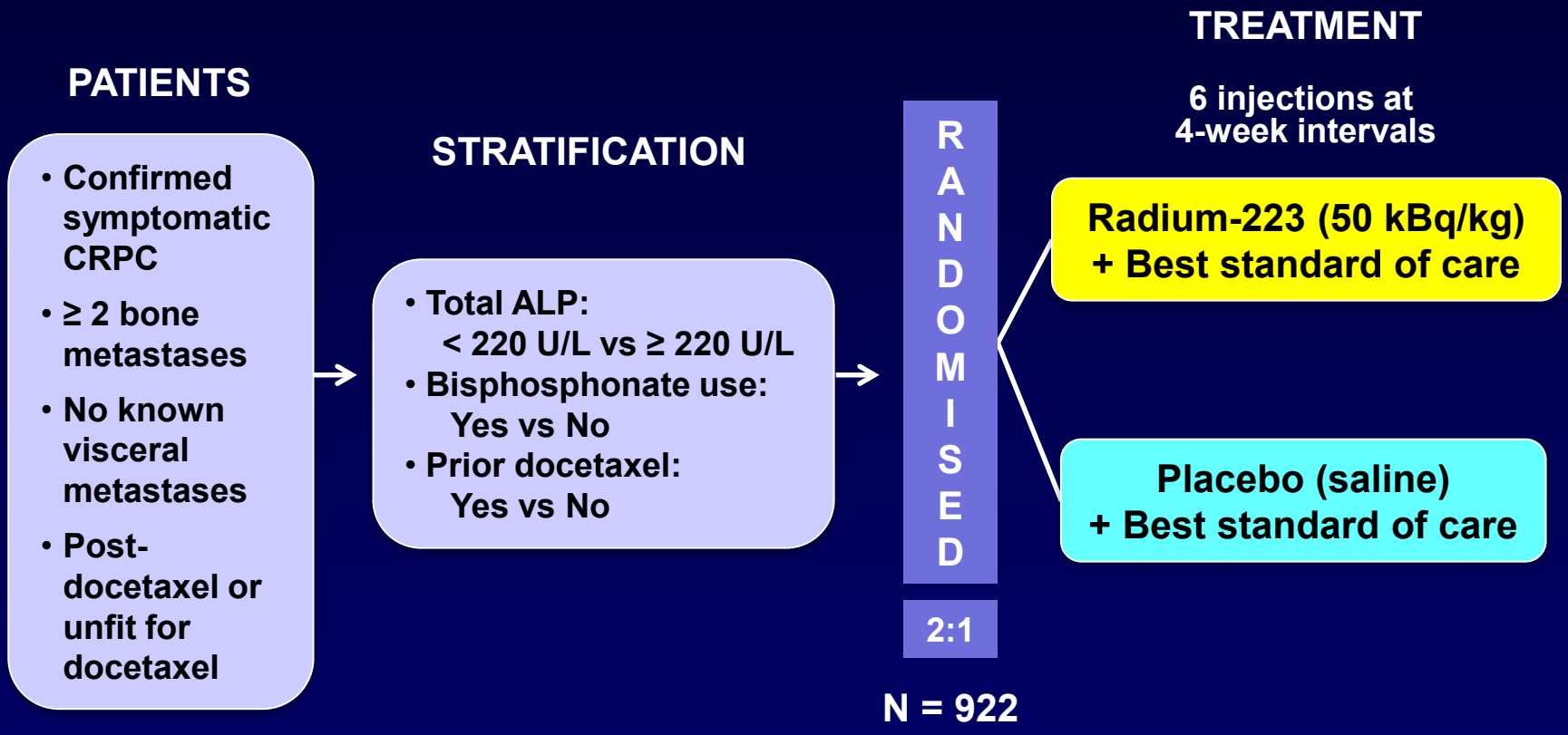
**Glucocorticoids were allowed but not required

Enzalutamide Prolonged Survival, Reducing Risk of Death



Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

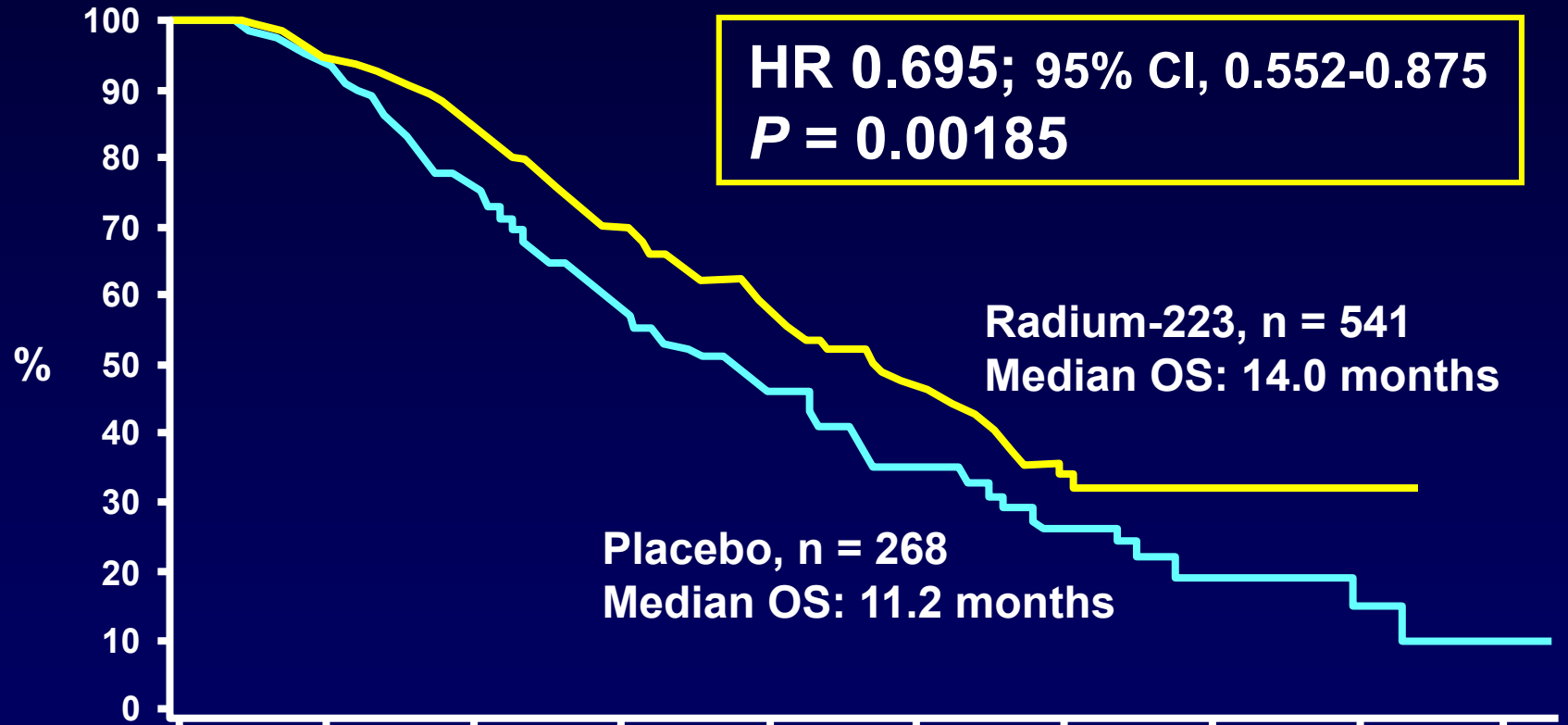
ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751.

ALSYMPCA Overall Survival



Month	0	3	6	9	12	15	18	21	24	27
Radium- 223	541	450	330	213	120	72	30	15	3	0
Placebo	268	218	147	89	49	28	15	7	3	0

Salvage Radical Prostatectomy in Nonmetastatic CRPC s/p XRT

N = 12

- Median time from primary tx to NM-CRPC: 49 m
- Median PSA at salvage surgery: 6.3 ng/ml
- pT3/T4: 11 patients
- pN1: 6 patients
- Median F/U: 40 m
- NED: 3/12
- Biochemical failure: 1/12
- DOD: 6/12
- Rectal injury with temporary colostomy: 1/12
- Rectourethral fistula with further exenteration: 1/12

Gontero et al: Eur Urol, 2014

Câncer de Próstata

Estratégias Locais na Doença Androgênio "Resistente":

Palliative Radiation for Metastatic CRPC

- Spinal cord compression

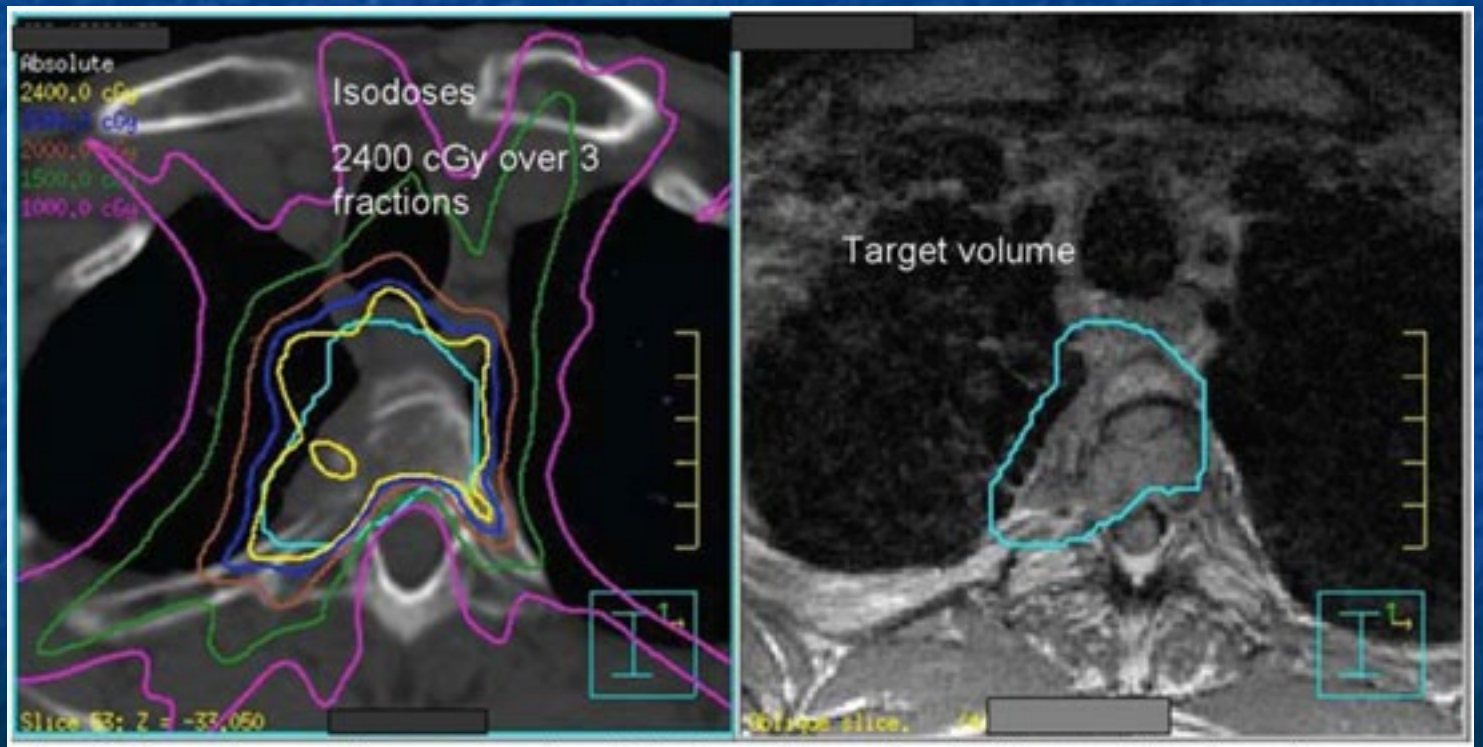
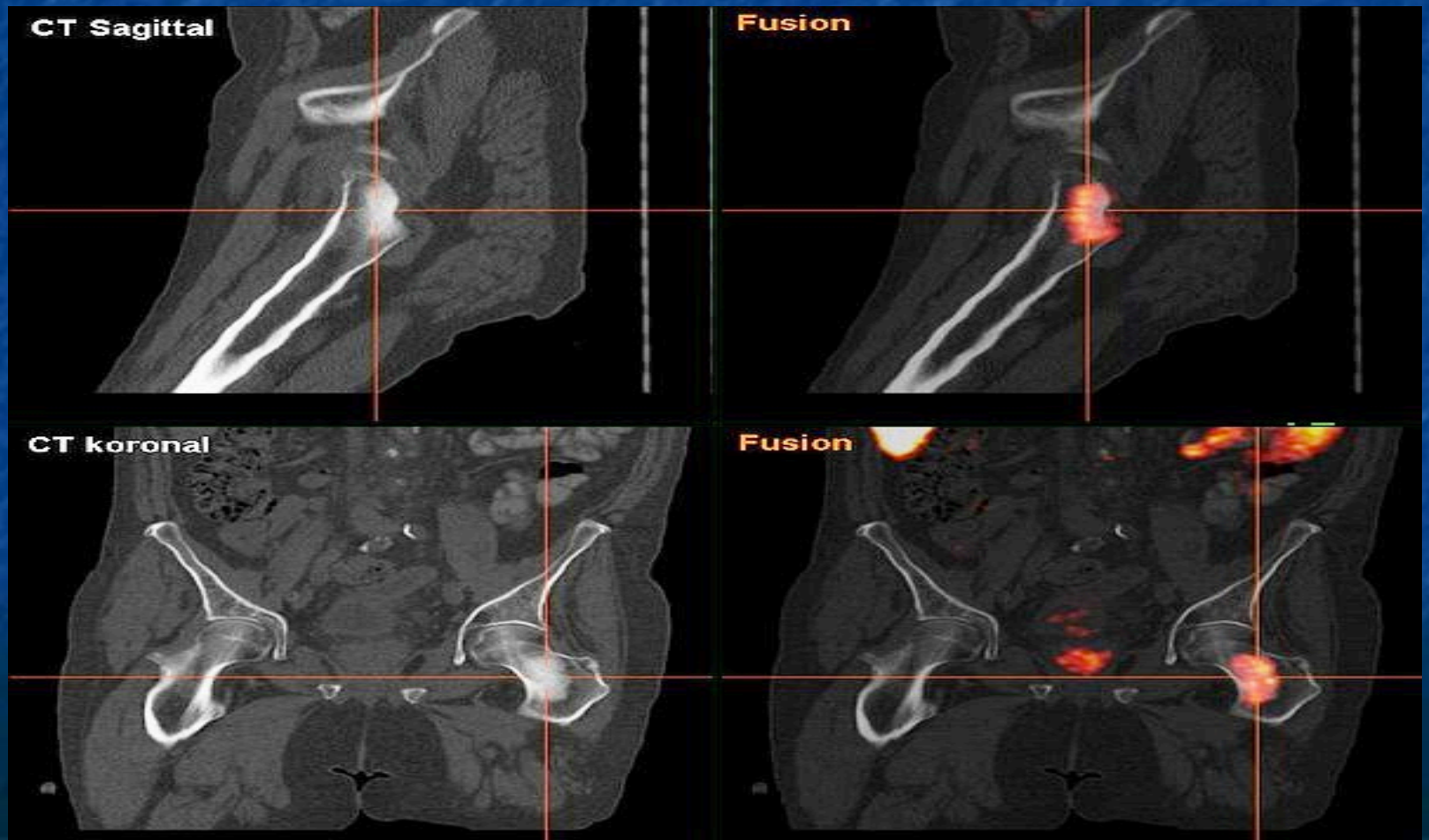


Figure 2. Spine radiosurgery planning target volume (PTV) shown in blue on the right of the image. The radiation dose prescription in this case was 2400 cGy to the PTV (yellow line on the isodose curve image).

Palliative Radiation for Metastatic CRPC

- Metastasis with fracture risk



Palliative Radiation for Metastatic CRPC

- Skull base Metastasis

Câncer de Próstata Androgênio Resistente

Da Literatura para o "Campo de Batalha"

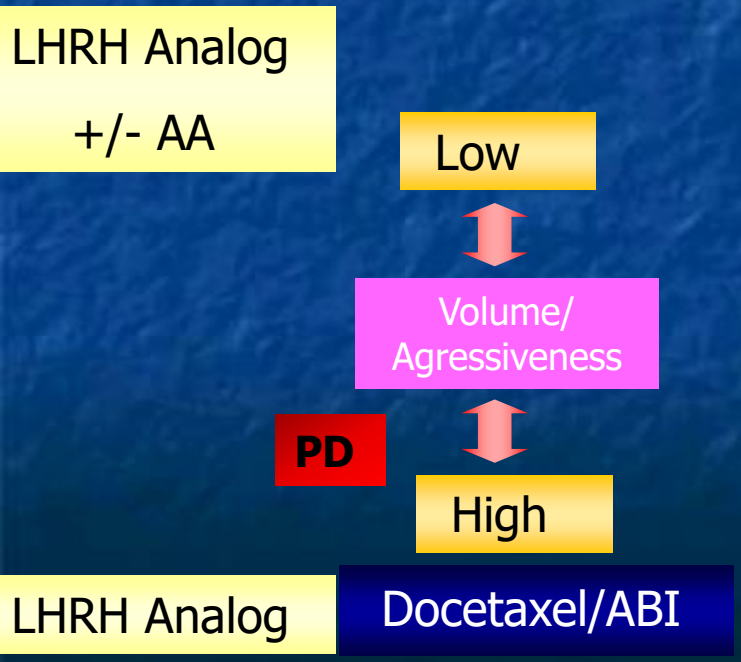
Therapeutic Strategy in CRPC

LHRH Analog

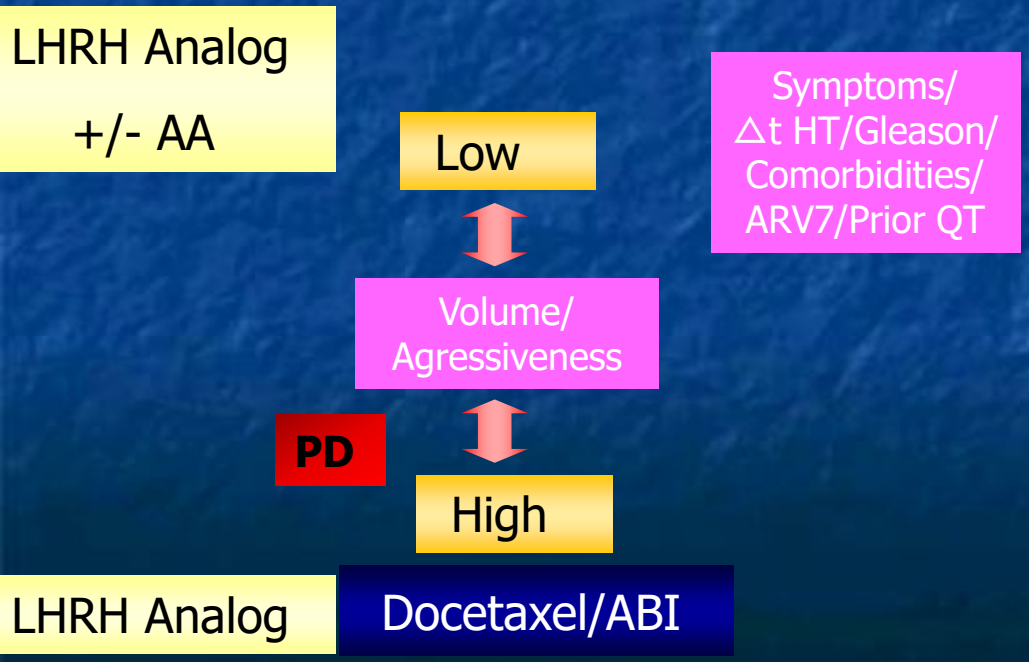
+/- AA

LHRH Analog

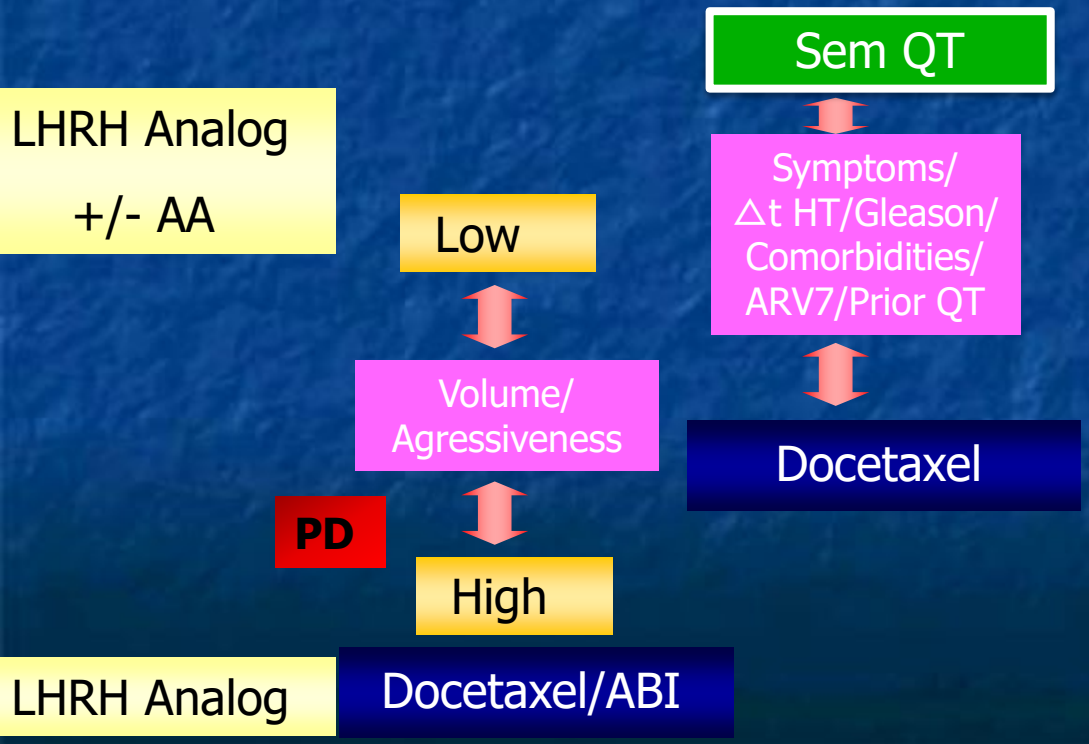
Therapeutic Strategy in CRPC



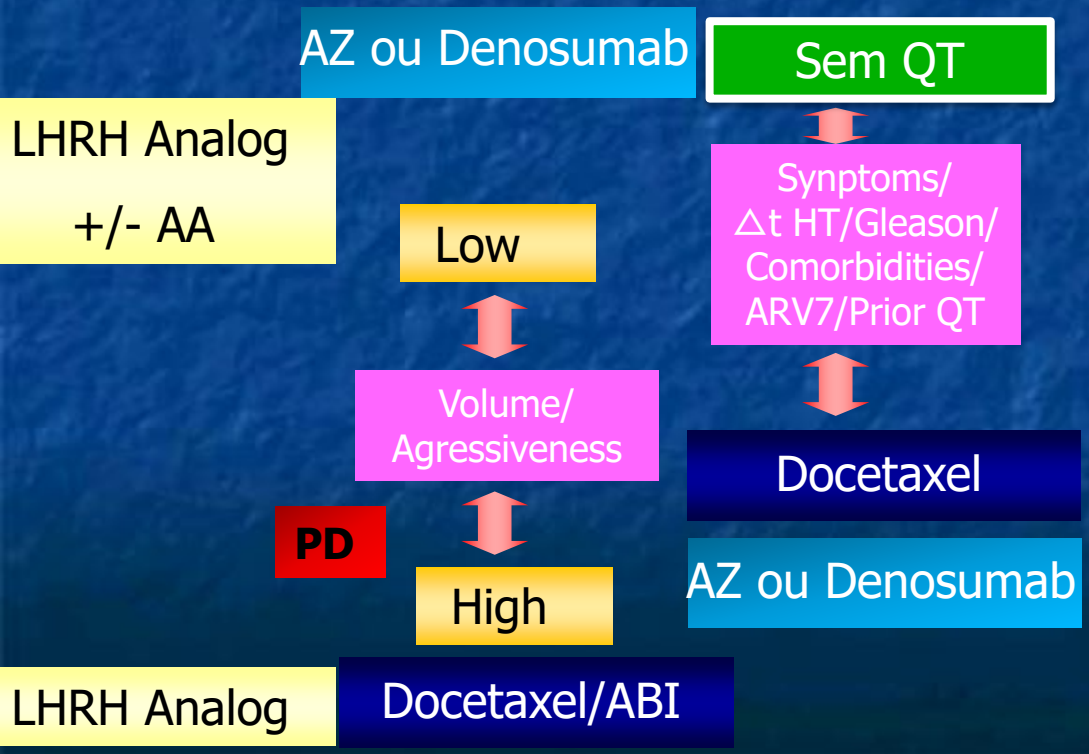
Therapeutic Strategy in CRPC



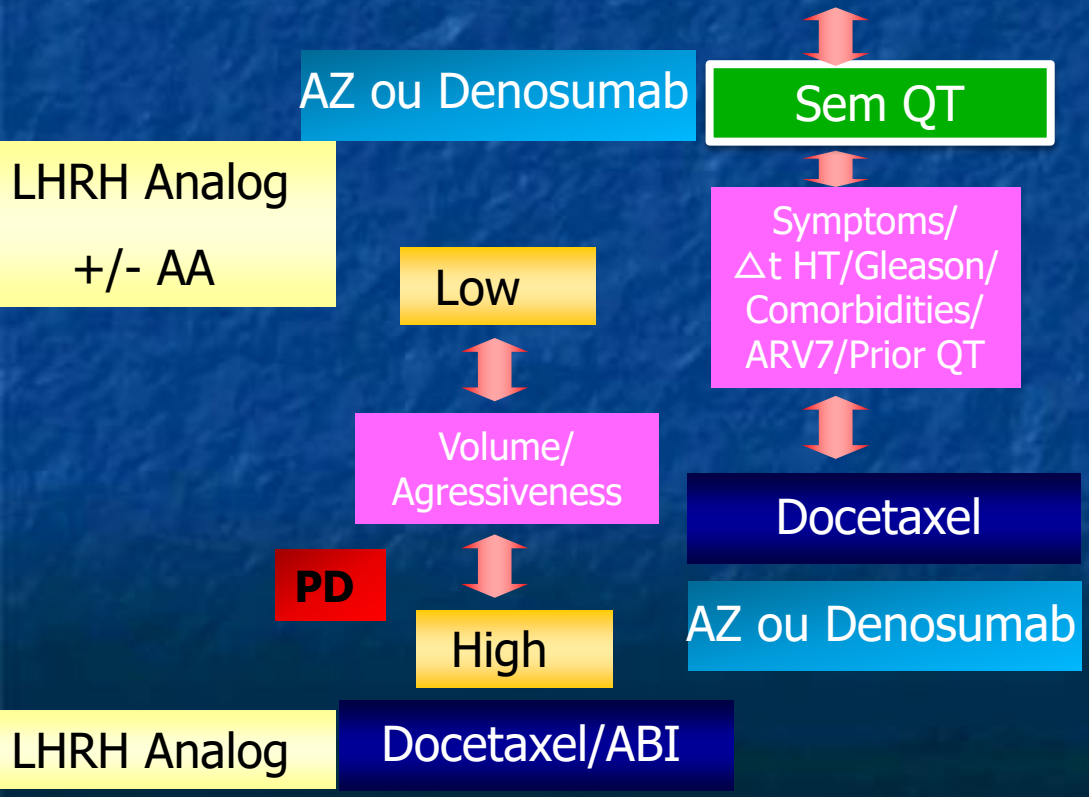
Therapeutic Strategy in CRPC



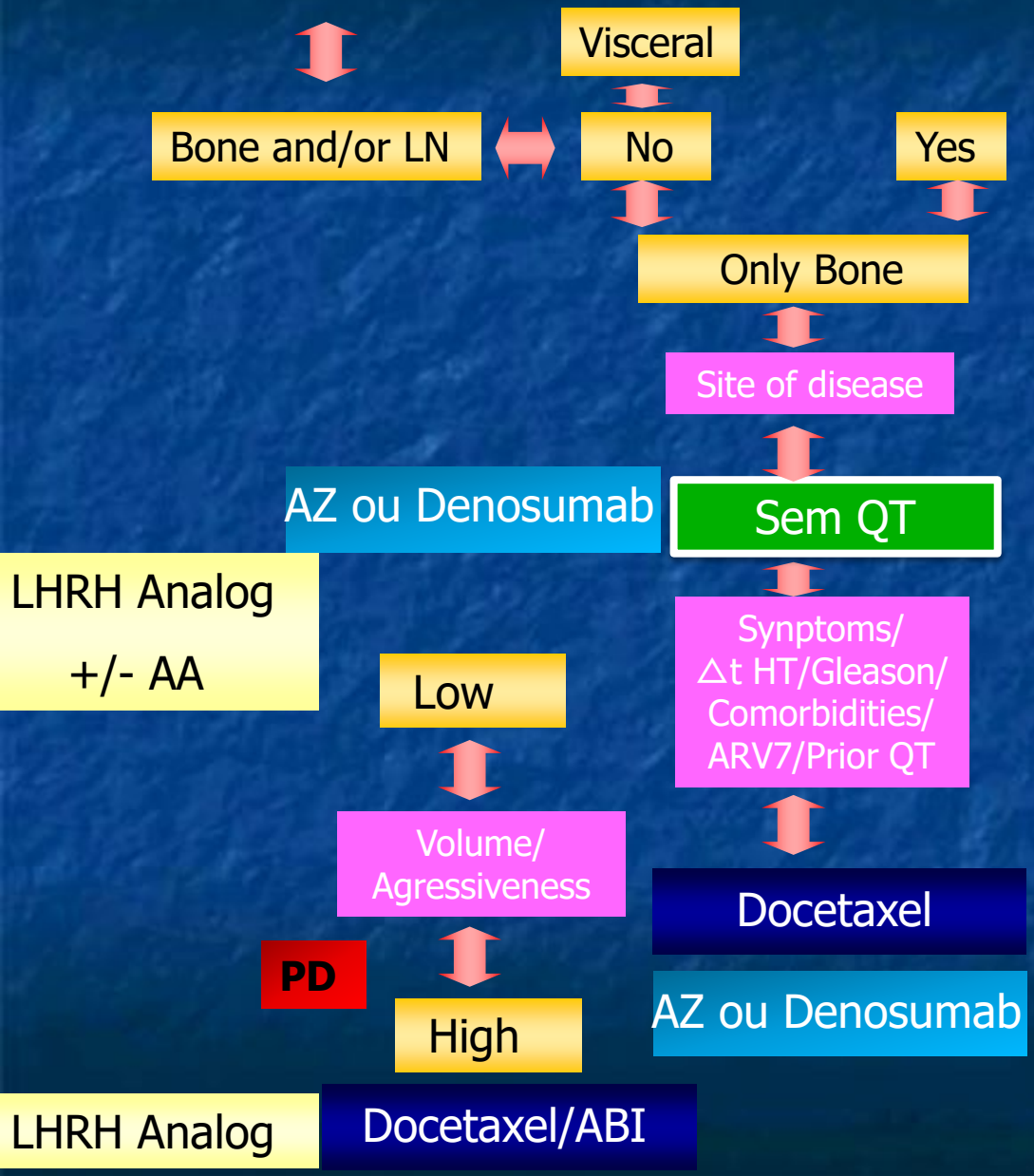
Therapeutic Strategy in CRPC



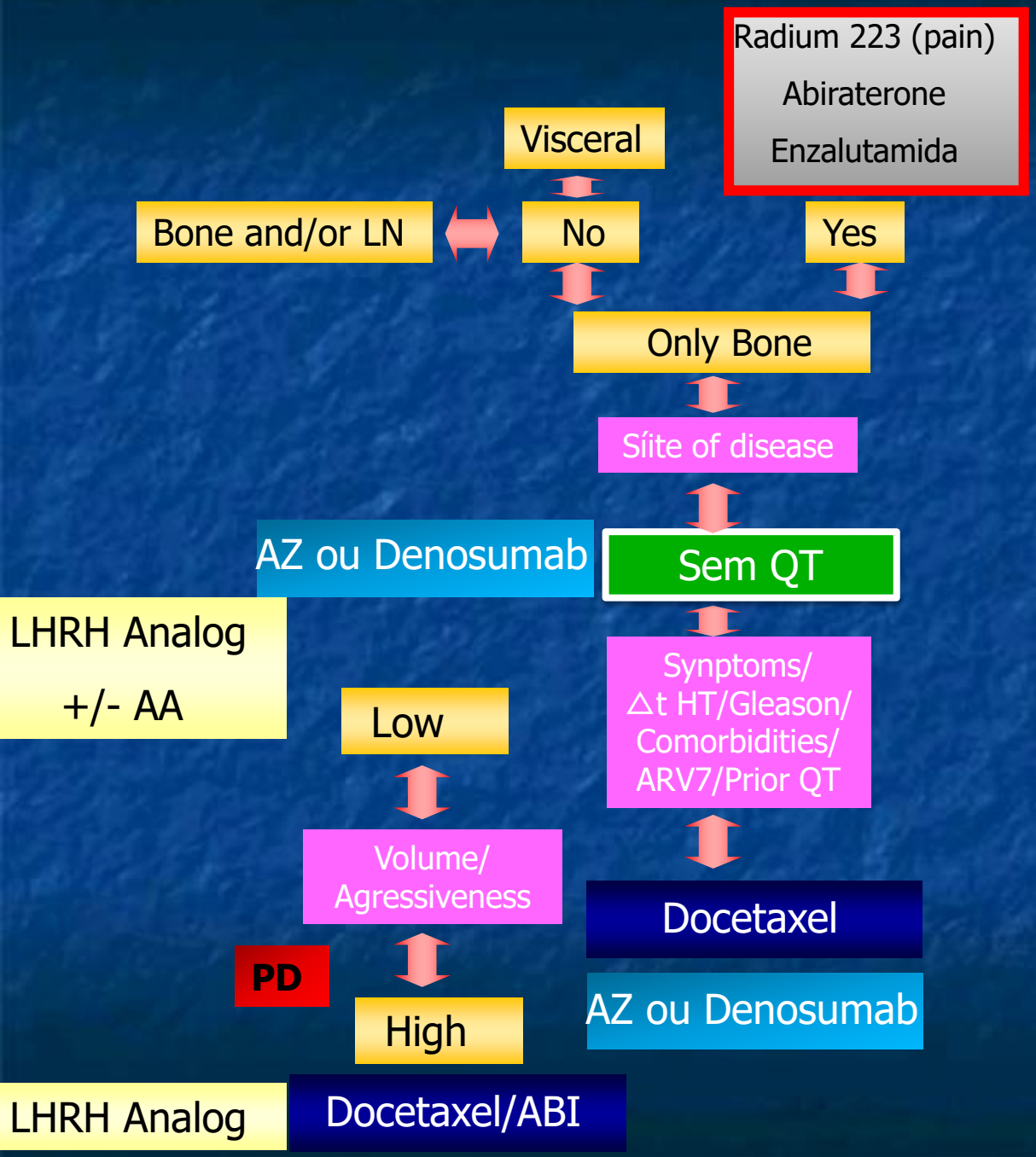
Therapeutic Strategy in CRPC



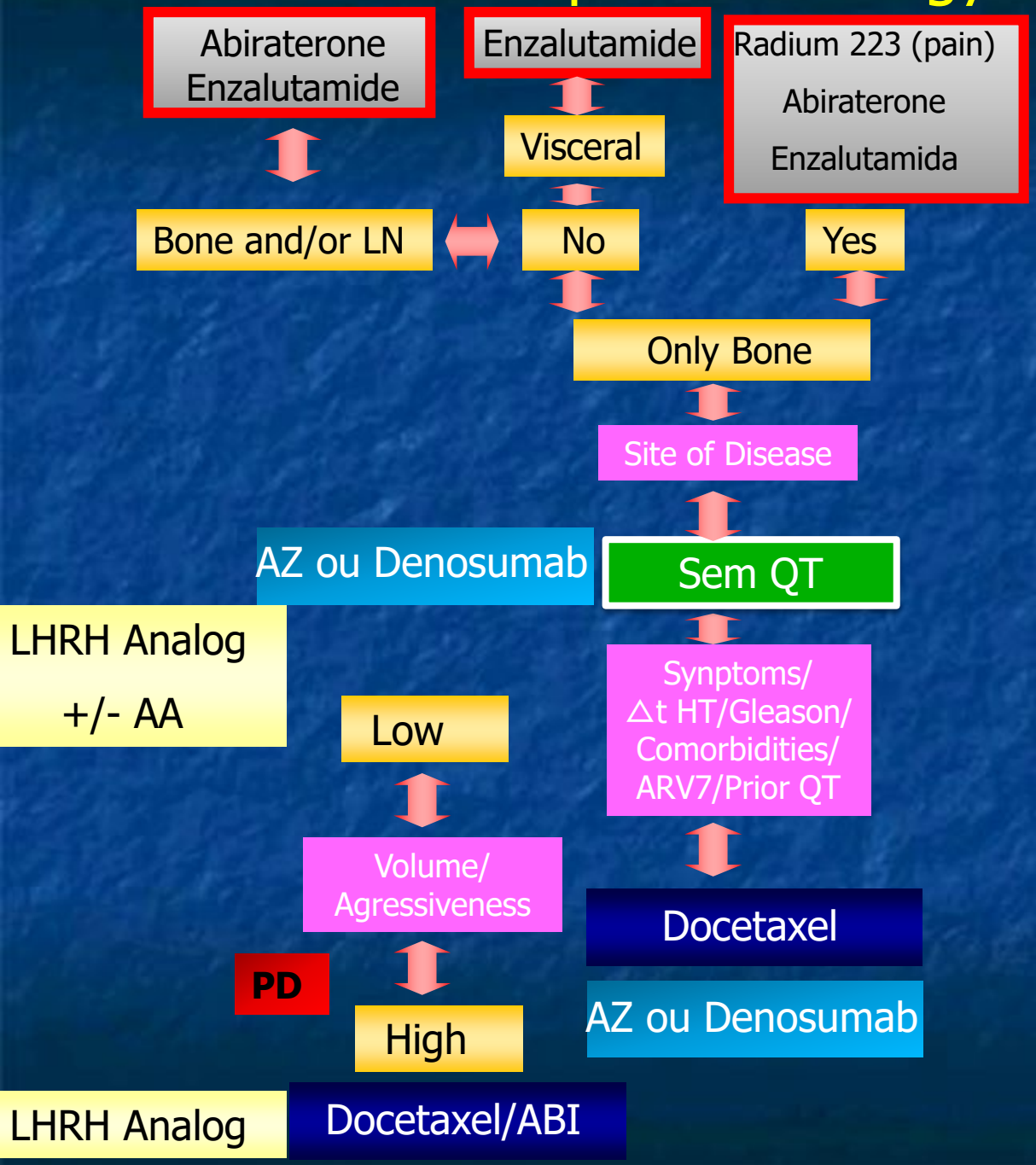
Therapeutic Strategy in CRPC



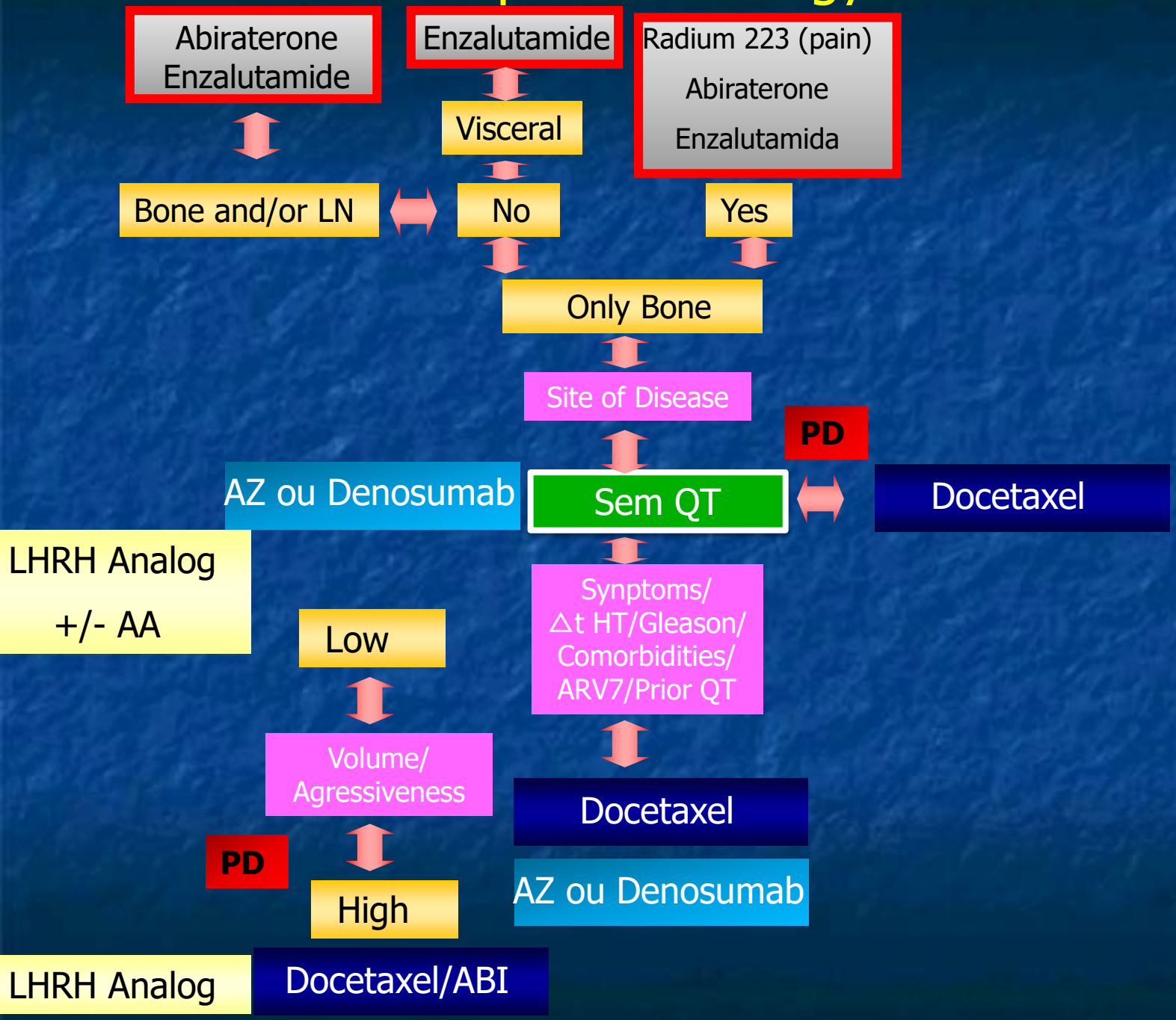
Therapeutic Strategy in CRPC



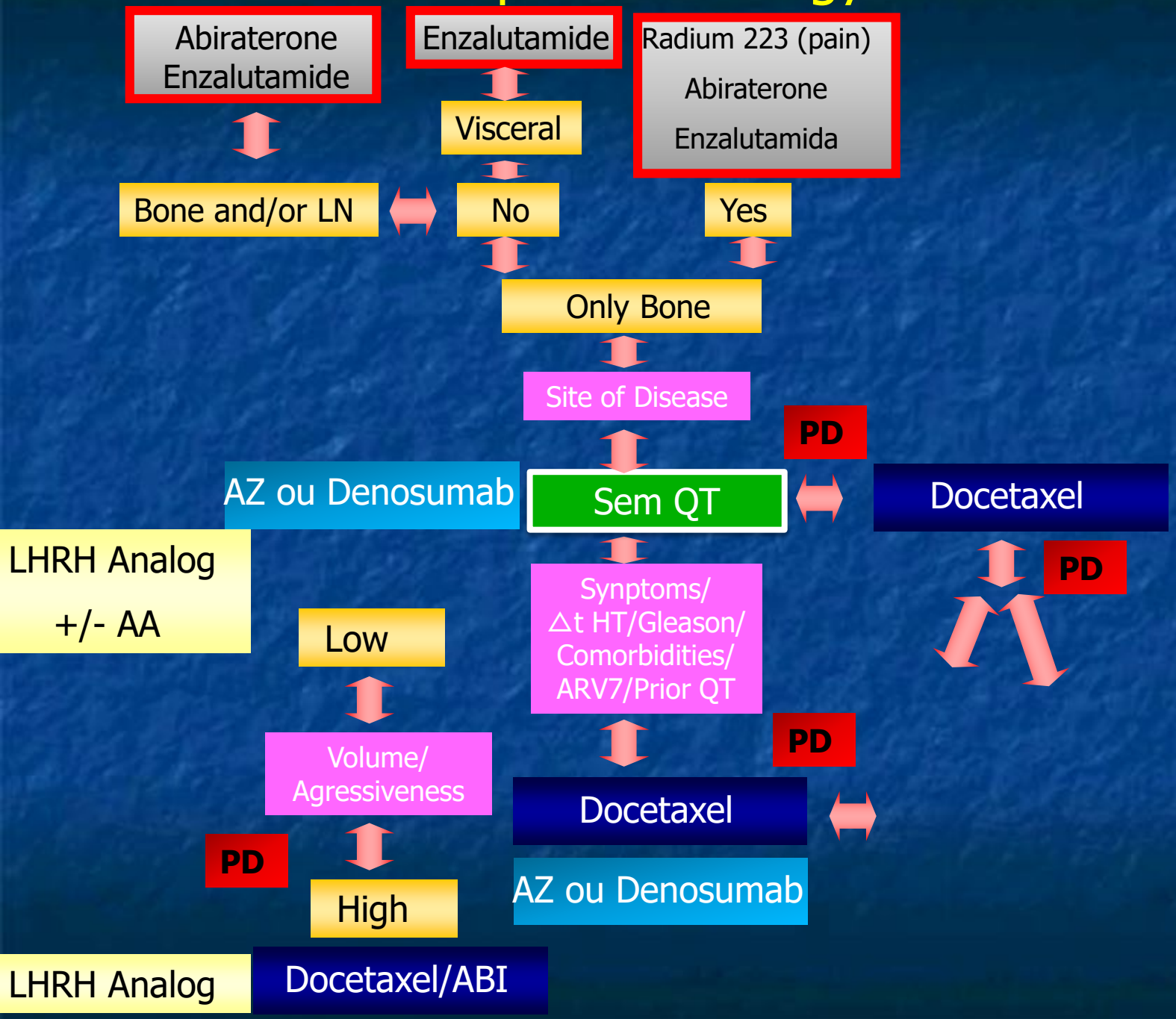
Therapeutic Strategy in CRPC



Therapeutic Strategy in CRPC



Therapeutic Strategy in CRPC



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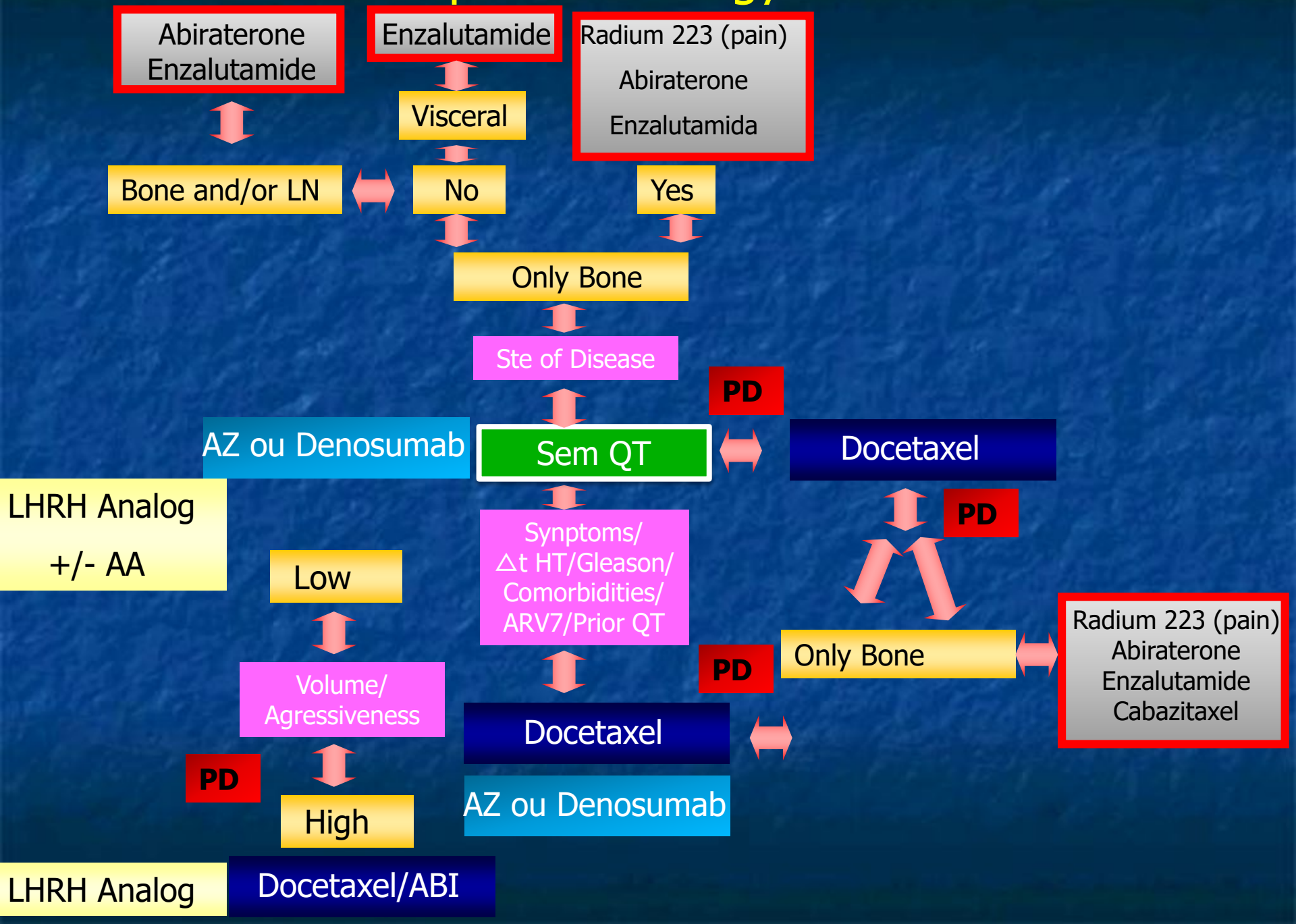
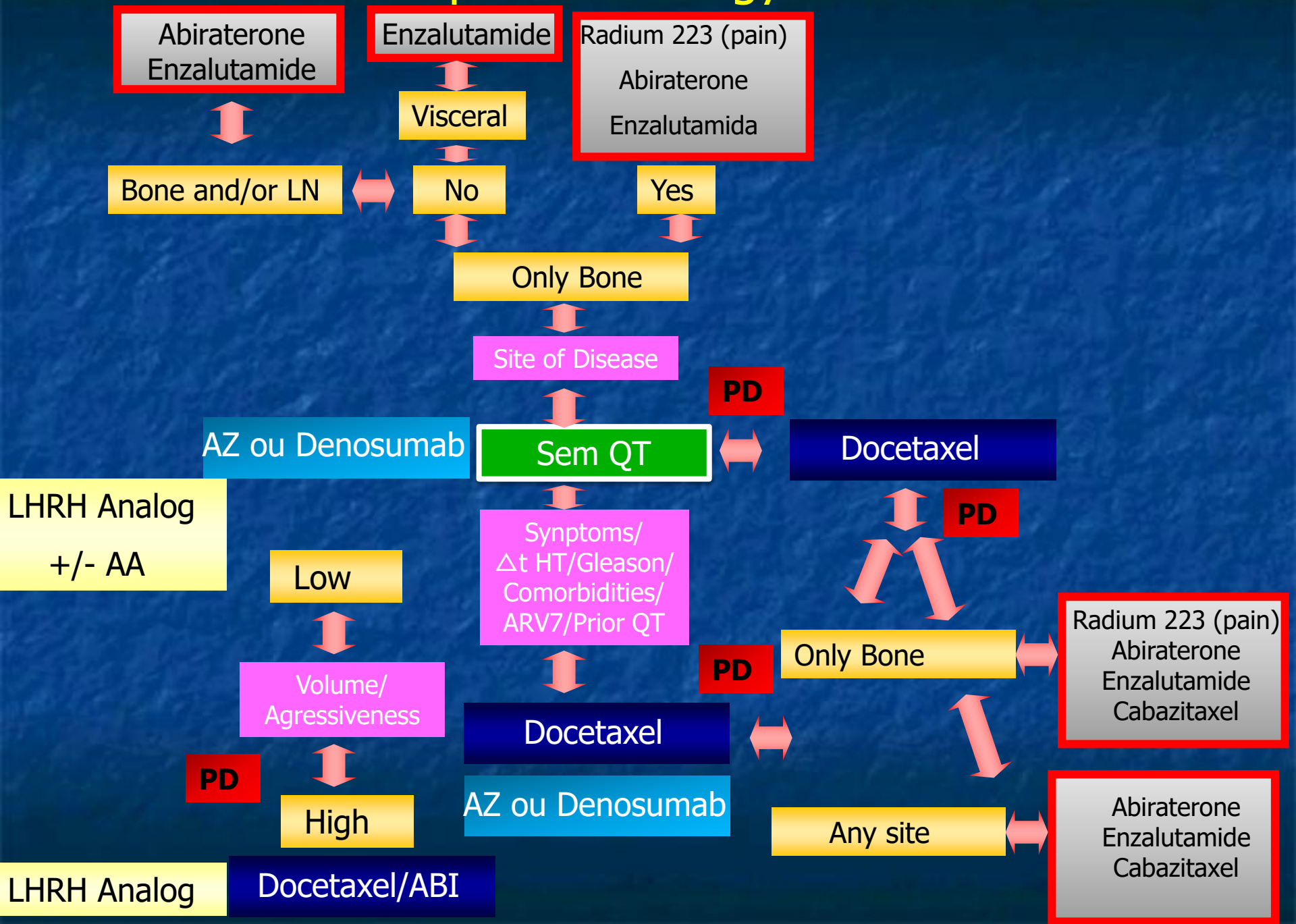
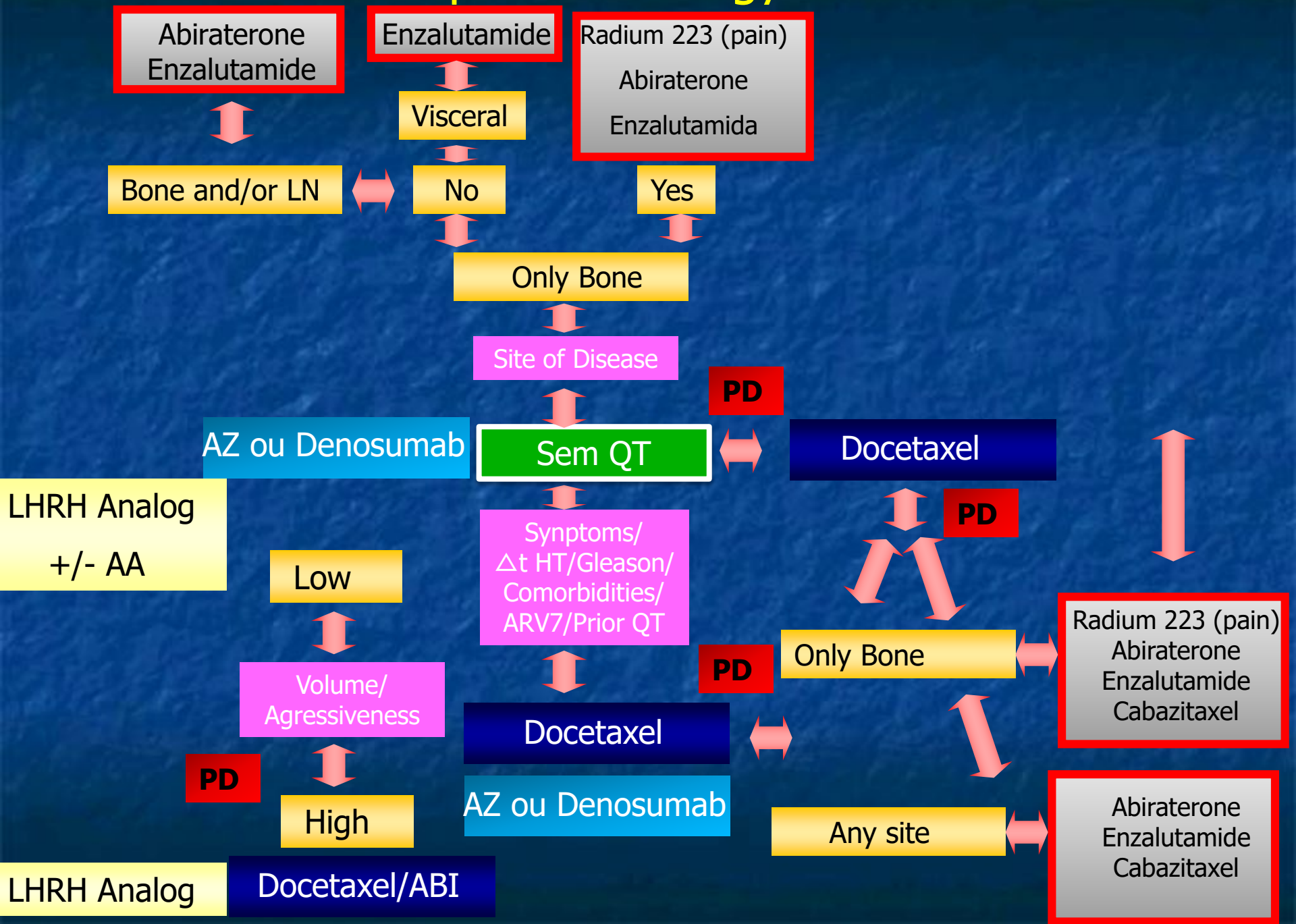


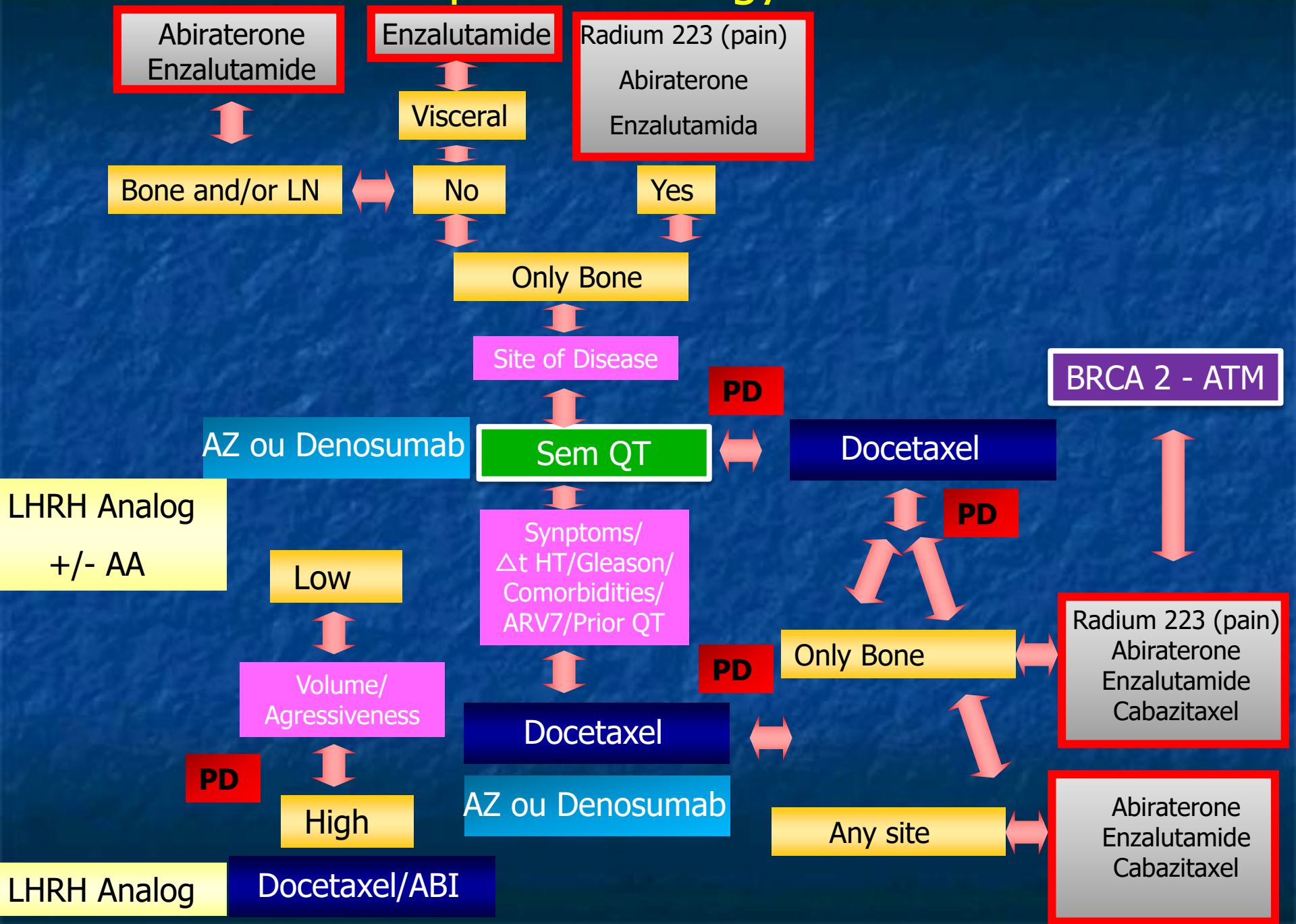
Therapeutic Strategy in CRPC



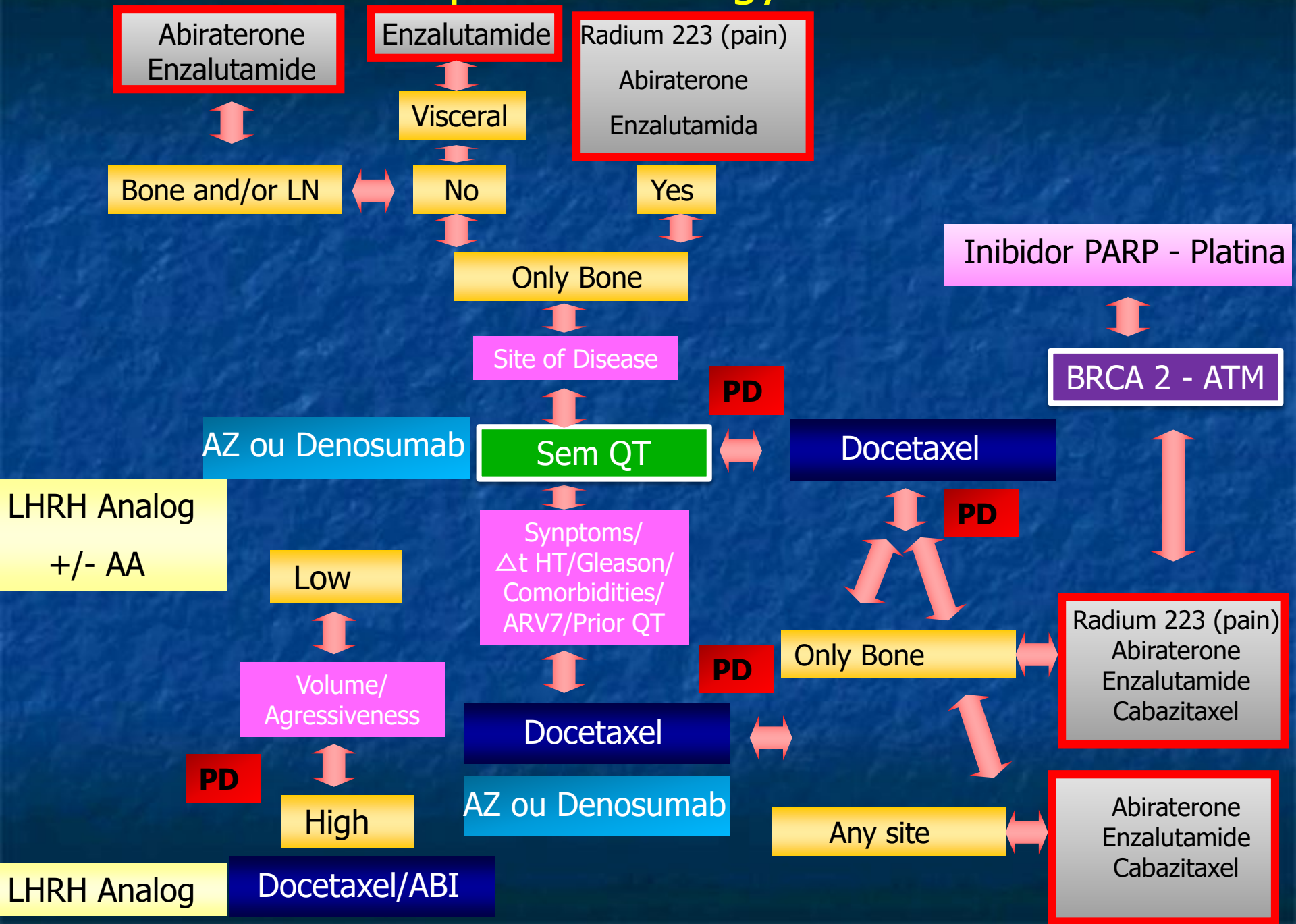
Therapeutic Strategy in CRPC



Therapeutic Strategy in CRPC



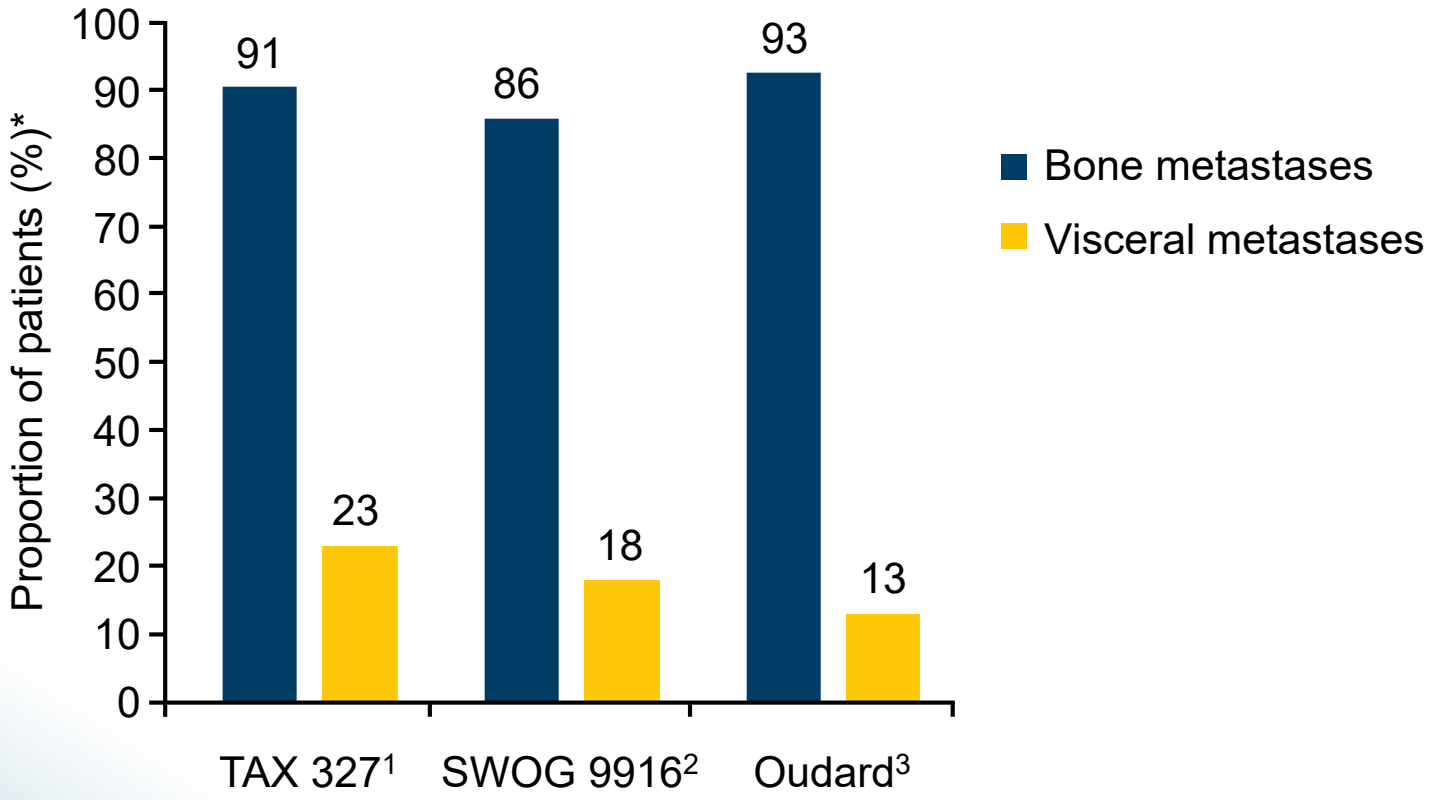
Therapeutic Strategy in CRPC



Câncer de Próstata Androgênio Resistente

Terapias direcionadas aos ossos

Bone is the most common site of metastasis in men with mCRPC



1. Tannock IF, et al. N Engl J Med 2004;351:1502–12;
2. Petrylak DP, et al. N Engl J Med 2004;351:1513–20;
3. Oudard S, et al. J Clin Oncol 2005;23:3343–51.

*Epidemiological data from docetaxel trials.
mCRPC, metastatic castration-resistant prostate cancer;
SWOG, Southwest Oncology Group.

Bone metastases can have serious and debilitating consequences – skeletal-related events (SREs)

- SREs are defined as:[1]

Radiation to bone

Pathological fracture

Spinal cord compression

Surgery to bone

- Incidence of SREs in metastatic prostate cancer:[2†]

29% **22%** **7%** **3%**

- Note that historically, some studies and definitions of SREs have included hypercalcaemia[3]

1.www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm071590.pdf (accessed 15-10-15);
2. Saad F, et al. J Nat Clin Inst 2002;94:1458–68;
3. Coleman RE, et al. Clin Cancer Res 2006;12:6243s–9s.

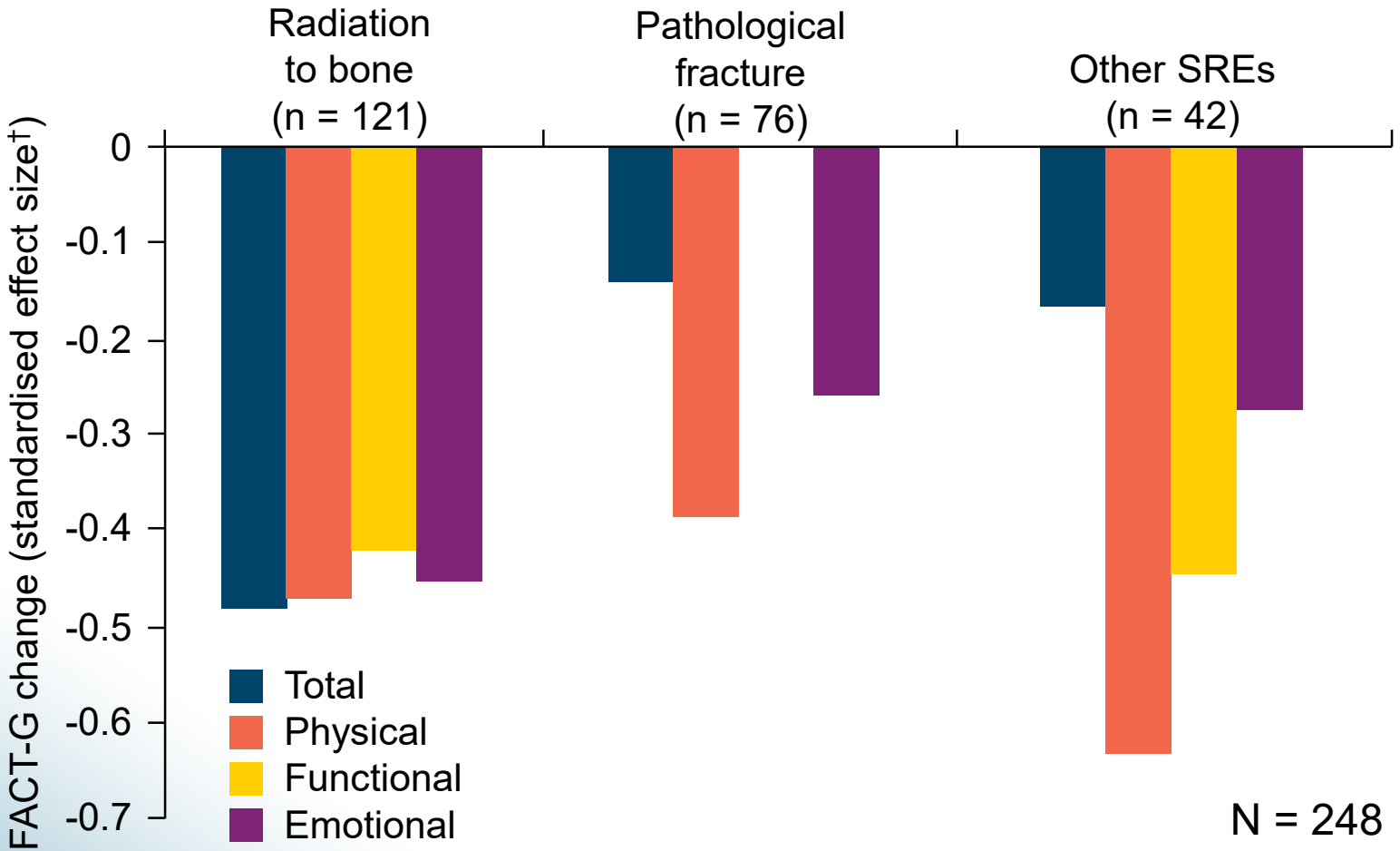
†Proportions of metastatic prostate cancer patients with SREs up to Month 15 in the placebo arm of a randomised, placebo-controlled Phase 3 trial of zoledronic acid.

Defining bone complications in prostate cancer

SRE[1,2] (Skeletal-related event)	SSE[1,3] (Symptomatic skeletal events)
• Radiation to bone • Pathological fractures (symptomatic or identified through imaging assessments) • Surgery to bone • Spinal cord compression	• Radiation to bone • Symptomatic pathological fractures • Surgery to bone • Spinal cord compression

1. Smith M, et al. Ann Oncol 2015;26:360–74;
2. Fizazi K, et al. Lancet 2011;377:813–22;
3. Parker C, et al. N Engl J Med 2013;369:213–23.

SREs are associated with reduced HRQoL in patients with CRPC and bone metastases

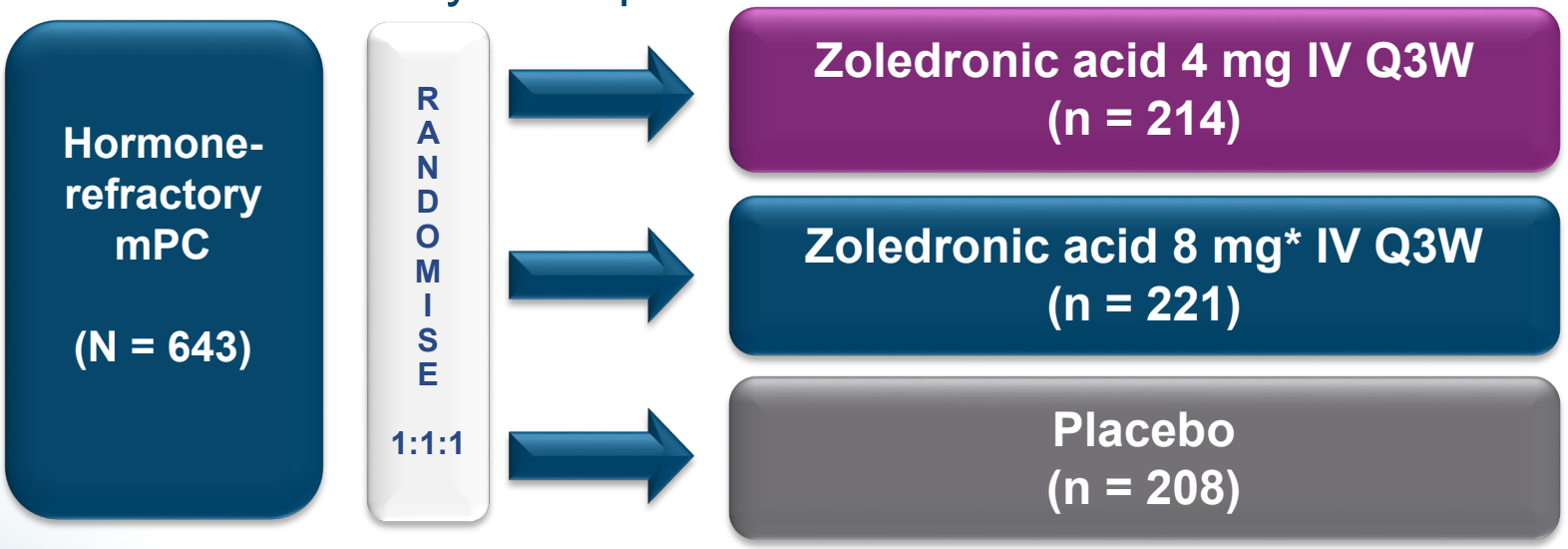


†Computed by dividing the adjusted mean change by the baseline standard deviation from the entire trial sample.
Data from 248 men with CRPC and bone metastases who experienced an SRE during a placebo-controlled Phase 3 trial of zoledronic acid.
FACT-G, Functional Assessment of Cancer Therapy-General; HRQoL, health-related quality of life.

Weinfurt KP, et al. Ann Oncol 2005;16:579–84.

Zoledronic acid protocol 039: study design

- Randomised, double-blind, placebo-controlled, Phase 3 trial in hormone-refractory mPC patients



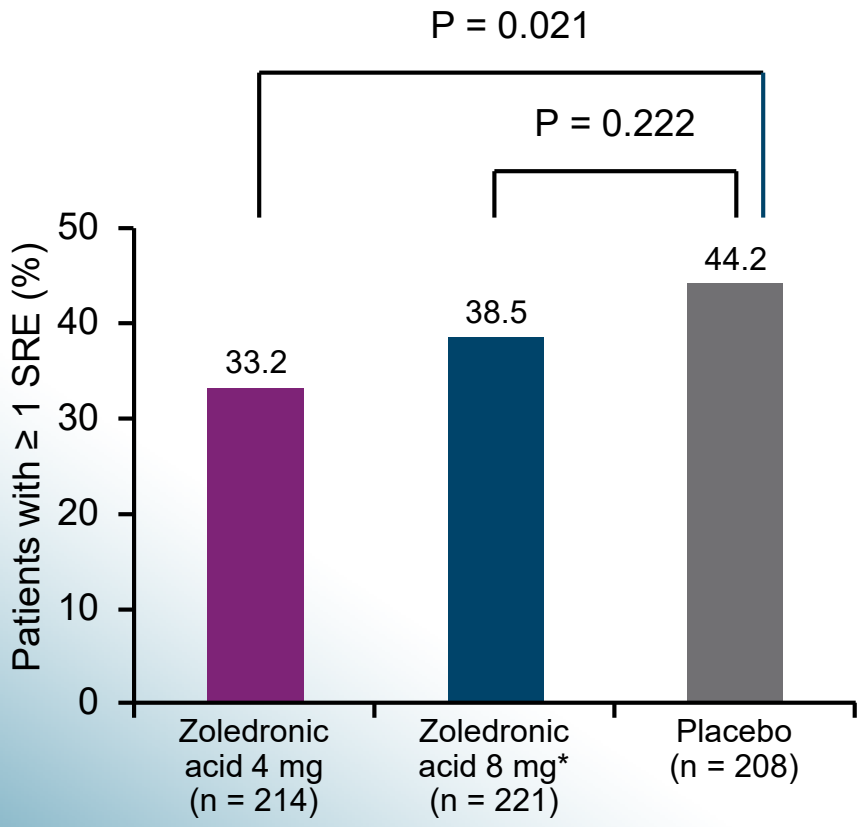
Primary endpoint: proportion of patients with ≥1 SRE
Relevant secondary endpoints: time to first SRE, skeletal morbidity rate
Incidence of bone metastases at baseline: 99.1% zoledronic acid 4 mg vs 99.1% zoledronic acid 8 mg* vs 98.6% placebo
Use of bone-targeted therapy at baseline: any prior bisphosphonate use not permitted

*Dose of 8 mg subsequently reduced to 4 mg.
IV, intravenous; mPC, metastatic prostate cancer; Q3W, every 3 weeks; SRE, skeletal-related event.

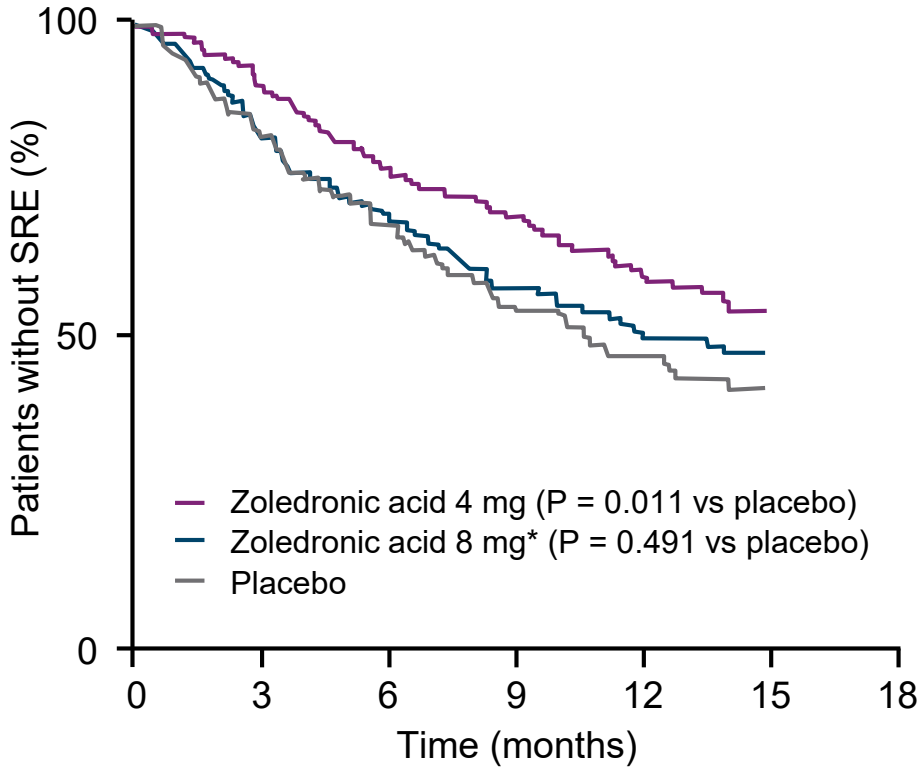
Saad F, et al. J Natl Cancer Inst 2002;94:1458–68.

Zoledronic acid protocol 039: frequency and timing of SREs

Reduced proportion of patients with ≥ 1 SRE



Increased time to first SRE

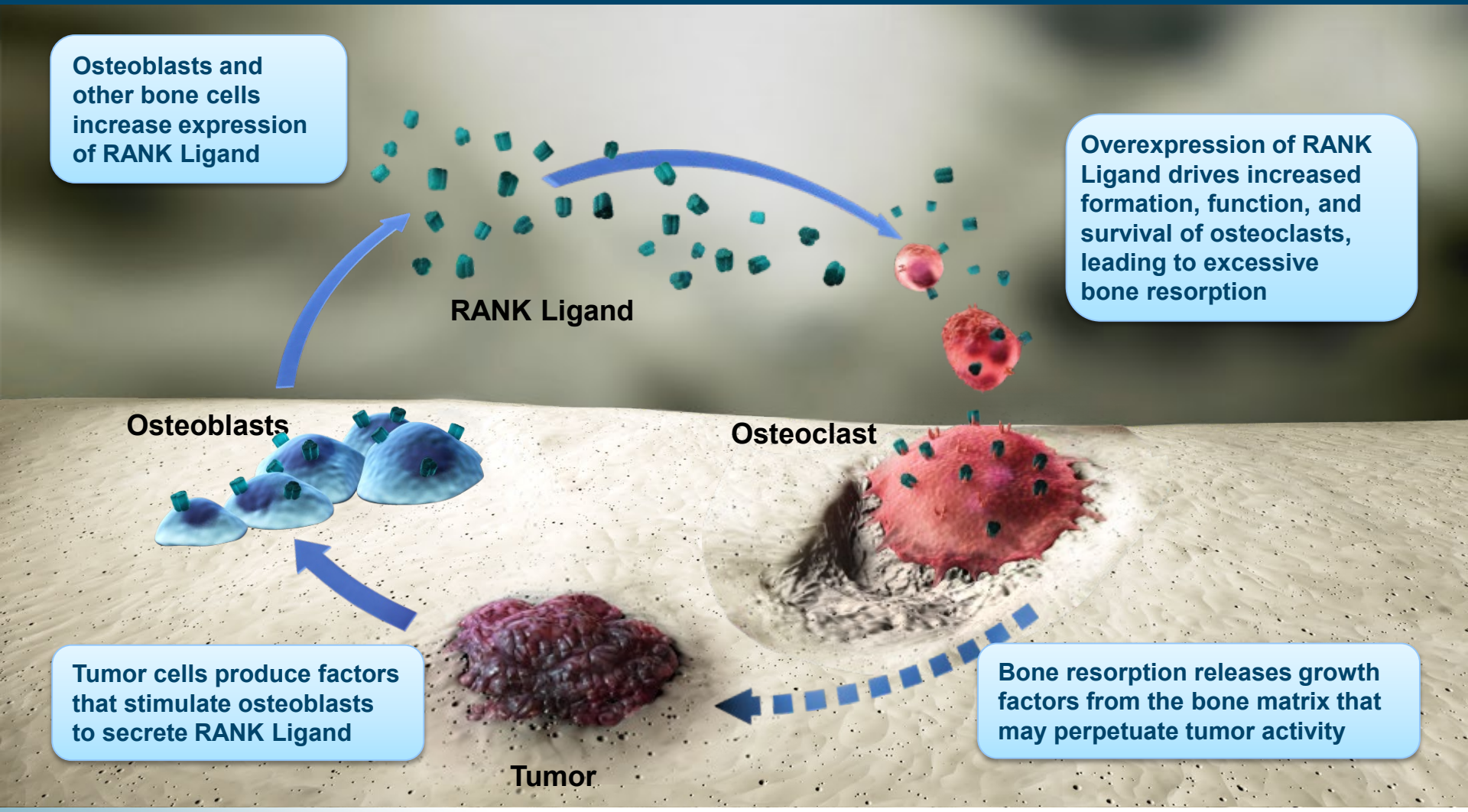


Adapted from Saad F, et al. J Natl Cancer Inst 2002;94:1458–68.

*Dose of 8 mg subsequently reduced to 4 mg.
SRE, skeletal-related event.

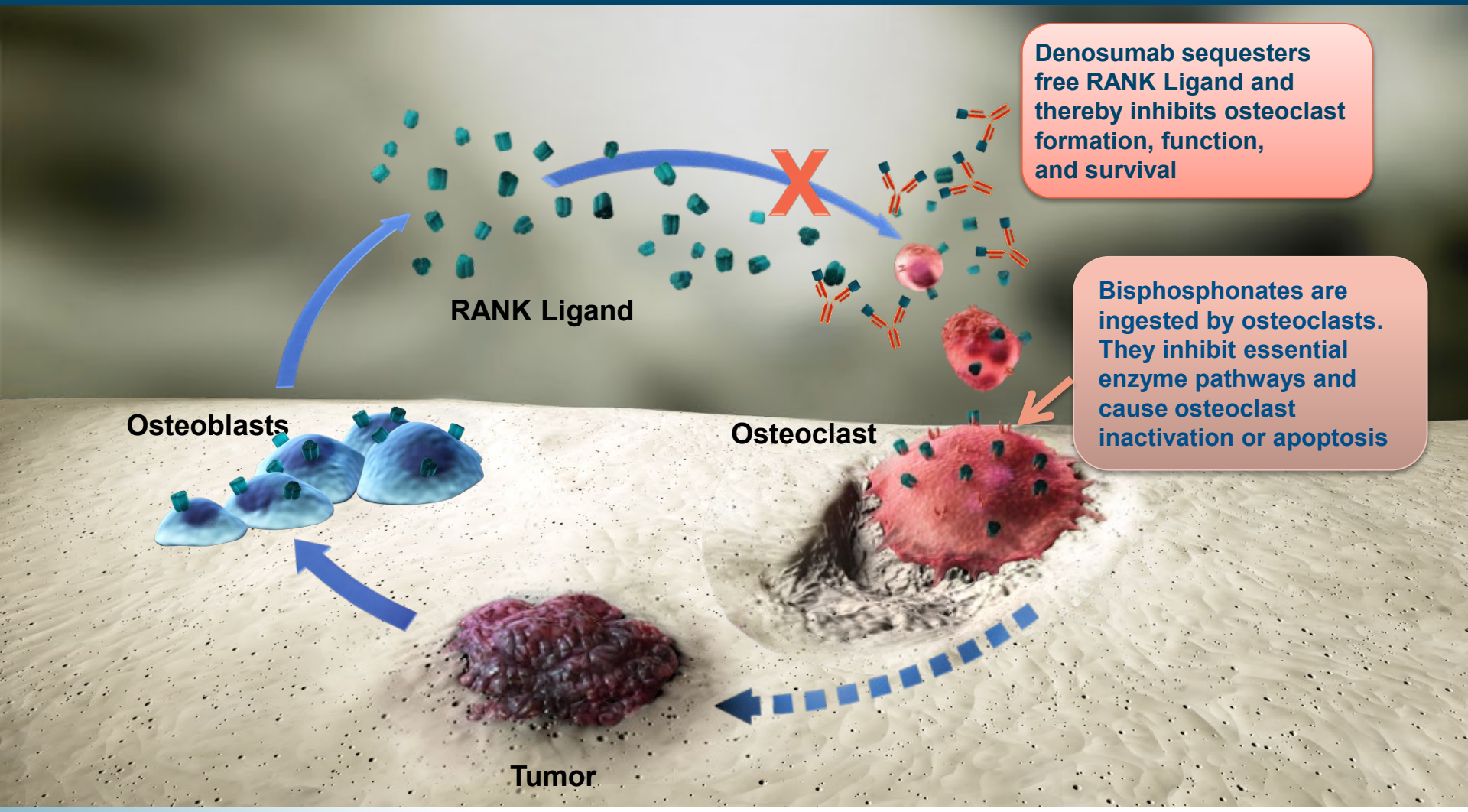
Denosumab MOA

Vicious Cycle of Bone Destruction in Prostate Cancer



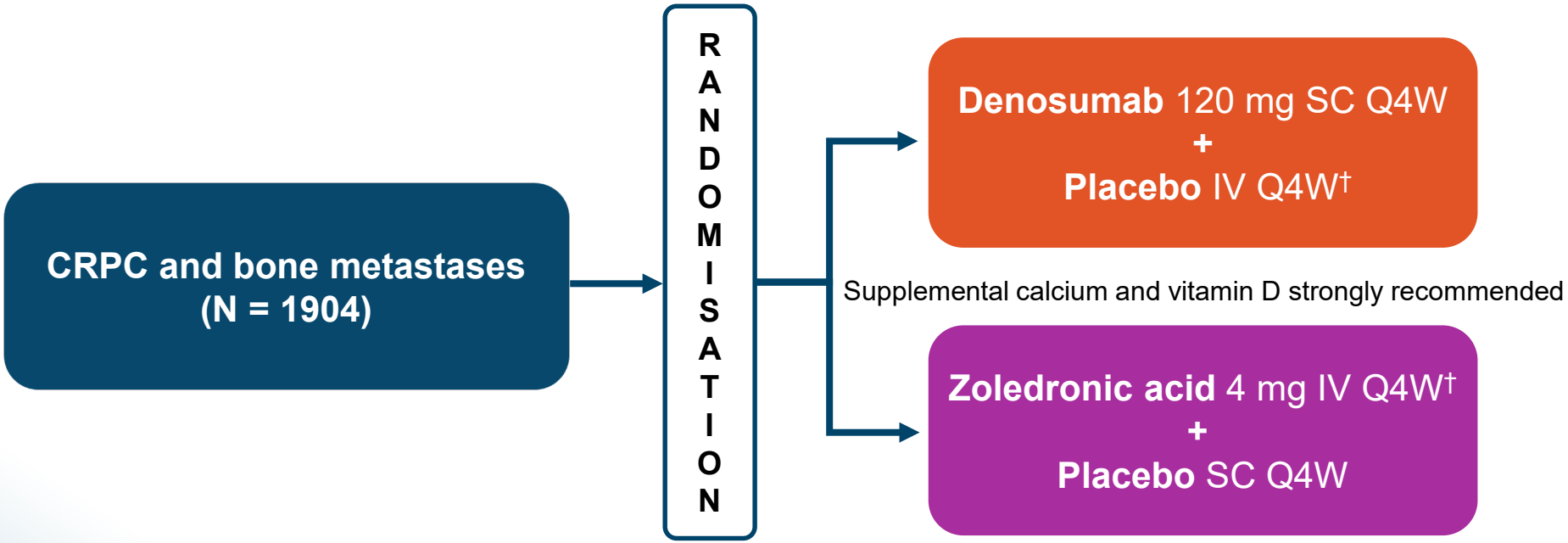
Adapted from Roodman GD. *N Engl J Med.* 2004;350:1655-1664.

Denosumab and Bisphosphonates Break the Vicious Cycle



Adapted from Roodman GD. *N Engl J Med.* 2004;350:1655-1664.

Phase 3 study 20050103
Denosumab vs zoledronic acid in men with CRPC and bone metastases



Primary endpoint:

Time to first on-study SRE (non-inferiority)

Secondary endpoints:

- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE (superiority, multiple event analysis)
- Safety and tolerability

†Per protocol and Zometa® (zoledronic acid) label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.

Fizazi K, et al. Lancet 2011;377:813–22.

Baseline Characteristics (1)

Characteristic	Denosumab (n=950)	Zoledronic Acid (n=951)
Median age, years (IQR)	71 (64-77)	71 (66-77)
<65, n (%)	253 (27)	216 (23)
≥65, n (%)	697 (73)	735 (77)
Race, n (%)		
White	829 (87)	810 (85)
Other	121 (13)	141 (15)
ECOG performance status of 0 or 1, n (%)	882 (93)	886 (93)
Time to randomization, months (IQR)		
From diagnosis of prostate cancer	37.5 (18.1-75.4)	41.2 (18.3-82.0)
From diagnosis of bone metastasis	3.94 (1.22-15.67)	5.19 (1.31-16.10)

IQR=interquartile range; ECOG=Eastern Cooperative Oncology Group

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Baseline Characteristics (2)

Characteristic	Denosumab (n=950)	Zoledronic Acid (n=951)
Presence of visceral metastases, n (%)	161 (17)	181 (19%)
Recent chemotherapy (≤ 6 weeks before randomization)*, n (%)	132 (14)	132 (14)
Hemoglobin concentration (g/l)	125 (16)	126 (16)
Creatinine clearance of ≥1.5 ml/s, n (%)	331 (35)	333 (35)
PSA at randomization (µg/l)*	58.5 (18.2-225.6)	60.0 (19.8-202.2)
<10 µg/l, n (%)	145 (15)	145 (15)
≥10 µg/l, n (%)	805 (85)	806 (85)

*Based on stratification at randomization
PSA=Prostate-specific antigen

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Baseline Characteristics (3)

Characteristic	Denosumab (n=950)	Zoledronic Acid (n=951)
Gleason score at diagnosis		
2-6	175 (18)	180 (19)
7	273 (29)	280 (29)
8-10	394 (41)	408 (43)
Missing	108 (11)	83 (9)
Bone turnover markers		
Bone-specific alkaline phosphatase (µg/l)	34.3 (17.5-90.0)	31.8 (17.2-82.2)
Urinary N-telopeptide (nmol/mmol)	53.9 (28.4-111.9)	49.7 (27.4-112.0)
Previous SRE, n (%)	232 (24)	231 (24)

SRE=Skeletal-related event

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Baseline Characteristics (4)

Characteristic	Denosumab (n=950)	Zoledronic Acid (n=951)
SRE status		
Prior SRE, n (%)	232 (24.4)	231 (24.3)
No prior SRE, n (%)	718 (75.6)	720 (75.7)
BP worst pain score, mean (SD)	3.9 (3.0)	3.9 (3.0)
0 to 4, n (%)	521 (54.8)	524 (55.1)
>4, n (%)	374 (39.4)	358 (37.6)
Missing, n (%)	55 (5.8)	69 (7.3)

Shore N, Smith M, Jievaltas M, et al. *ASCO 2011*: abstract 4533 and poster presentation.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Adjustments for Renal Function

Adjustments for Renal Function	Denosumab (n=942)	Zoledronic Acid (n=946)
Subjects with dose adjustments for creatinine clearance at baseline, n (%)	NA	213 (22)
Subjects with doses withheld for serum creatinine increases on study, n (%)	NA	143 (15)

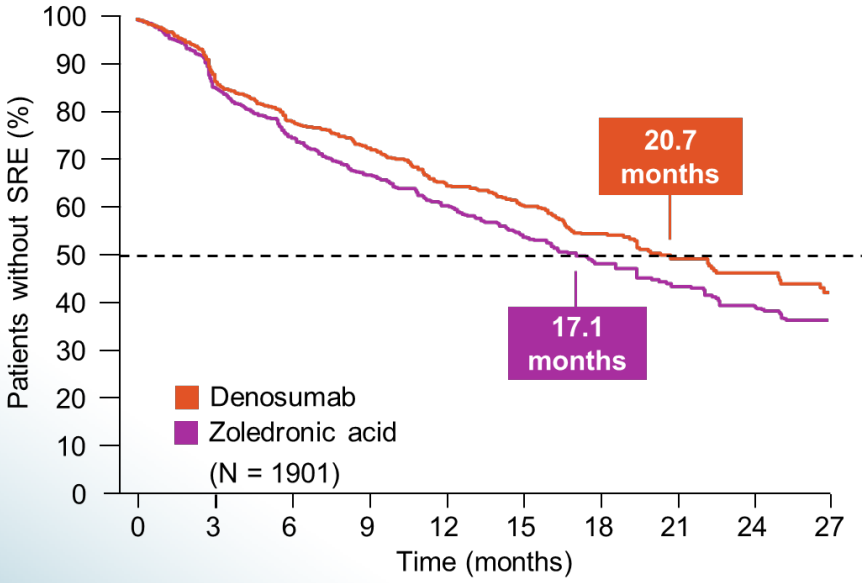
NA=not applicable per protocol

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

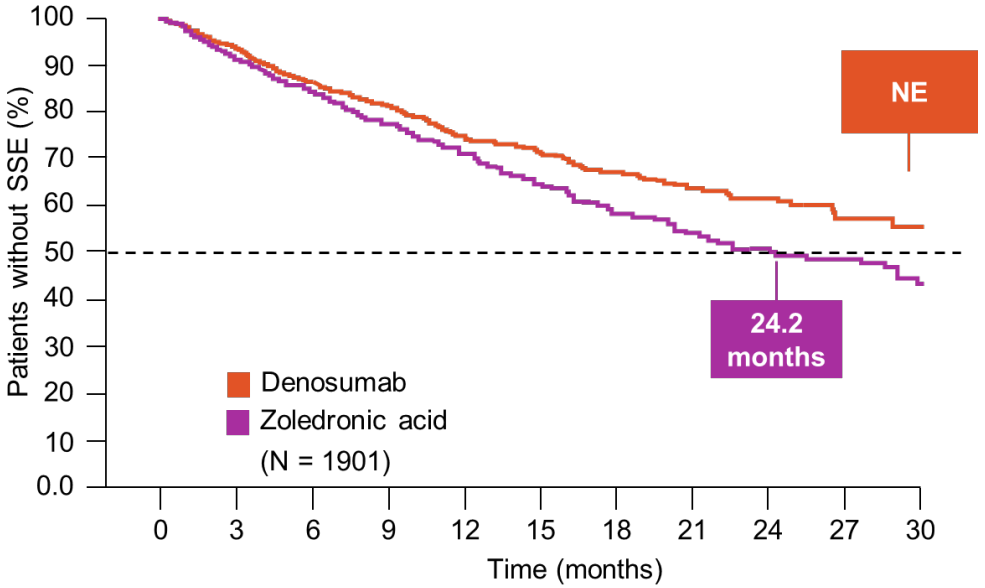
Phase 3 study 20050103
Denosumab significantly delayed time to first on-study SRE and SSE vs zoledronic acid

Time to first on-study SRE[1]



HR = 0.82
(95% CI, 0.71–0.95)
P = 0.008 (superiority)

Time to first on-study SSE[2†]



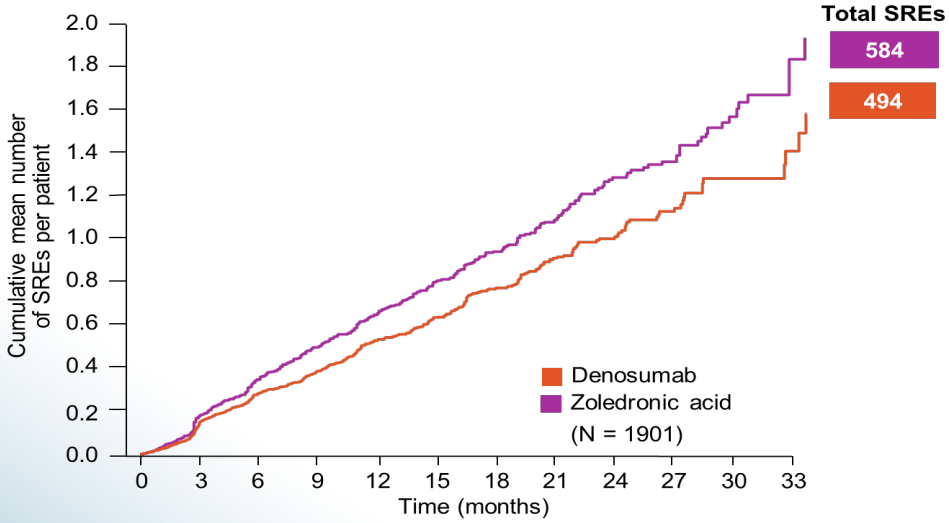
HR = 0.78
(95% CI, 0.66−0.93)
P = 0.005

1. Fizazi K, et al. Lancet 2011;377:813–22;
2. Smith MR, et al. Ann Oncol 2015;26:368−74.

†Post-hoc analysis.
NE, not estimable (not yet reached).

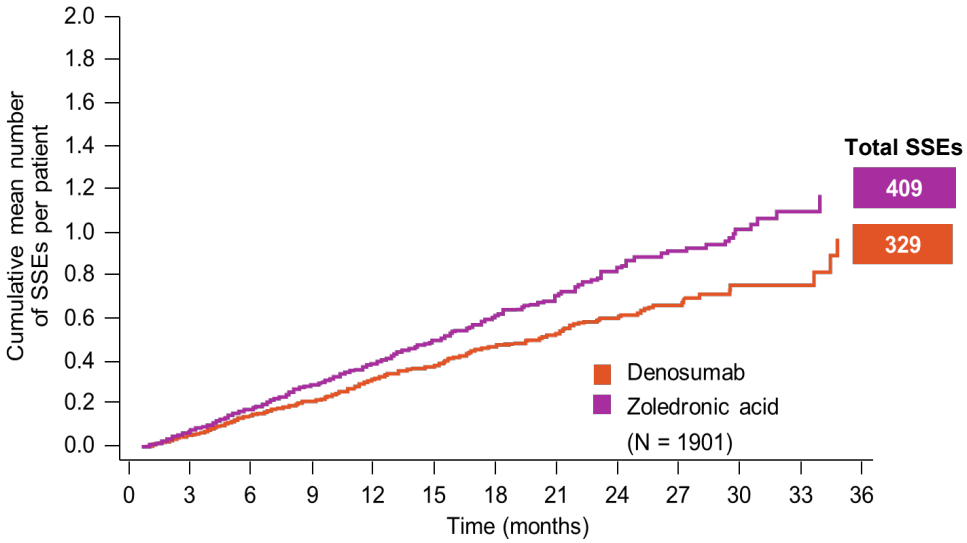
Phase 3 study 20050103
Denosumab significantly reduced the total number of SREs and SSEs vs zoledronic acid

Time to first and subsequent on-study SRE[1]



Rate ratio = 0.82
(95% CI, 0.71–0.94)
P = 0.008 (superiority)

Time to first and subsequent on-study SSE[2†]



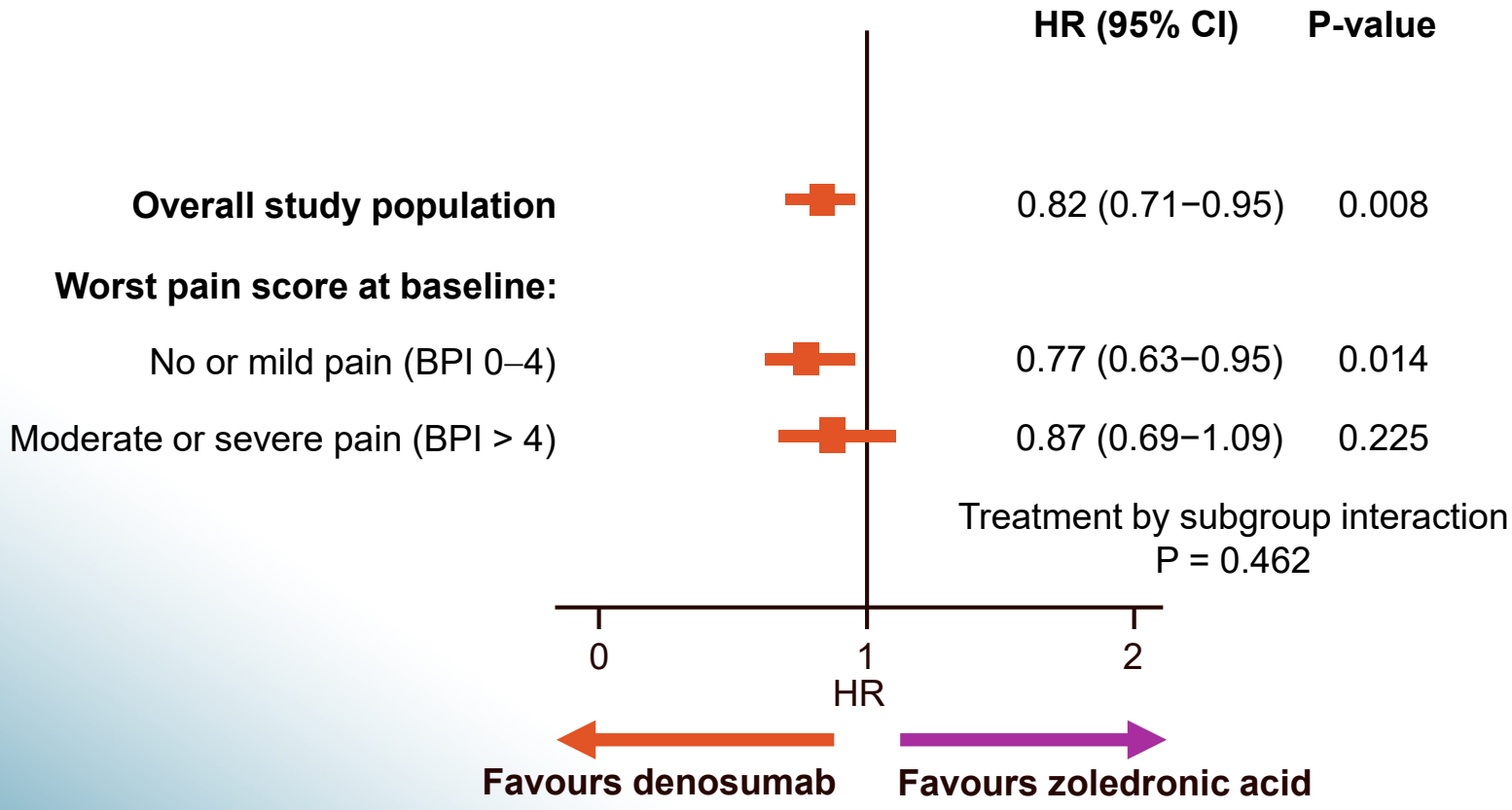
Rate ratio = 0.78
(95% CI, 0.65−0.92)
P = 0.004

1. Fizazi K, et al. Lancet 2011;377:813–22;
2. Smith MR, et al. Ann Oncol 2015;26:368−74.

†Post-hoc analysis.

Phase 3 study 20050103
Denosumab delayed time to first SRE vs zoledronic acid regardless of pain status at baseline

Time to first SRE by worst pain score at study entry



Shore ND, et al. J Clin Oncol 2011;29(Suppl):abstract 4533 (and poster).

BPI, Brief Pain Inventory – Short Form.

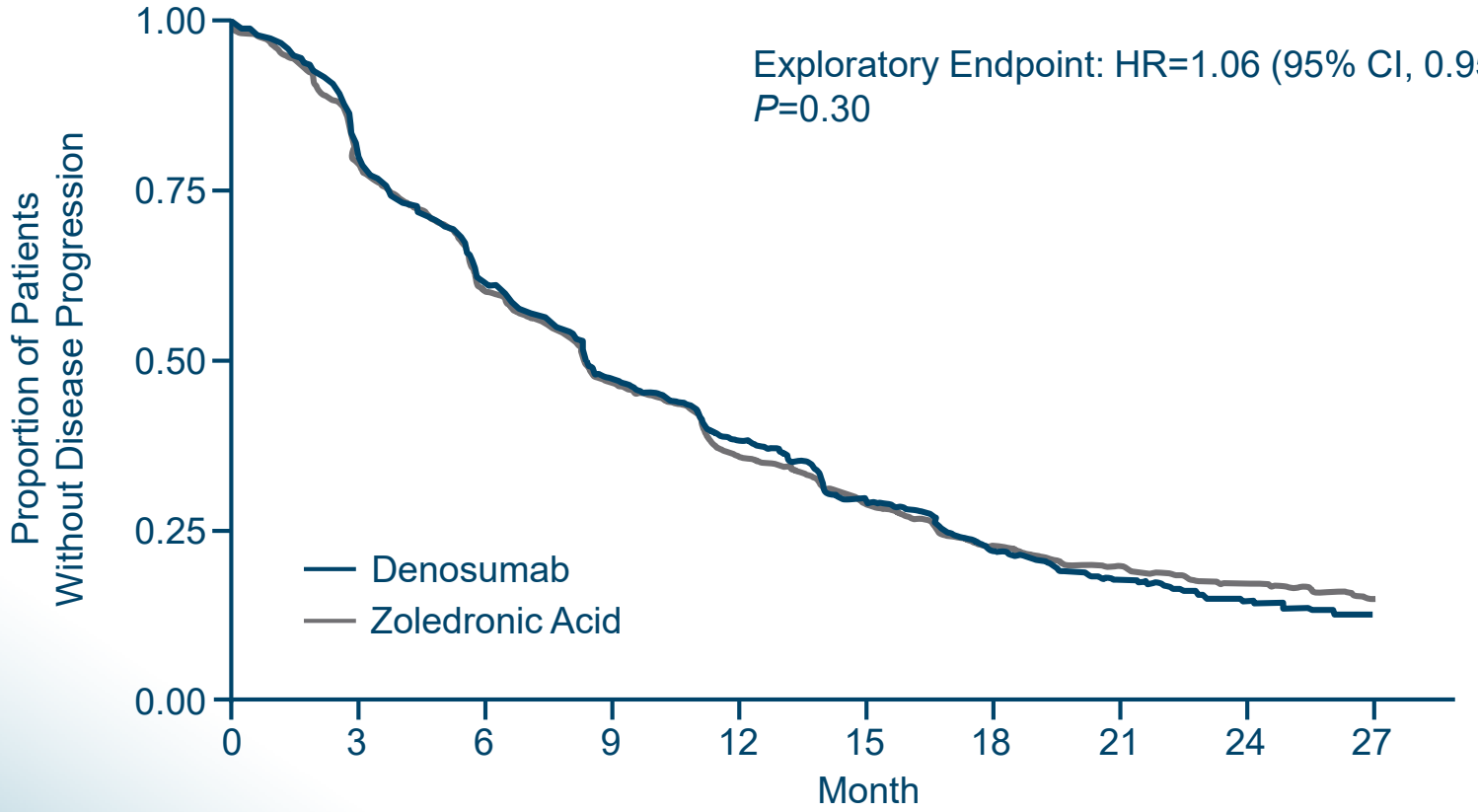
First On-Study SRE by Type

Patient Incidence	Denosumab (n=950) n (%)	Zoledronic Acid (n=951) n (%)
Total confirmed events	341 (36)	386 (41)
Radiation to bone	177 (19)	203 (21)
Pathological fracture	137 (14)	143 (15)
Spinal cord compression	26 (3)	36 (4)
Surgery to bone	1 (<1)	4 (<1)

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Time to Disease Progression

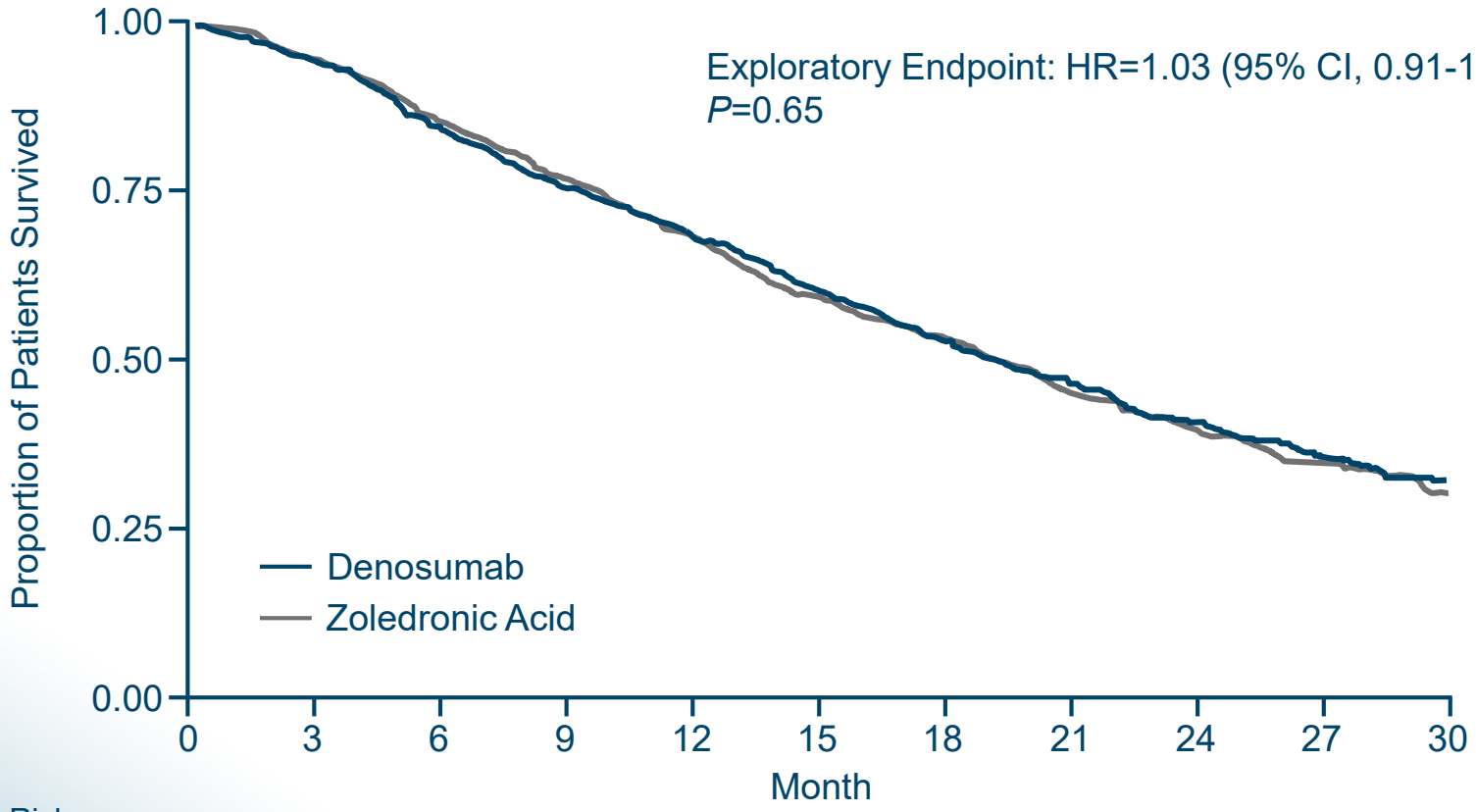


Patients at Risk:										
Denosumab	950	715	518	370	273	180	111	71	51	32
Zoledronic Acid	951	708	507	356	246	168	108	74	50	33

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Overall Survival



Patients at Risk:											
Denosumab	950	872	746	645	552	427	310	233	156	99	54
Zoledronic Acid	951	864	745	635	519	401	297	207	143	98	55

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Phase 3 study 20050103
Safety results of interest

AE, %[1]	Zoledronic acid (n = 945)	Denosumab (n = 943)
Infectious AEs	375 (40)	402 (43)
Acute phase reactions (first 3 days)*	168 (18)	79 (8)
Cumulative ONJ (total)† Year 1 Year 2	12 (1) 5 (1) 8 (1)	22 (2) 10 (1) 22 (2)
Hypocalcaemia, all grades Hypocalcaemia, Grade 3 or 4	55 (6) 13 (1)	121 (13)‡ 48 (5)‡
New primary malignancy	10 (1)	18 (2)

1. Fizazi K, et al. Lancet 2011;377:813–22;
2. Denosumab (XGEVA®) Summary of Product Characteristics, Amgen.

*Flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias and myalgias. †P = 0.09. ‡P < 0.0001; §Pooled data from breast and prostate cancer patients participating in an open-label extension study. ONJ, osteonecrosis of the jaw.

Minimizing the Risk of Hypocalcemia During Denosumab 120 mg Q4W Treatment

Pre-existing hypocalcemia must be corrected prior to initiating therapy

Supplementation with calcium and vitamin D is required in all patients unless hypercalcemia is present

Monitoring of calcium levels should be conducted:

- Prior to the initial dose of denosumab
- Within 2 weeks after the initial dose
- If suspected symptoms of hypocalcemia occur

Consider monitoring calcium levels more frequently in patients with risk factors for hypocalcemia (eg, patients with severe renal impairment, creatinine clearance < 30 ml/min), or if otherwise indicated based on the clinical condition of the patient

- Risk of hypocalcemia increases with the degree of renal impairment

Tell patients to report symptoms of hypocalcemia

If hypocalcemia occurs, additional calcium supplementation and monitoring may be necessary

Denosumab (XGEVA®). Summary of Product Characteristics, Amgen. 2013.

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Preventing and Managing ONJ

Risk factors[1,2]	■ Invasive dental procedures ■ Poor oral hygiene or pre-existing dental disease ■ Advanced malignancies, infections, concomitant therapies
Before bone-targeted treatment	■ Consider dental examination and preventive dentistry in patients[1–3] with active dental/jaw conditions[2]
During treatment	■ Avoid invasive dental procedures[1,2] ■ Maintain good oral hygiene[1]
Suspected cases	■ Refer to dentist or oral surgeon[1] ■ Extensive dental surgery may exacerbate[1]

ONJ = osteonecrosis of the jaw.

1. Denosumab (XGEVA®). Summary of Product Characteristics, Amgen. 2013.
2. Zoledronic acid (Zometa®) Summary of Product Characteristics, Novartis. 2012. 3. Van Poznak CH, et al. *J Clin Oncol.* 2011:29;1221-1227.

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Summary

- Denosumab was superior to zoledronic acid in delaying the time to
  - First SRE
  - First and subsequent SRE(s)
- Notable adverse events occurring in both treatment groups included ONJ and hypocalcemia
  - Hypocalcemia was more frequent in the denosumab arm
  - Incidence of ONJ was similar between arms and not statistically significantly different (initial and 2-year analysis)
- Denosumab had several select attributes
  - Administered as a 120 mg SC injection once every 4 weeks
  - No dose adjustment necessary for patients with renal impairment
  - Fewer acute phase reactions in the denosumab arm

Fizazi K, Carducci M, Smith M, et al. *Lancet* 2011;377:813-22.

Denosumab (120 mg Q4W) is approved for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Summary

- Denosumab and zoledronic acid delay time to skeletal complications† in patients with CRPC and bone metastases[1–3]
  - Denosumab significantly delayed time to first (and time to first and subsequent) on-study SRE and SSE vs zoledronic acid[2,3]
- Concomitant use of a bone-targeting antiresorptive agent with either radium-223 or abiraterone may have an added clinical benefit in patients with CRPC and bone metastases, including delaying the time to symptomatic progression[4–6]
  - Preliminary evidence suggests potential OS benefit[4,6]
- A bone-targeting agent (denosumab or zoledronic acid) should be started in patients with CRPC and bone metastases, whether they are symptomatic or not[7]
- Bone-targeting antiresorptive therapy remains clinically relevant in the era of an emerging portfolio of new treatments for mCRPC

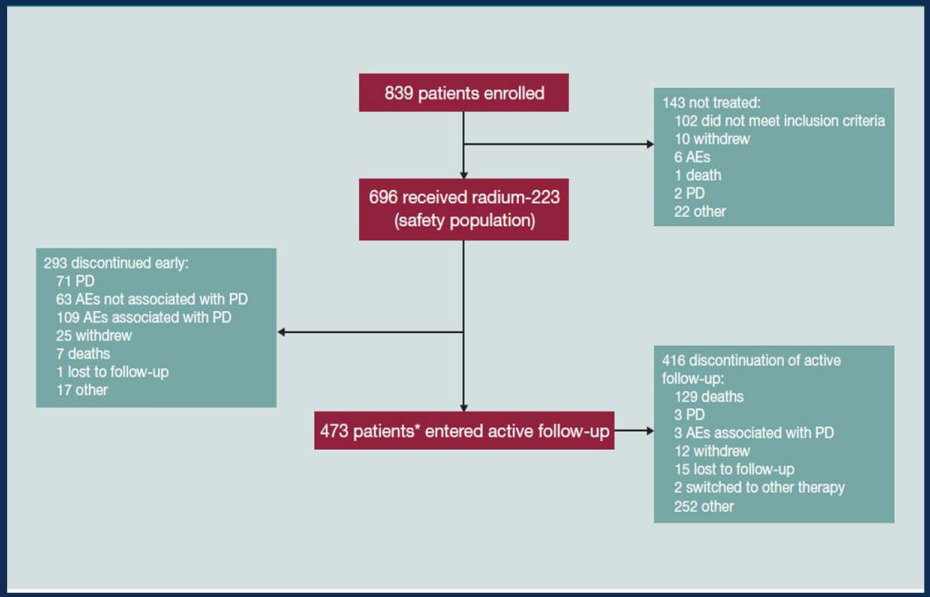
1. Saad F, et al. J Natl Cancer Inst 2002;94:1458–68; 2. Fizazi K, et al. Lancet 2011;377:813–22;
3. Smith MR, et al. Ann Oncol 2015;26:368−74; 4. Saad F, et al. Eur Urol 2015;68:570–7;
5. Sartor O, et al. Lancet Oncol 2014;15:738–46; 6. Saad F, et al. J Clin Oncol 2015;33(Suppl):abstract 5034 (and poster); 7. Coleman R, et al. Ann Oncol 2014;25(Suppl 3):iii124−37.

†vs zoledronic acid and placebo, respectively.

Concomitant use of mCRPC treatments and anti-resorptive bone-targeted agents

Concomitant therapies with radium 223: abiraterone and denosumab

Radium in the real world



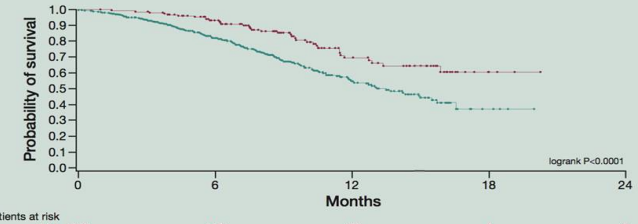
Saad et al. ASCO 2015

Concomitant therapies with radium 223: abiraterone and denosumab

Concomitant Abiraterone

Figure 7. OS in patients grouped by concomitant abiraterone use at baseline

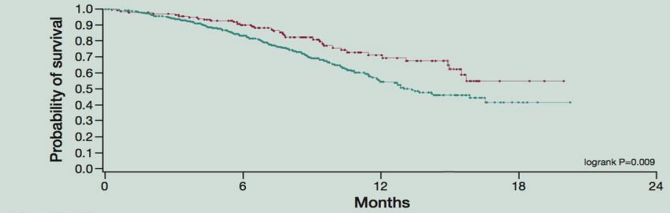
	Current use of abiraterone (N=696) Yes	No
Patients, n	156	540
No of events (%)	35 (22%)	175 (32%)
No of censored patients (%)	121 (78%)	365 (68%)
Median OS, months (95% CI)	NA (16–NE)	14 (12–16)



Concomittant Denosumab

Figure 8. OS in patients grouped by concomitant denosumab use at baseline

	Concomitant use of denosumab (N=696) Yes	No
Patients, n	138	558
No of events (%)	35 (25%)	175 (31%)
No of censored patients (%)	103 (75%)	383 (69%)
Median OS, months (95% CI)	NA (15–NE)	13 (12–NE)



Saad et al. ASCO 2015

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