



**Contemporary Management
Strategies for Patients with
Hormone-Refractory
Prostate Cancer (HRPC)**

Objectives



To assist Canadian urologists, oncologists, radiation oncologists, internists, palliative care physicians in their decision making process, daily practice, and other aspects of the contemporary management of advanced prostate cancer by:

- Providing an overview of the latest clinical trial data in the management of Hormone-Refractory Prostate Cancer (HRPC)**
- Establishing optimal interventions and therapeutic strategies in patients with HRPC**
- Examining the evolving role of zoledronic acid and docetaxel in the contemporary management of HRPC**

HRPC – Definitions

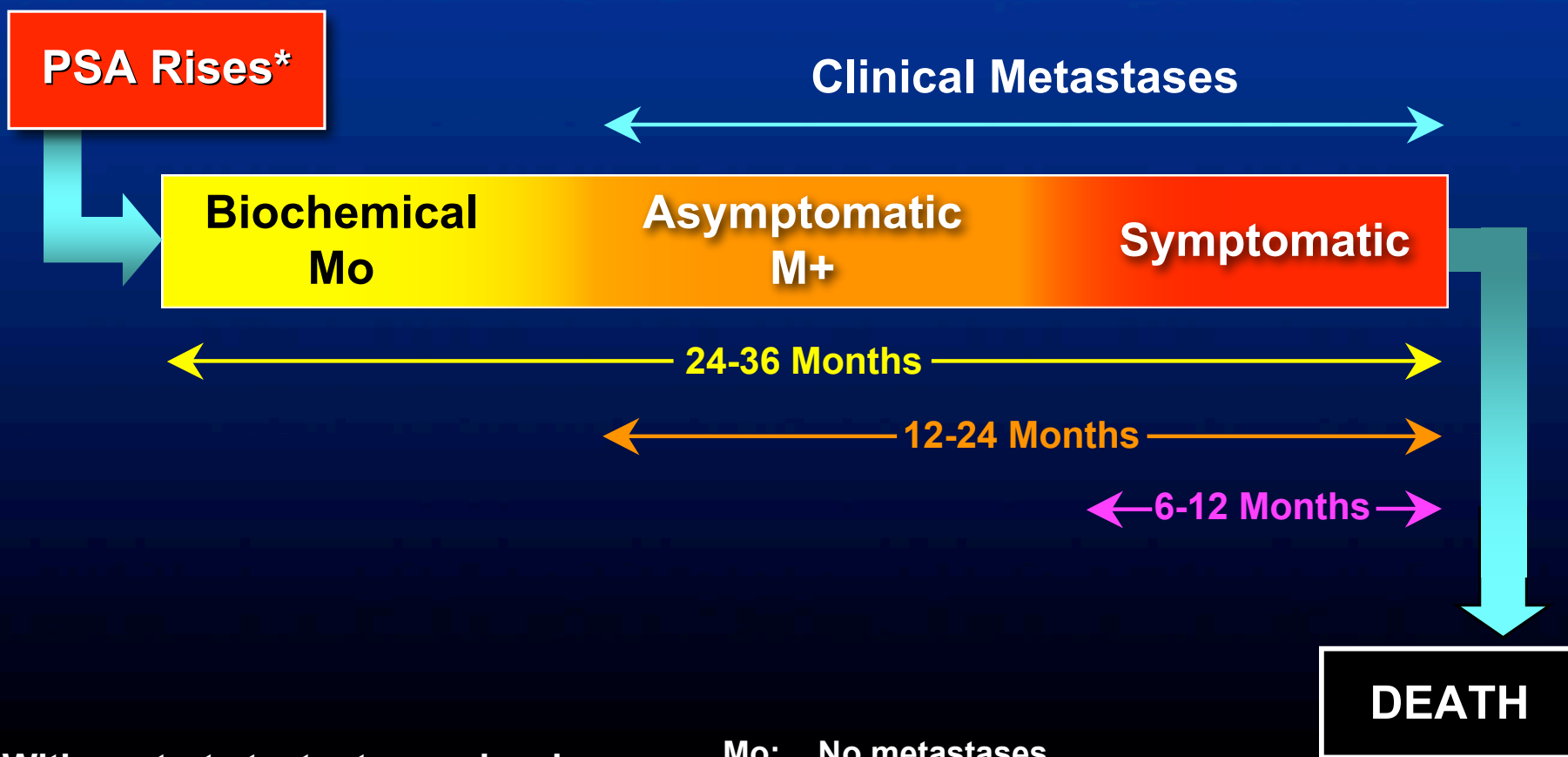


- **Presence of castrate testosterone levels and one or more of the following:**
 - Radiologic progression (asymptomatic and symptomatic)
 - Clinical progression
 - PSA progression
 - Serial rise in PSA with castrate testosterone levels (\leq 50 ng/dL)

Progression of Advanced Prostate Cancer



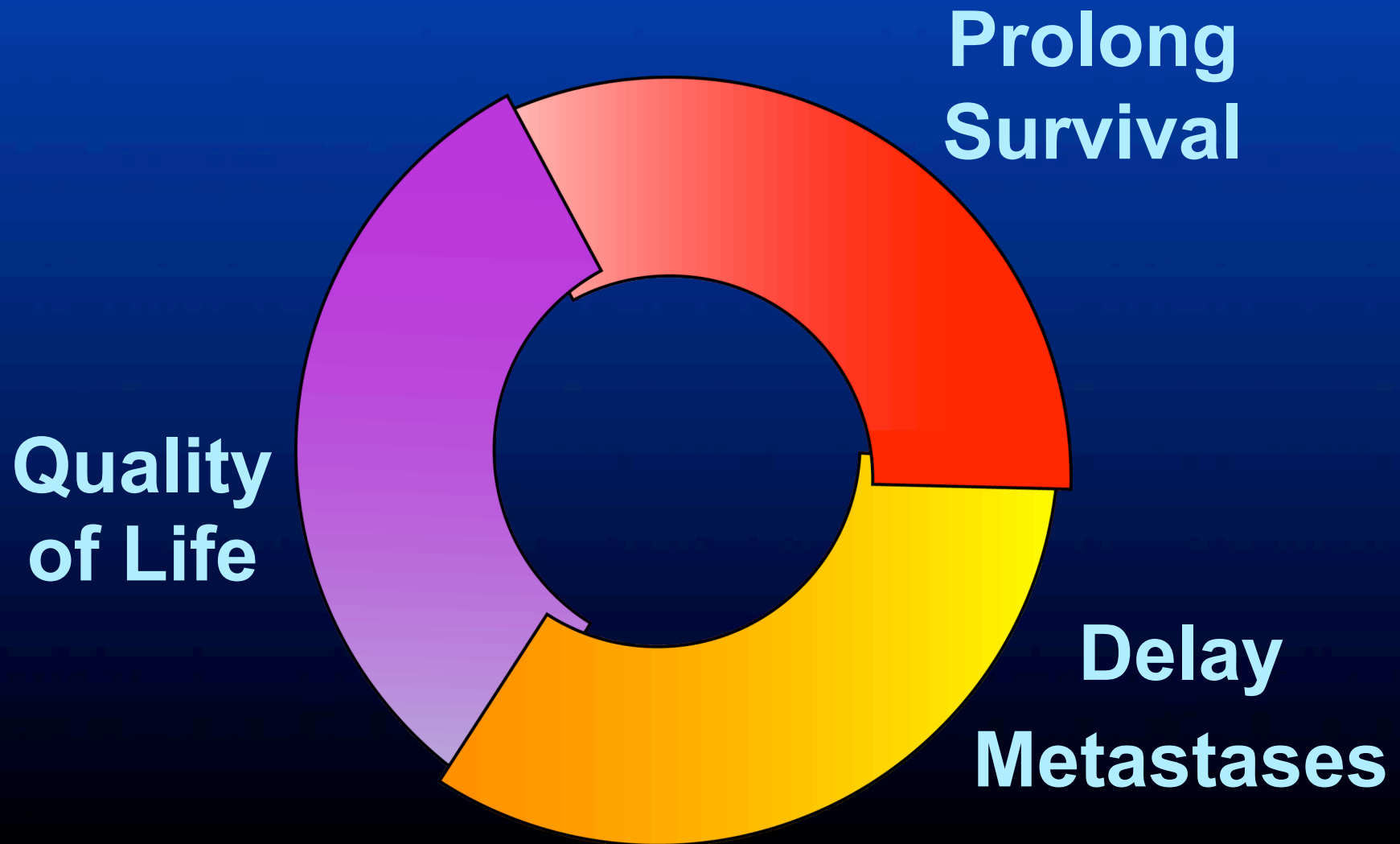
HORMONE REFRACTORY PROSTATE CANCER



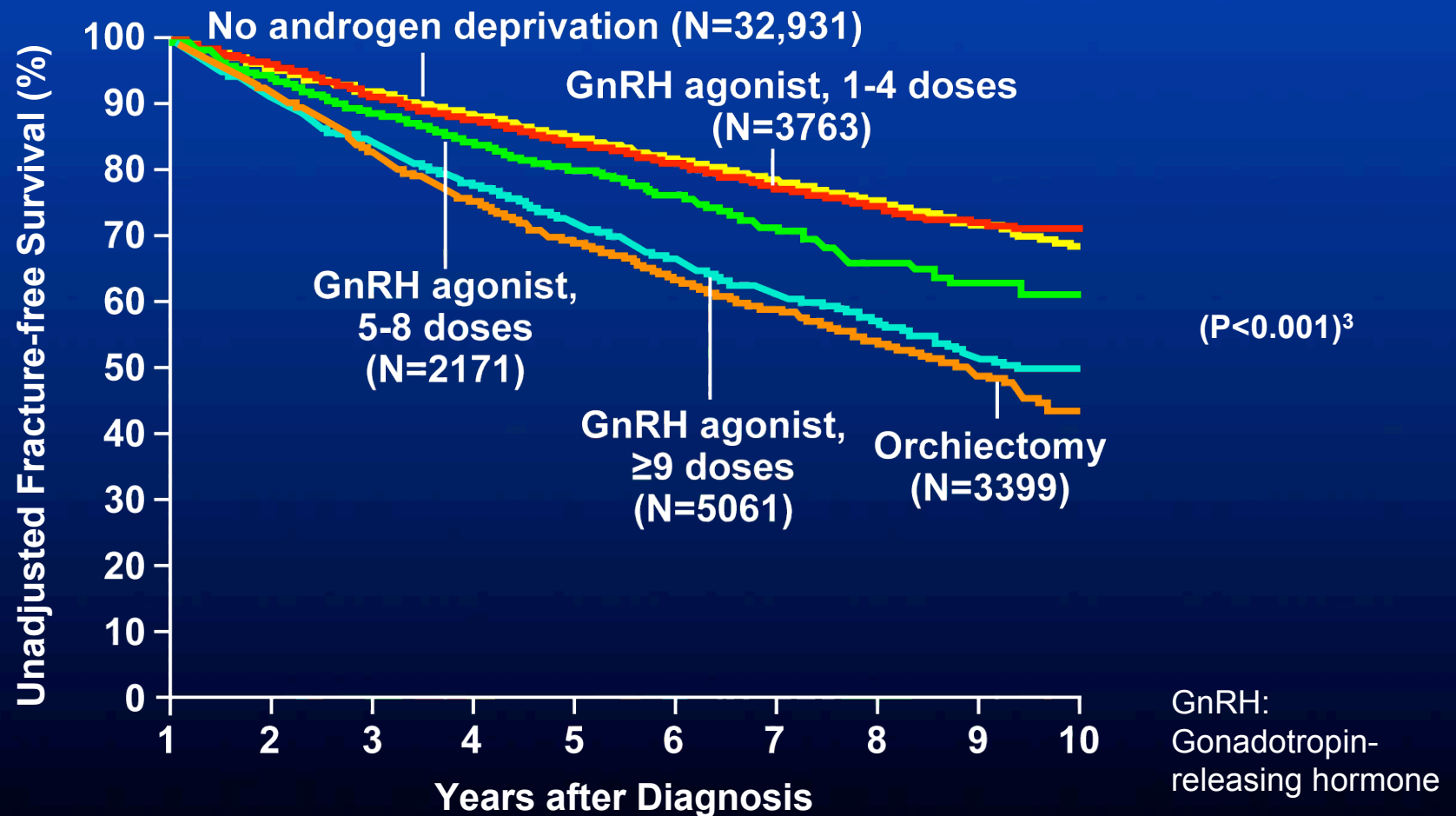
* With castrate testosterone levels

Mo: No metastases
M+: Presence of metastases

HRPC – Goals of Therapy



Bone Complications in Prostate Cancer



HRPC – Considerations



- **The MAJOR problem in HRPC is related to BONE:**
 - Approximately 65% to 75% of patients will develop bone metastases
 - Patients with bone metastases are at high risk of developing multiple bone complications

HRPC – Considerations



- **Bone complications:**

- Bone pain is the most common cause of cancer-related pain and often requires palliative radiotherapy¹
- Bone complications have been correlated with reduced overall survival² and Quality of Life³ in retrospective studies and subset analyses

- **Heterogeneity of the disease:**

- Unpredictable prognosis and response to therapy
- Markers need to be further validated to identify patients who are more or less likely to have better outcomes

1. Mercadante S. *Pain* 1997;69:1-18; 2. Oefelein MG, et al. *J Urol* 2002;168:1005-1007;
3. Weinfurt KP, et al. *Ann Oncol* 2002;13(Suppl 5):180(Abstract 662P).

Progression of Advanced Prostate Cancer



HORMONE REFRACTORY PROSTATE CANCER

PSA Rises*

Clinical Metastases

**Biochemical
Mo**

**Asymptomatic
M+**

Symptomatic

24-36 Months

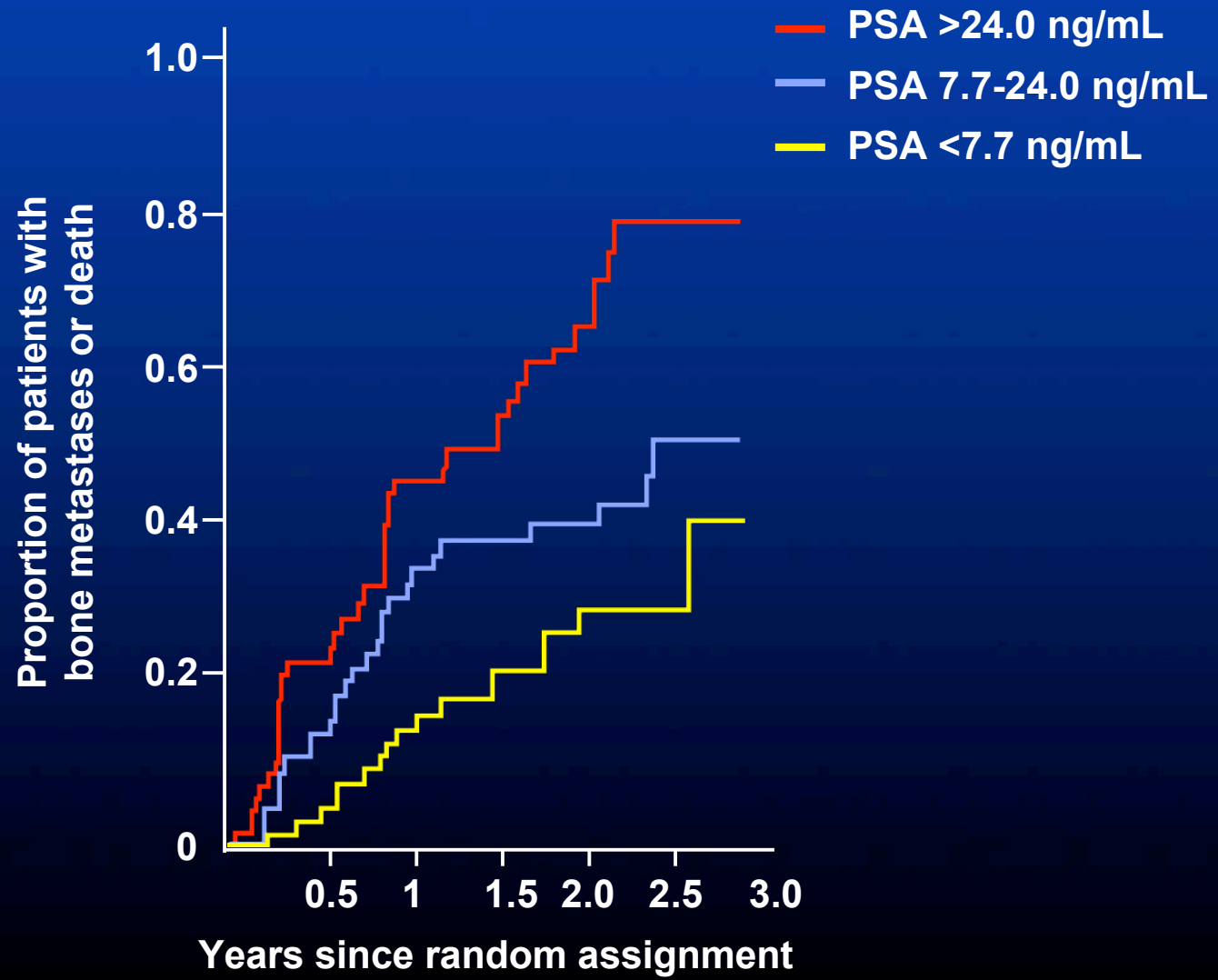
12-24 Months

6-12 Months

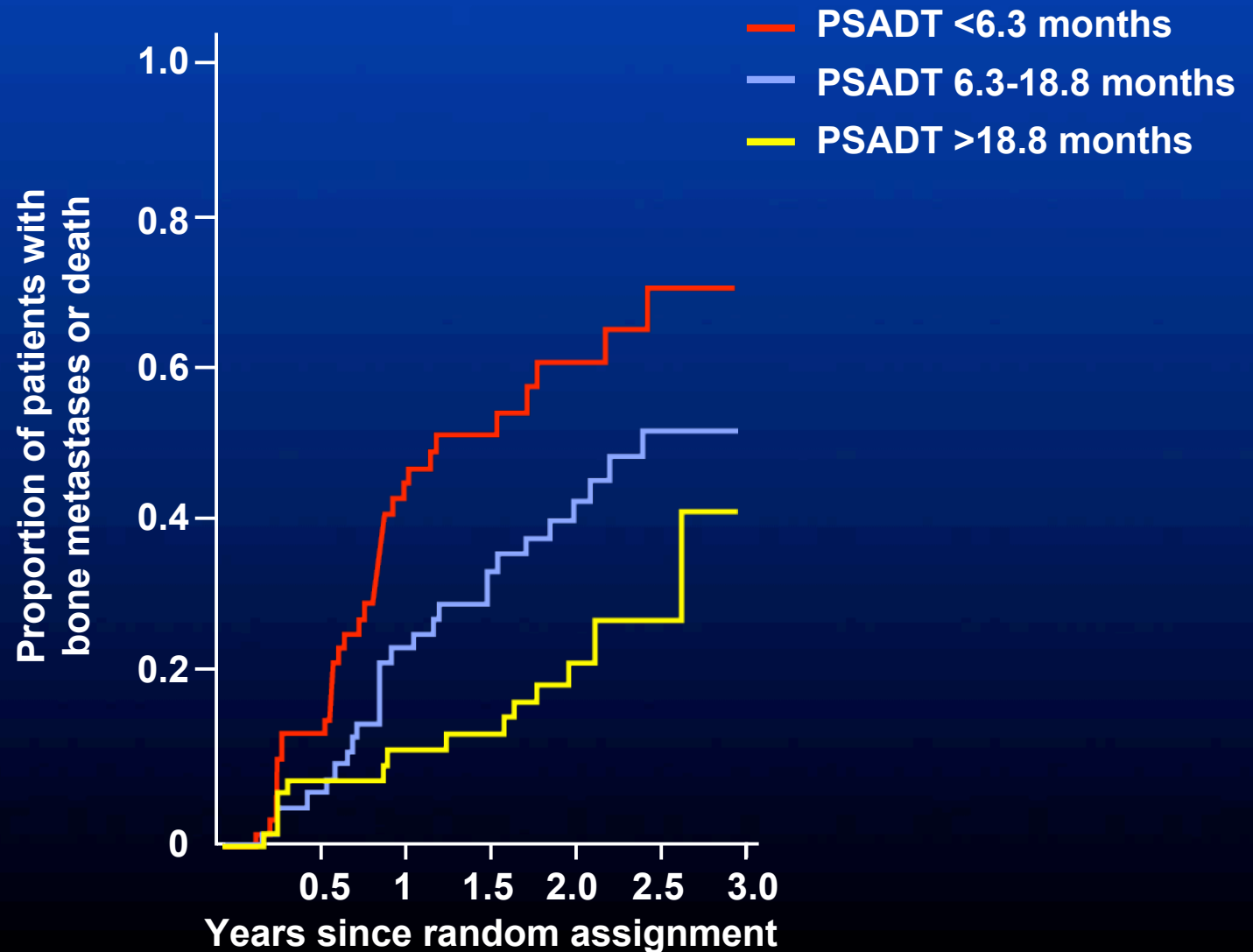
DEATH

* With castrate testosterone levels

Rising PSA in Non-Metastatic HRPC: PSA Levels



Rising PSA in Non-Metastatic HRPC: PSA Doubling Time (PSADT)



Treatment Options for HRPC



- **Second-line hormonal manipulations**
- **Radiation therapy /
Radiopharmaceuticals**
- **Bisphosphonates**
- **Chemotherapy**
- **Novel / Investigational agents**

Treatment Options for HRPC



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Should Primary Hormonal Therapy Be Continued?



- **No prospective studies designed to answer this question**
- **Retrospective data analyses are conflicting and address survival rather than quality of life**
- **All trials require continuation of LHRH**
 - **Distant metastasis expresses the androgen receptor, which remains functional**
- **If LHRH is not continued, testosterone needs to be monitored**

LHRH: Lutenizing hormone-releasing hormone

Summary of Hormonal Manipulation Clinical Management



- Maintain castrate testosterone level
- Trial of AA if no prior AA
- If on AA, stop and look for AAW response
- Change of AA (ie, second-line AA)
- Other hormonal maneuvers
 - Ketoconazole + hydrocortisone
 - Low-dose corticosteroids
 - Estrogenic therapy
- Do these change natural history?

Sartor AO, et al. 38th Annual Meeting of the American Society of Clinical Oncology; May 18-21, 2002; Orlando, USA. Abstract 785.

Kucuk O, et al. *Urology* 2001;58:53-58.

Desai A, et al. *Urology* 2001;58:1016-1020.

AA: Antiandrogen

AAW: Antiandrogen Withdrawal

Second-line Hormonal Maneuvers: Prospective Randomized Phase II Trial



AAW Alone vs. AAW plus Ketoconazole / HC N = 260

	AAW Alone	AAW + Ketoconazole / HC	AAW ≥ Ketoconazole (Crossover)
PSA Response Rate	11%	27%	32%
		<i>P=0.0002</i>	
Objective Response Rate	2%	20%	7%
		<i>P=0.020</i>	

Methodological Issues:

- QoL was not assessed
- No difference in survival was observed, though the study was not designed to test early versus late use of ketoconazole

Phase III Studies of Steroid Synthesis Inhibitors



EORTC: Flutamide vs. Prednisone

N = 201 symptomatic patients

	TTP	OS	Palliative Response	Median Response Duration	PSA Response
Flutamide	2.3	11.2	45%	4.2 m	23%
Prednisone	3.4	10.6	56%	4.8 m	21%
P value	NS	NS	NS	NS	NS

The QoL assessment parameters favored the use of prednisone with statistically significant differences in pain, fatigue, role functioning, appetite loss, gastrointestinal distress, and overall QoL.

Clinical Impact of Second-line Hormonal Manipulation Therapy

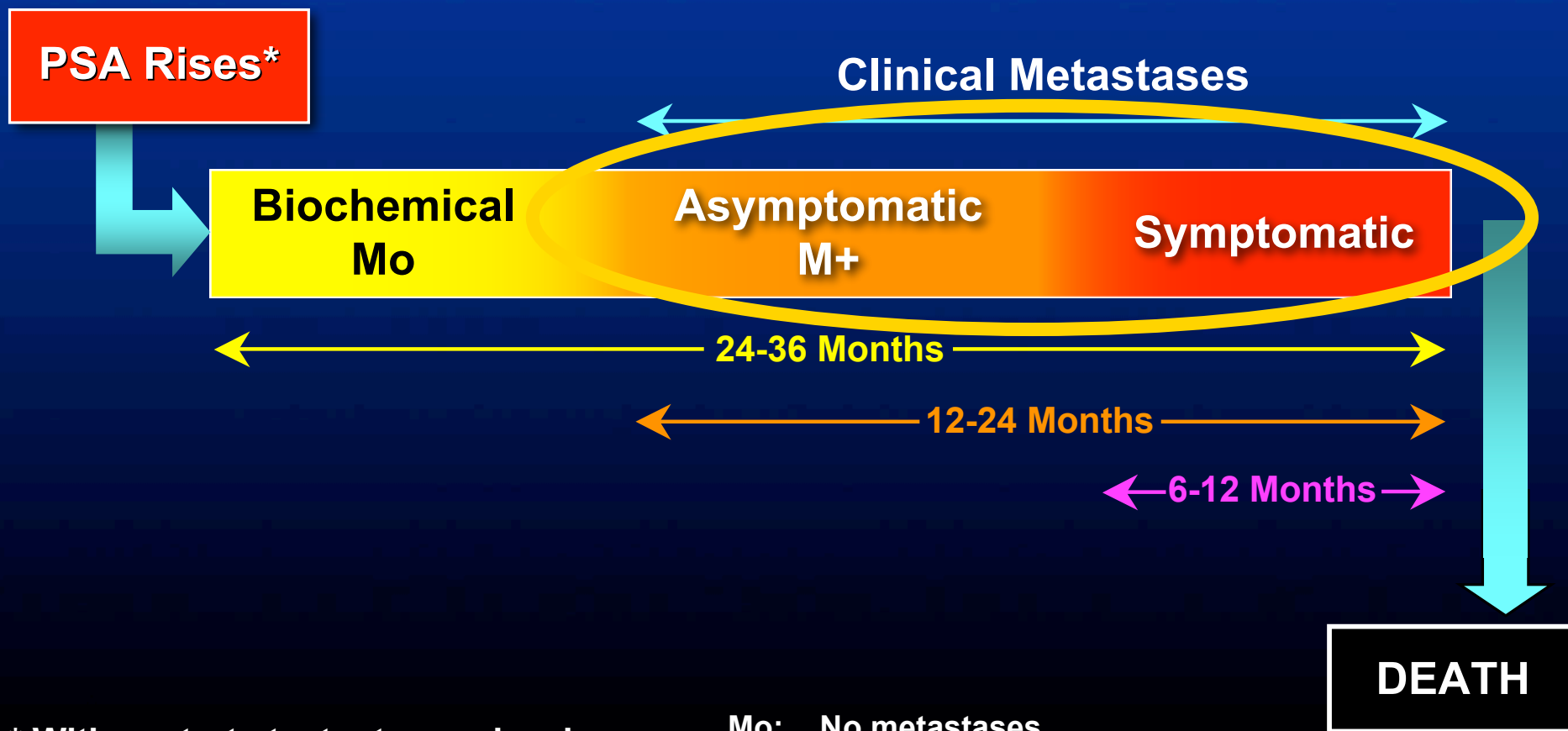


- **Clinical and objective responses**
 - PSA response in about 20% - 30% of patients, but typically has only short-term value
- **Minimal side effects**
- **No survival benefit has been shown**
- **Short-term quality of life benefits**

Progression of Advanced Prostate Cancer



HORMONE REFRACTORY PROSTATE CANCER



* With castrate testosterone levels

Mo: No metastases

M+: Presence of metastases

Treatment Options for HRPC



- Second-line hormonal manipulations
- **Radiation therapy /
Radiopharmaceuticals**
- Bisphosphonates
- Chemotherapy
- Novel / Investigational agents

Radiation Therapy



- **External beam radiation**
 - **Single versus multiple fractions**
 - Equal palliation and quality of life benefits
 - Higher re-treatment rate associated with single fraction may not necessarily lower therapeutic efficacy
 - **Provides pain relief in up to 80% of patients**
 - **Improves quality of life**
 - **Rare myelosuppression**

Radiation Therapy



- **Radiopharmaceuticals**

- **Strontium-89 and samarium-153**

- **Strontium-89 can cause transient myelosuppression ranging from mild to severe**

- **Strontium-98 is therefore reserved for patients who will not be considered for chemotherapy in further treatment plans**

- **Usually reserved for patients with diffuse bone pain secondary to widespread bone metastases**

Clinical Impact of Radiation Therapy



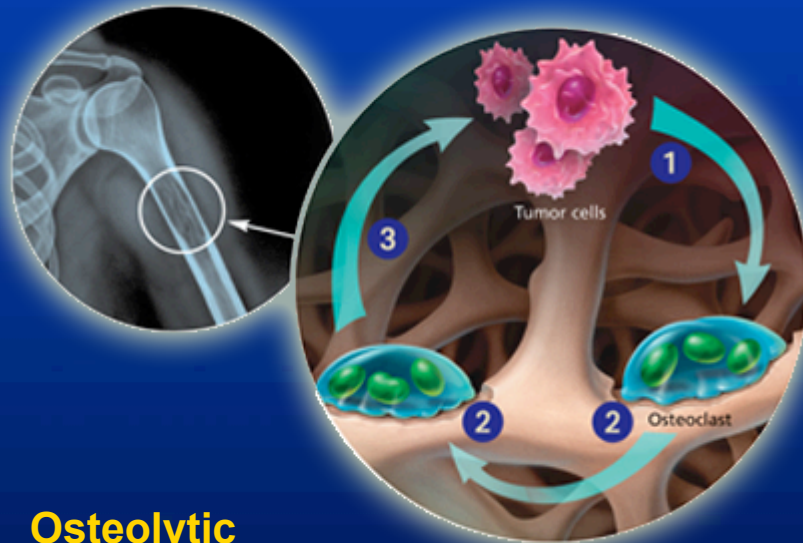
- Palliation of bone pain
- Well tolerated
- Temporary or prolonged myelosuppression

Treatment Options for HRPC



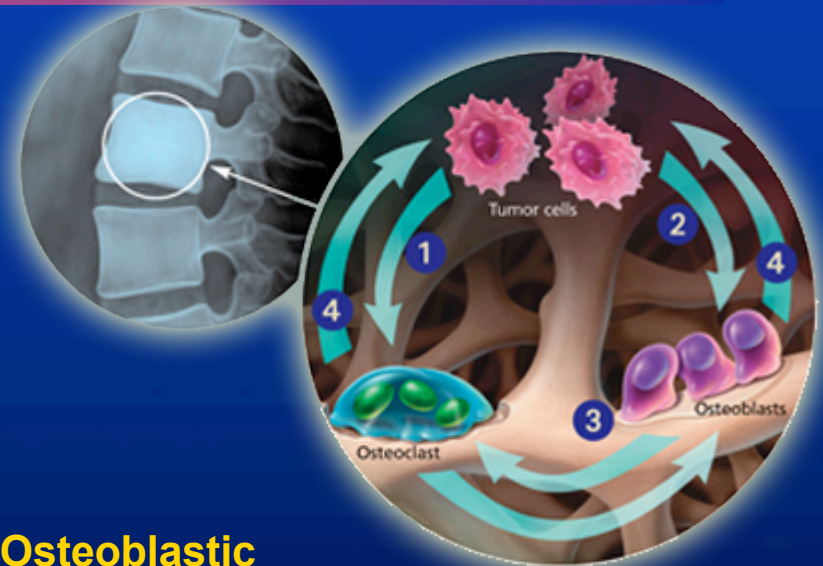
- Second-line hormonal manipulations
- Radiation therapy /
Radiopharmaceuticals
- **Bisphosphonates**
- Chemotherapy
- Novel / Investigational agents

Pathogenesis of Osteolytic and Osteoblastic Bone Metastases: An Ongoing and Aggressive Cycle



Osteolytic metastasis

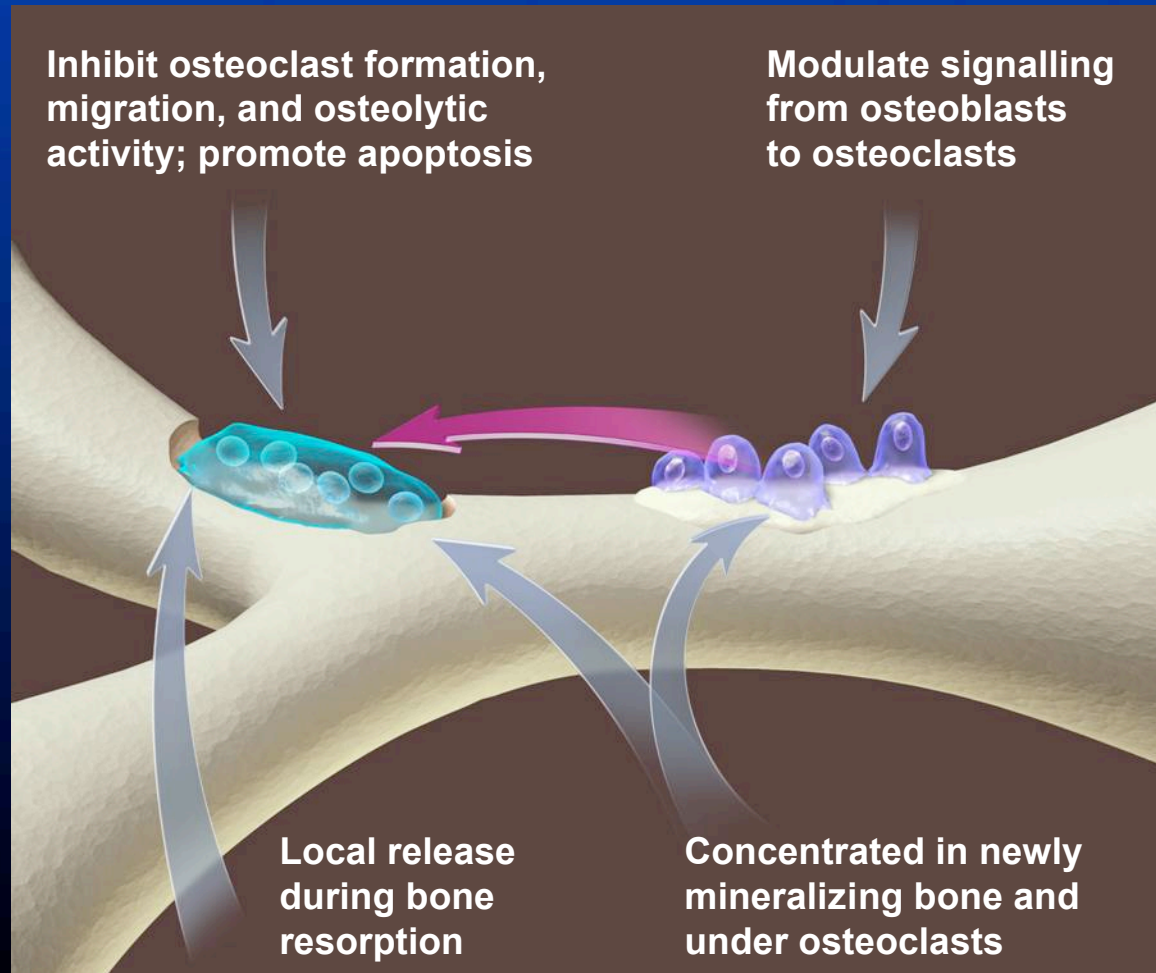
1. Tumor cells secrete humoral factors that induce osteoclast recruitment
2. Osteoclasts resorb bone
3. Bone resorption stimulates the release of growth factors that stimulate additional tumor growth, further driving the destructive cycle



Osteoblastic metastasis

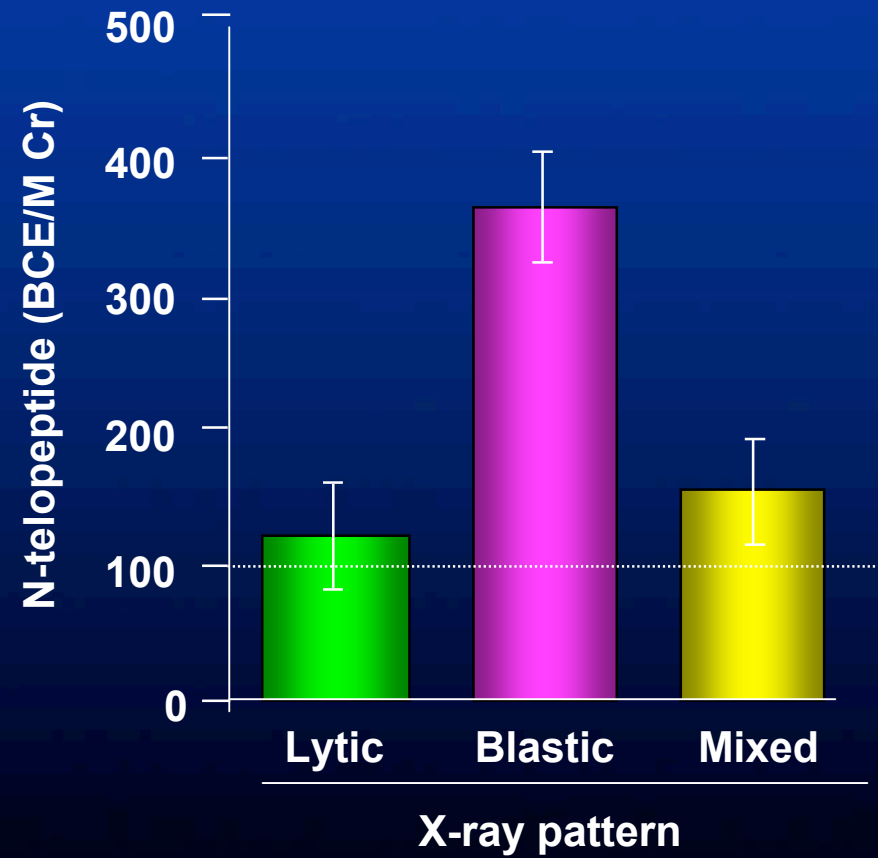
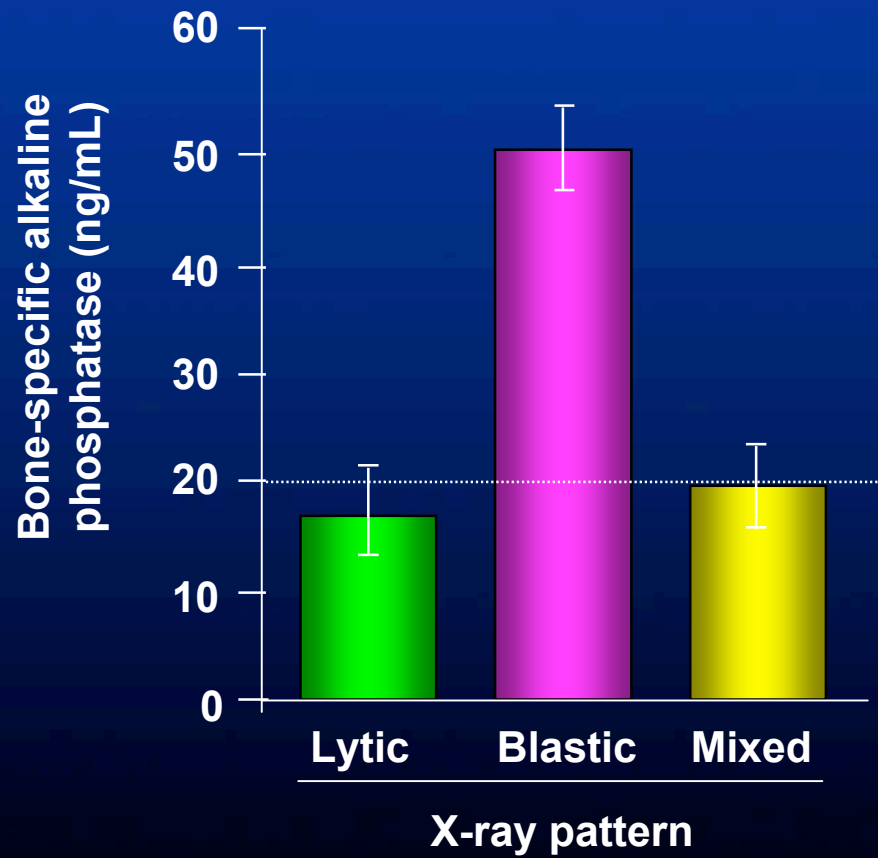
1. Tumor cells secrete humoral factors that stimulate osteoclast activity
2. Tumor cells secrete growth factors that stimulate osteoblast activity
3. Osteoblasts lay down excess but structurally weak new bone
4. Osteoblasts and osteoclasts both release growth factors that stimulate tumor growth

Mechanism of Action of Bisphosphonates





Bone Markers in Metastatic Bone Disease



BCE/M Cr: Bone collagen equivalents normalized to excreted creatinine

Coleman RE, et al. *J Clin Oncol* 2005;23:4925-4935.

Results With Earlier Bisphosphonates in Studies with Pain as Primary Outcome



Test Drug	Author	N	1° Outcome	Result
Etidronate	Smith 1989 ¹	57	Pain	No significant benefit
Clodronate	Elomaa 1992 ²	99	Pain	No significant benefit
Clodronate	Strang 1997 ³	55	Pain	No significant benefit
Clodronate + Estramustine	Kylmäla 1997 ⁴	57	Pain	No significant benefit
Mitox/Pred ± IV clodron	Ernst 2003 ⁵	204	Pain	No significant benefit
IV Pamidronate vs placebo	Small 2003 ⁶	378	Pain	No significant benefit

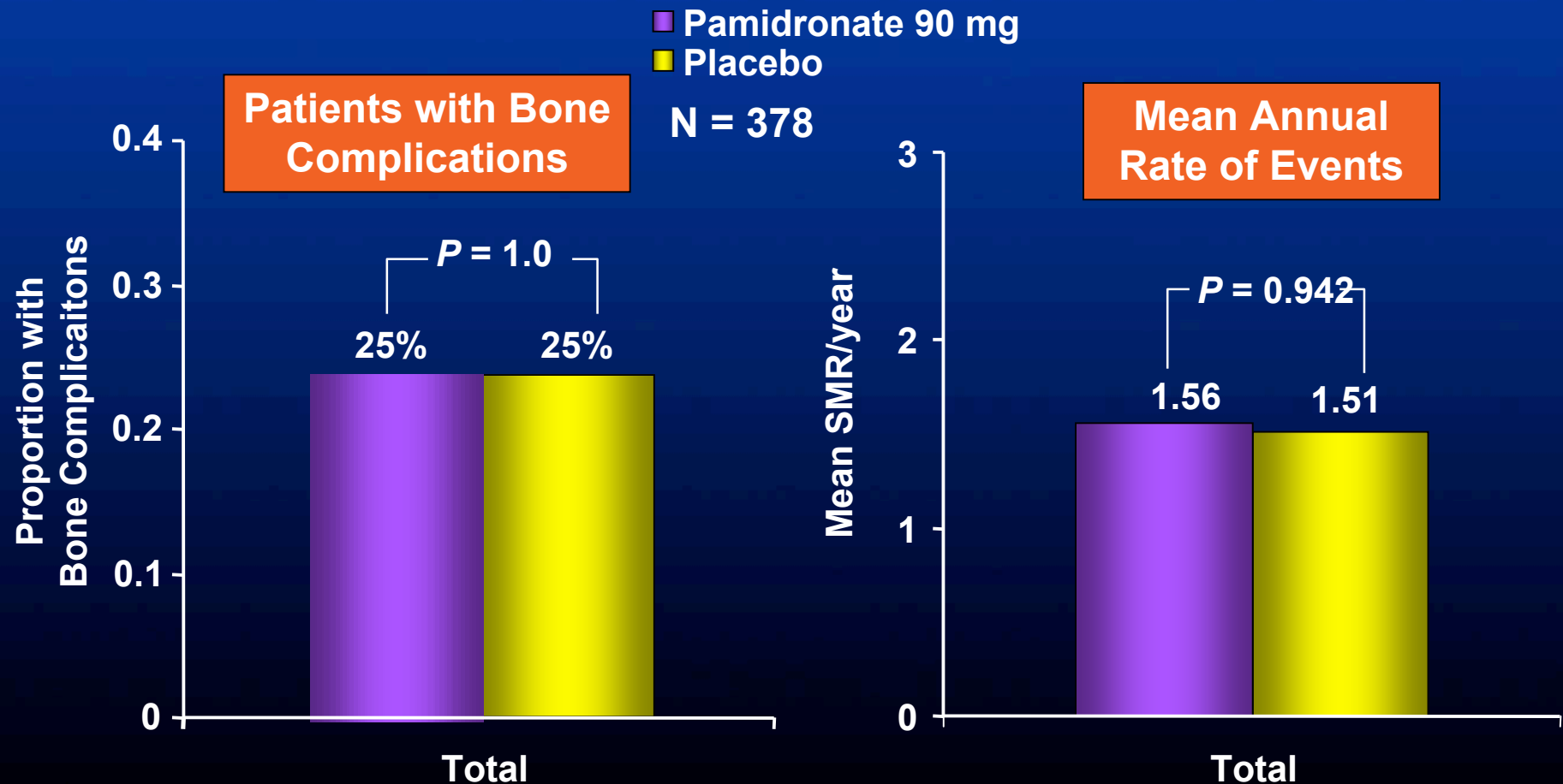
Randomized studies of patients with HRPc

1. Smith JA. *J Urol* 1989;141:85-87; 2. Elomaa I, et al. *Int Urol Nephrol* 1992;24:159-166; 3. Strang P, et al. *Anticancer Res* 1997;17:4717-4721; 4. Kylmäla T, et al. *Br J Cancer* 1997;76:939-942; 5. Ernst DS, et al. *J Clin Oncol* 2003;21:3335-3342 6. Small EJ, et al. *J Clin Oncol* 2003;21:4277-4284.

Pamidronate in Prostate Cancer



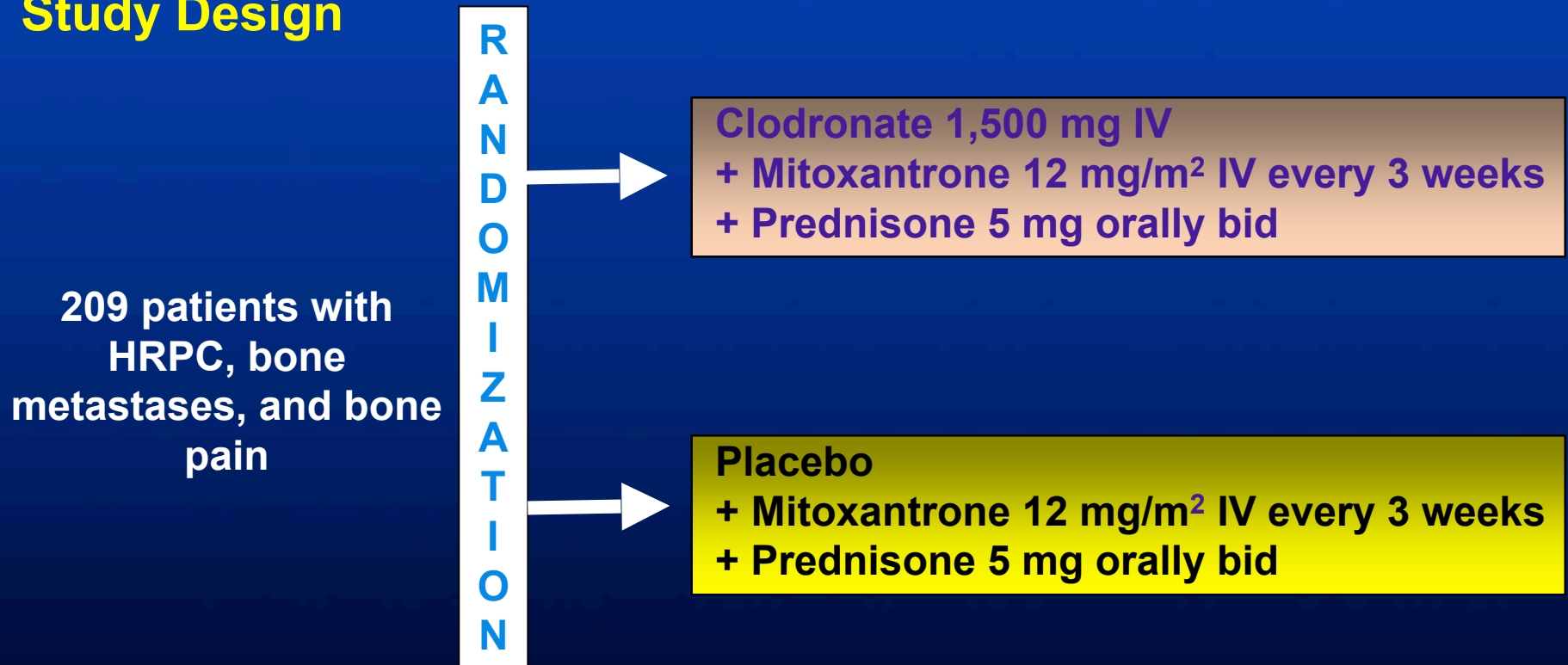
No difference compared with placebo



NCIC CTG Trial: Mitoxantrone/Prednisone +/- Clodronate in Patients with HRPC



Study Design



Primary End Point: Palliative Response

- Reduction to zero or of two points in the PPI or a decrease of 50% in analgesic intake, without increase in either

NCIC CTG: National Cancer Institute of Canada Clinical Trials Group

HRPC: Hormone-refractory prostate cancer

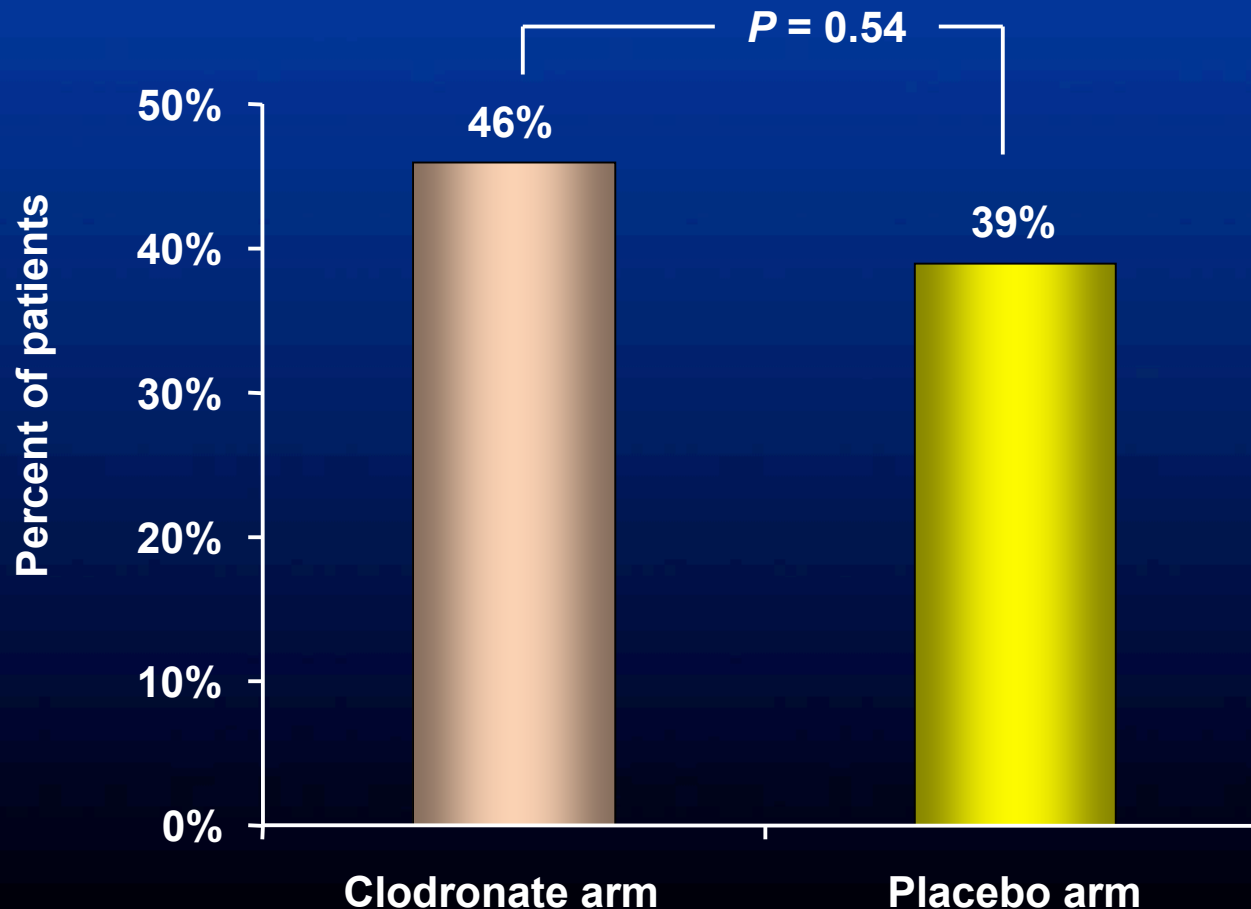
IV: Intravenously

PPI: Present Pain Intensity

NCIC CTG Trial: Mitoxantrone/Prednisone +/- Clodronate in Patients with HRPC



Clodronate does not increase the rate of palliative response

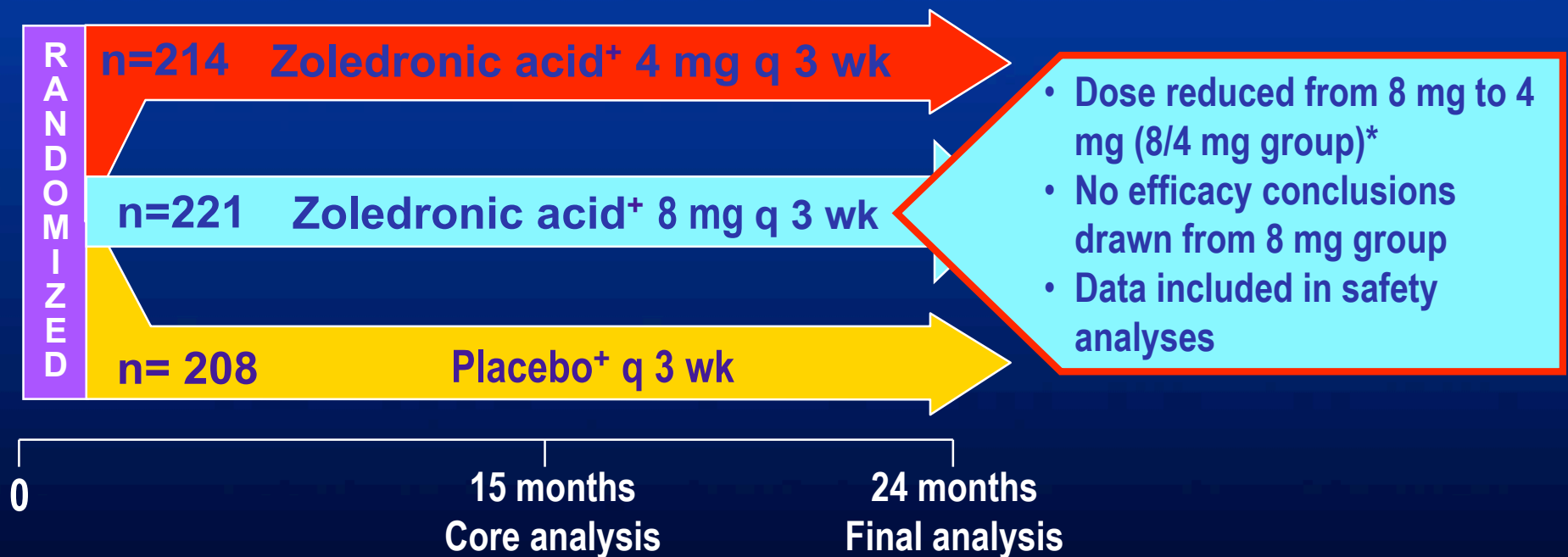


Treatment Options for HRPC



- Second-line hormonal manipulations
- Radiation therapy / Radiopharmaceuticals
- **Bisphosphonates**
 - **Zoledronic Acid**
- Chemotherapy
- Novel / Investigational agents

Zoledronic Acid in HRPC: Trial Design



Vitamin D 400 IU
Calcium 500 mg

* Due to rise in serum creatinine

Zoledronic Acid in HRPc: Study Demographics



	Zoledronic acid 4 mg	Zoledronic acid 8/4 mg	Placebo
Mean age, years	71.8	71.2	72.2
Performance status ECOG 0 - 1, %	92.1	91.4	91.3
Baseline PSA (ng/mL)			
Mean	277	351	211
Median	80	88	61
Previous bone complications, n (%)	66 (30.8)	71 (32.1)	78 (37.5)
Pain at baseline, n (%)	140 (72.5)	158 (79.4)	140(73.3)
Mean Brief Pain Inventory score	2.0±2.0	2.5±2.1	2.1±2.0

Skeletal-related Event (SRE): Definition



SREs include the following bone complications:

- Radiation for bone pain or to treat or prevent pathologic fractures or spinal cord compression**
- Pathologic fracture**
- Spinal cord compression**
- Change in antineoplastic therapy for pain**
- Surgery to bone**

Zoledronic Acid in HRPc: Study Endpoints



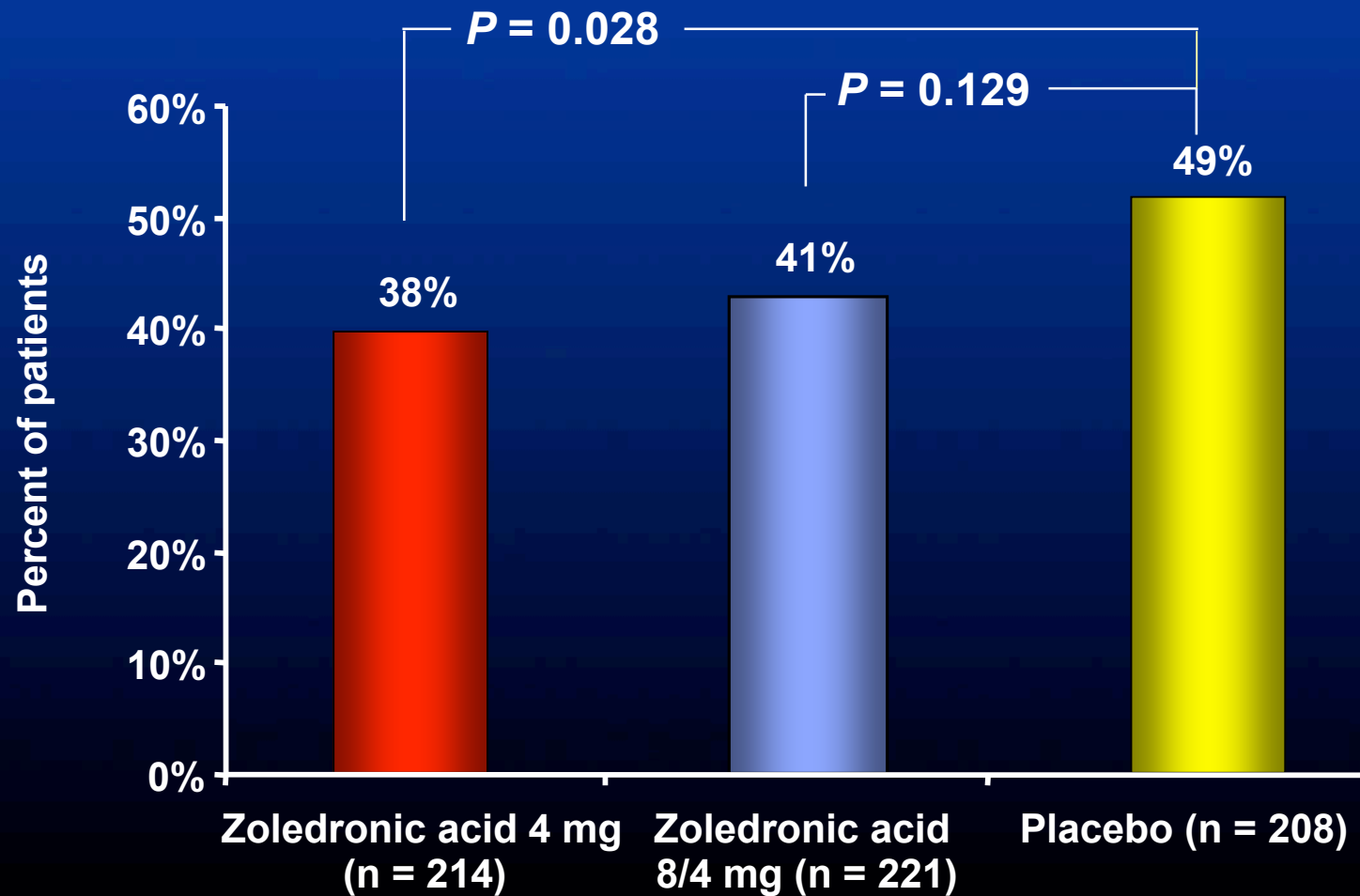
- **Primary Endpoint**
 - Proportion or percentage of patients with an SRE

- **Secondary Endpoints**
 - Time to first SRE
 - Skeletal morbidity rate (SMR)*
 - mean annual rate of bone complications (>21 days)
 - Multiple-event analysis*
 - considers all events and time between events
 - Pain/analgesic scores
 - Bone lesion response
 - Time to progression of disease
 - Safety
 - Survival

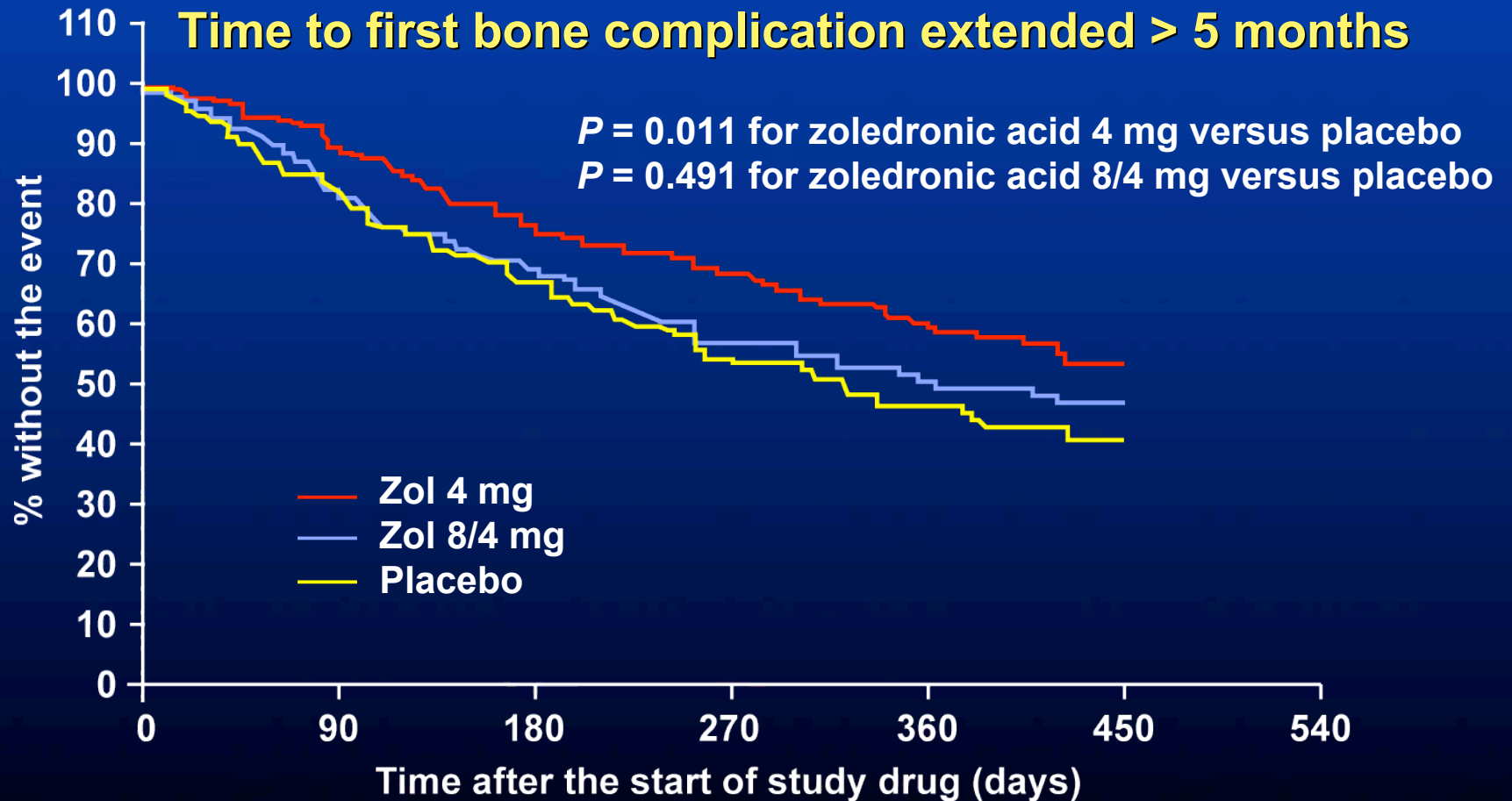
Zoledronic Acid in HRPC



22% Relative reduction in patients with bone complication



Zoledronic Acid in HRPc

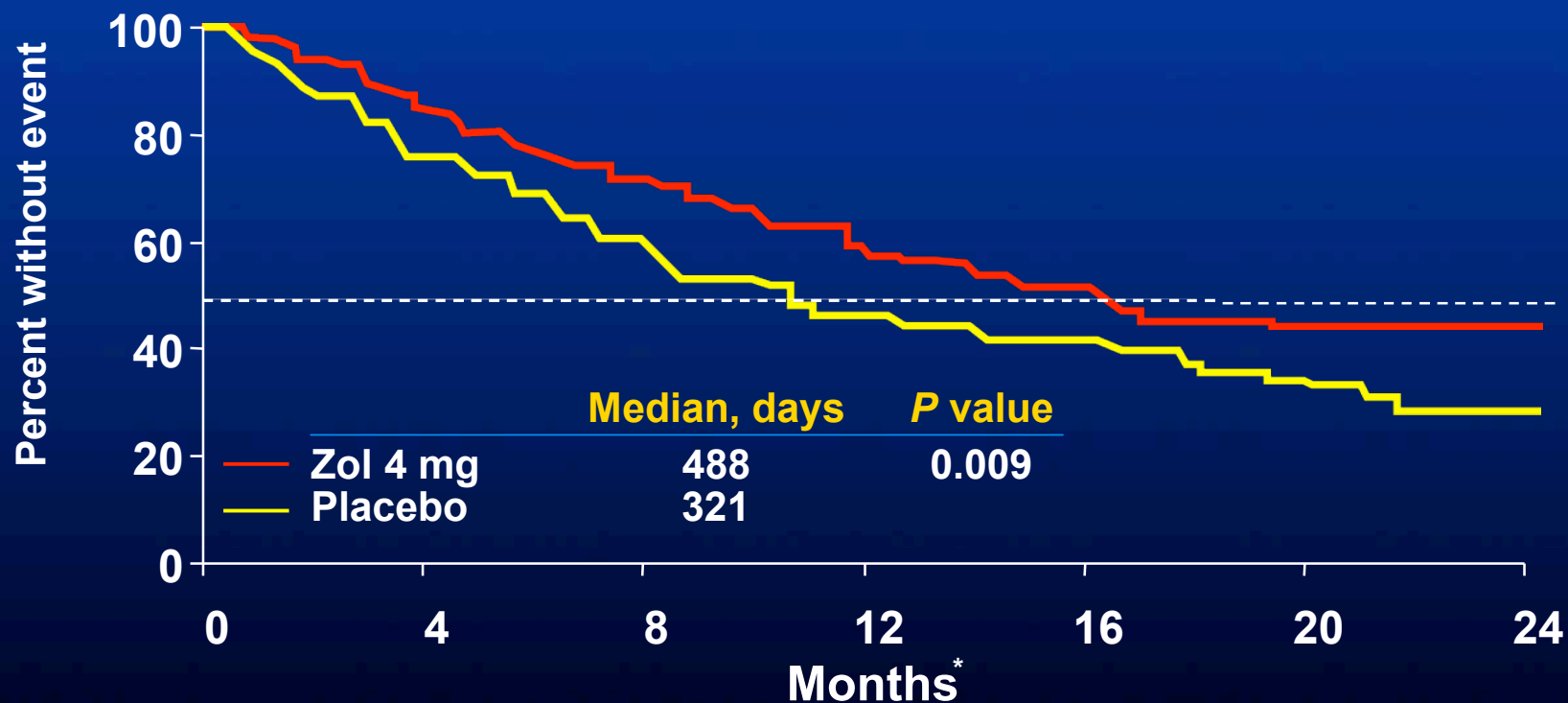


Zol 4 mg:	214	163	113	92	70	5	0
Zol 8/4 mg:	221	155	102	68	46	4	0
Placebo:	208	149	103	69	43	1	0

Zoledronic Acid in HRPc: 24 Month Follow-Up

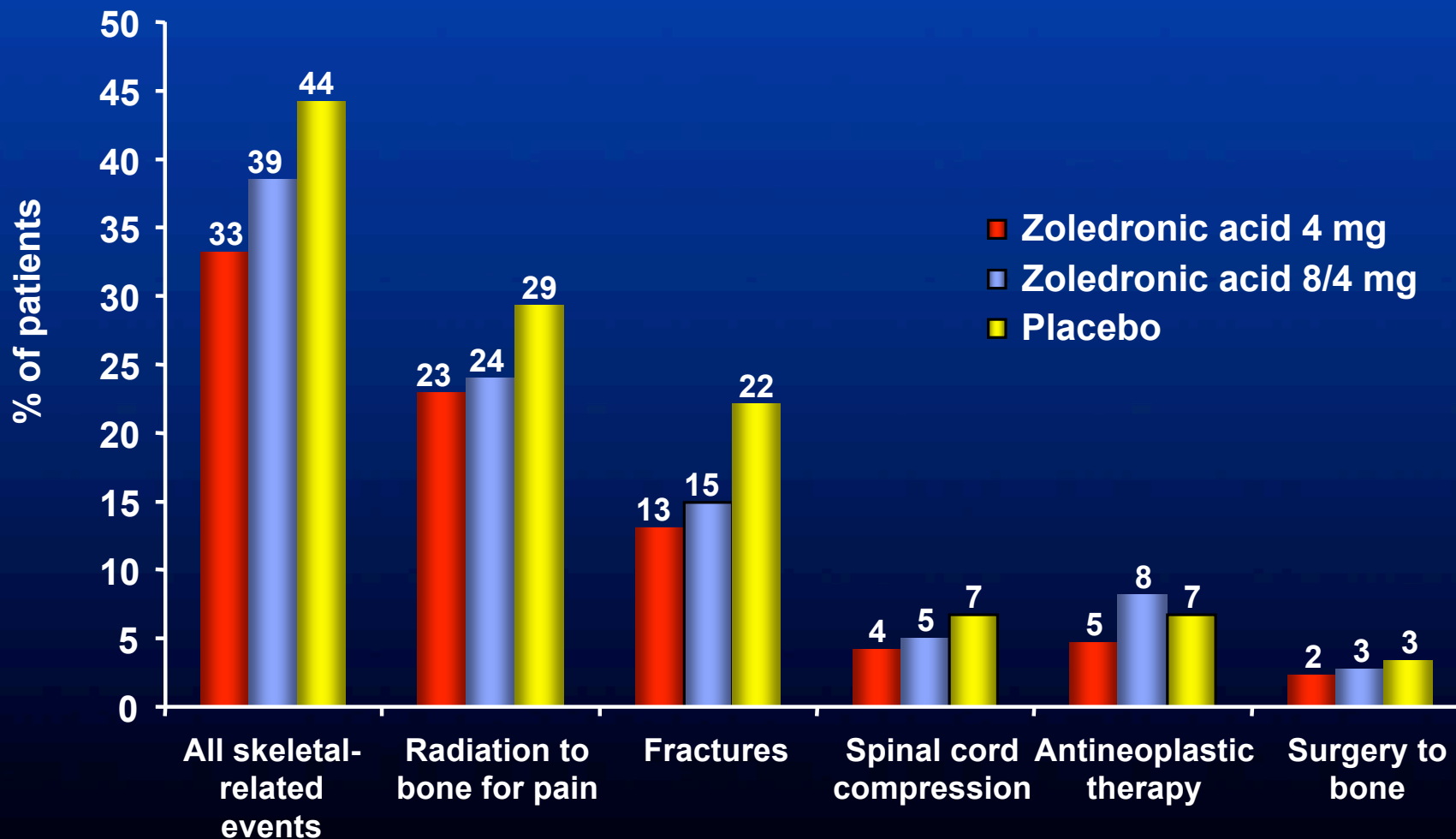


Time to first bone complication extended > 5 months



Zoledronic Acid in HRPC:

Proportion of Patients with each Bone Complication

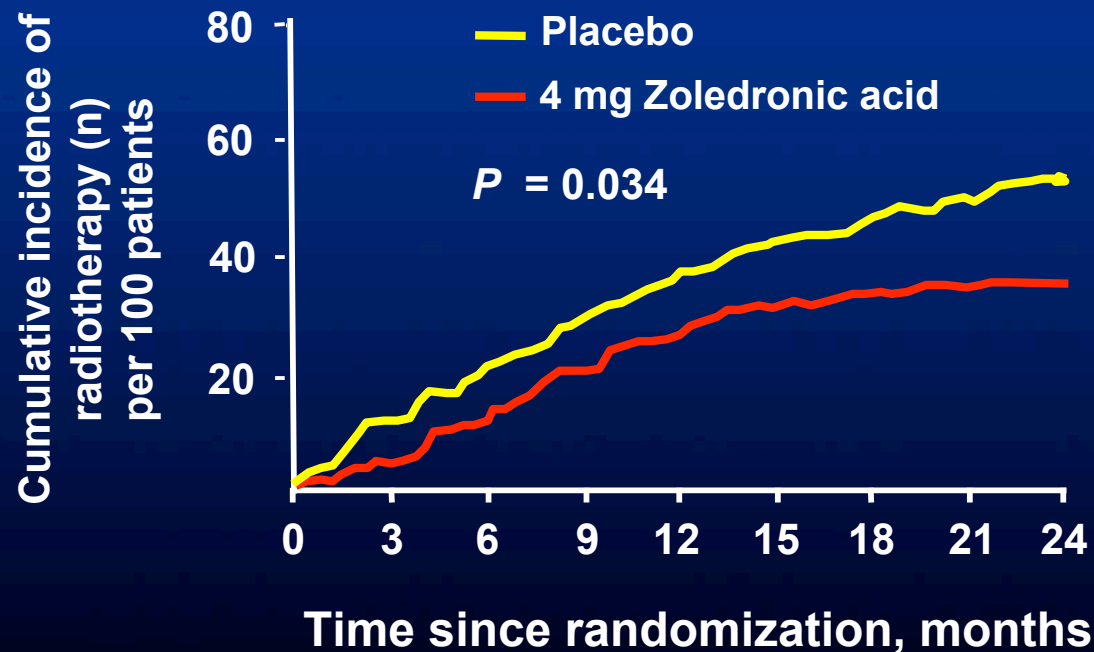


Zoledronic Acid in HRPC:

Cumulative Incidence of Radiation to Bone for Pain



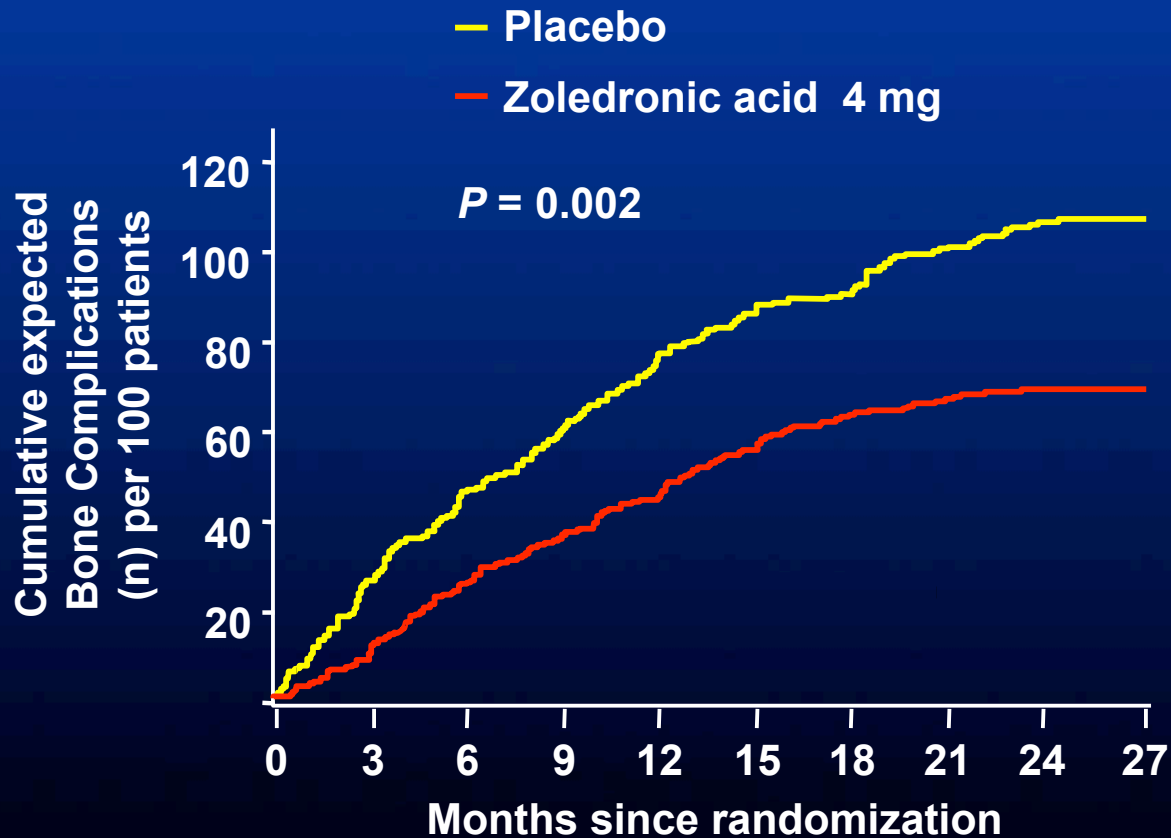
Reduced by 33%



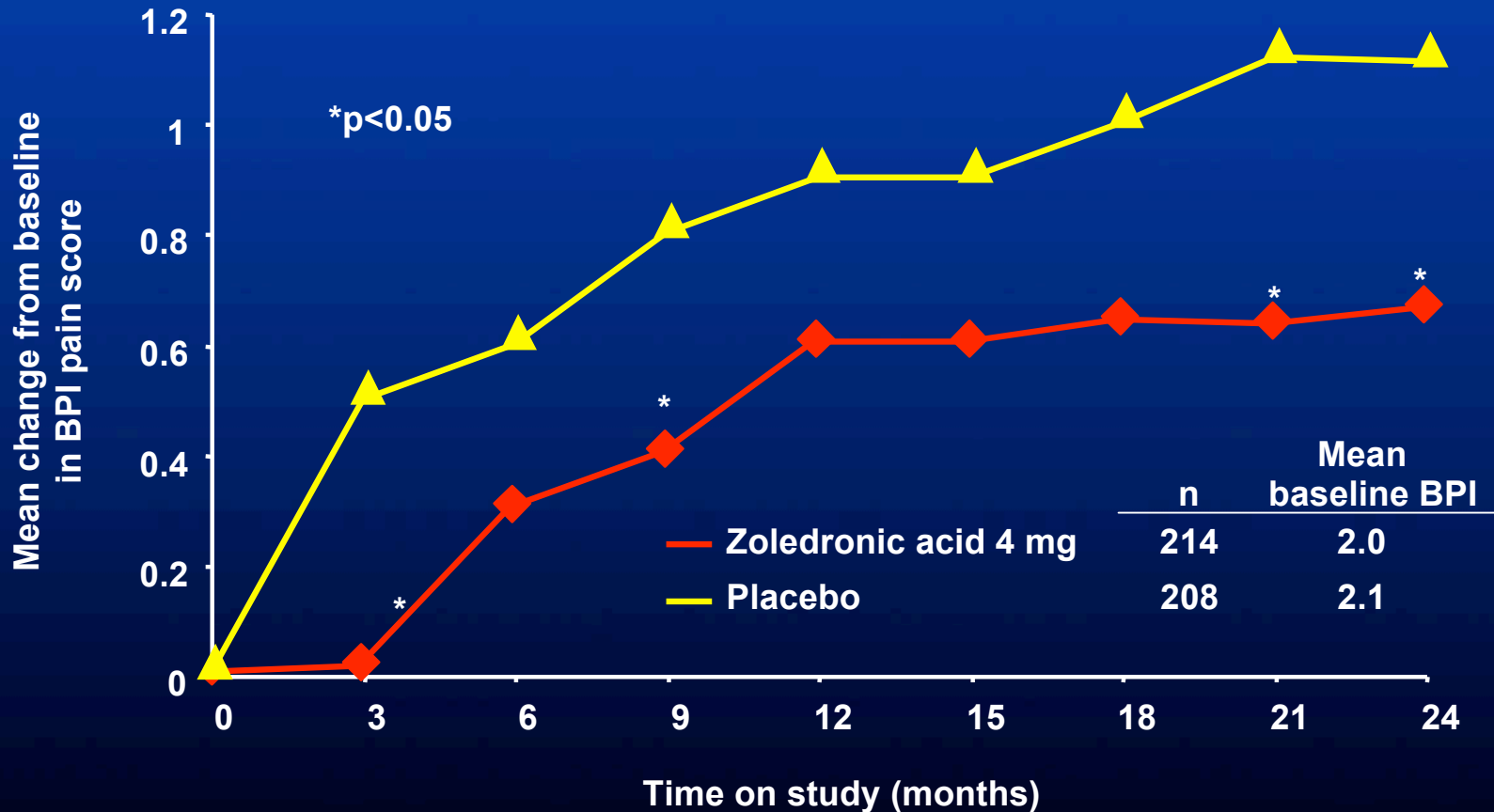
Zoledronic Acid in HRPc: Risk of Developing a Bone Complication



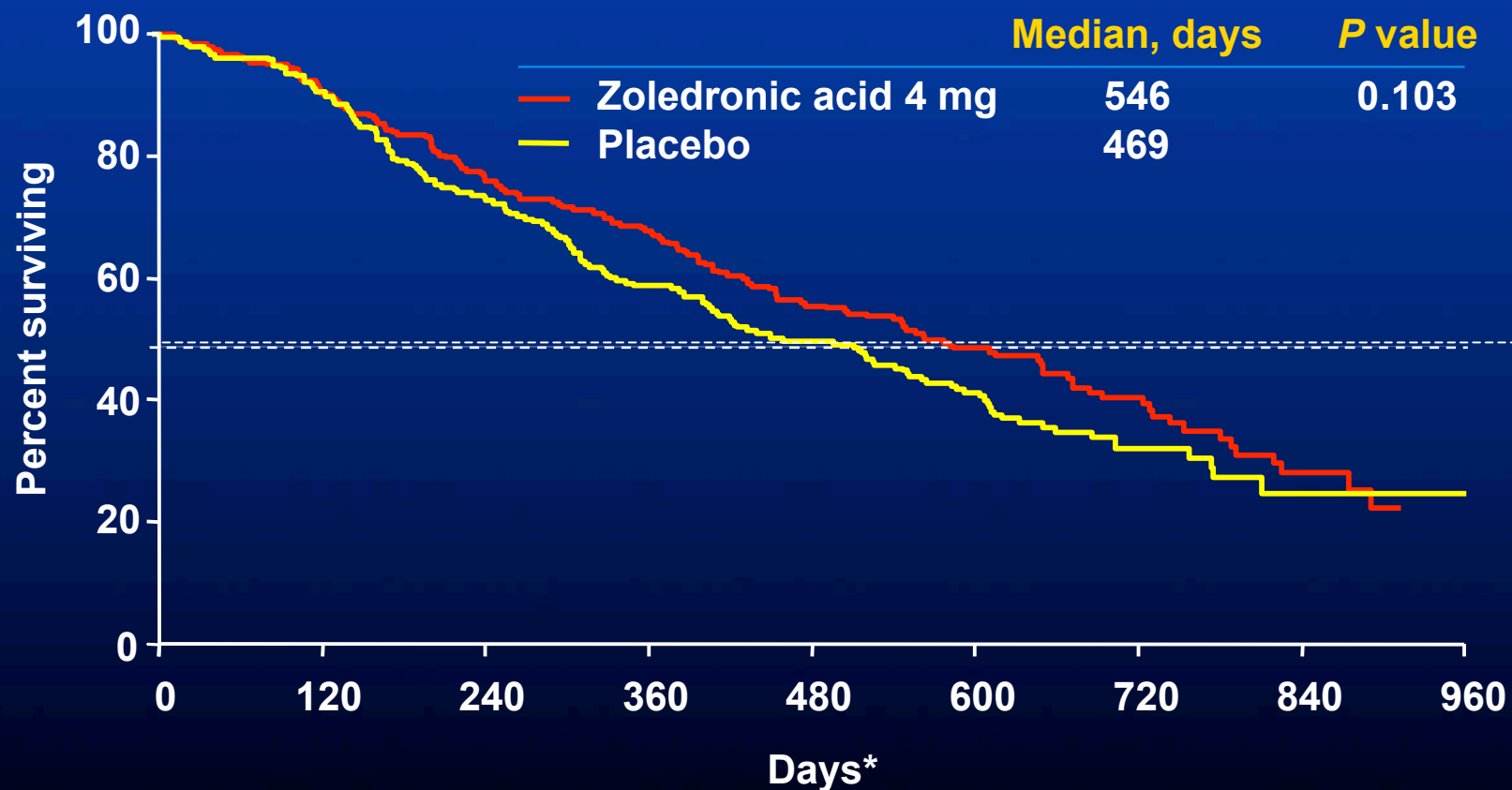
Reduced by 35%



Zoledronic Acid in PCa: Change from Baseline Pain Score



Zoledronic Acid in HRPC: Survival

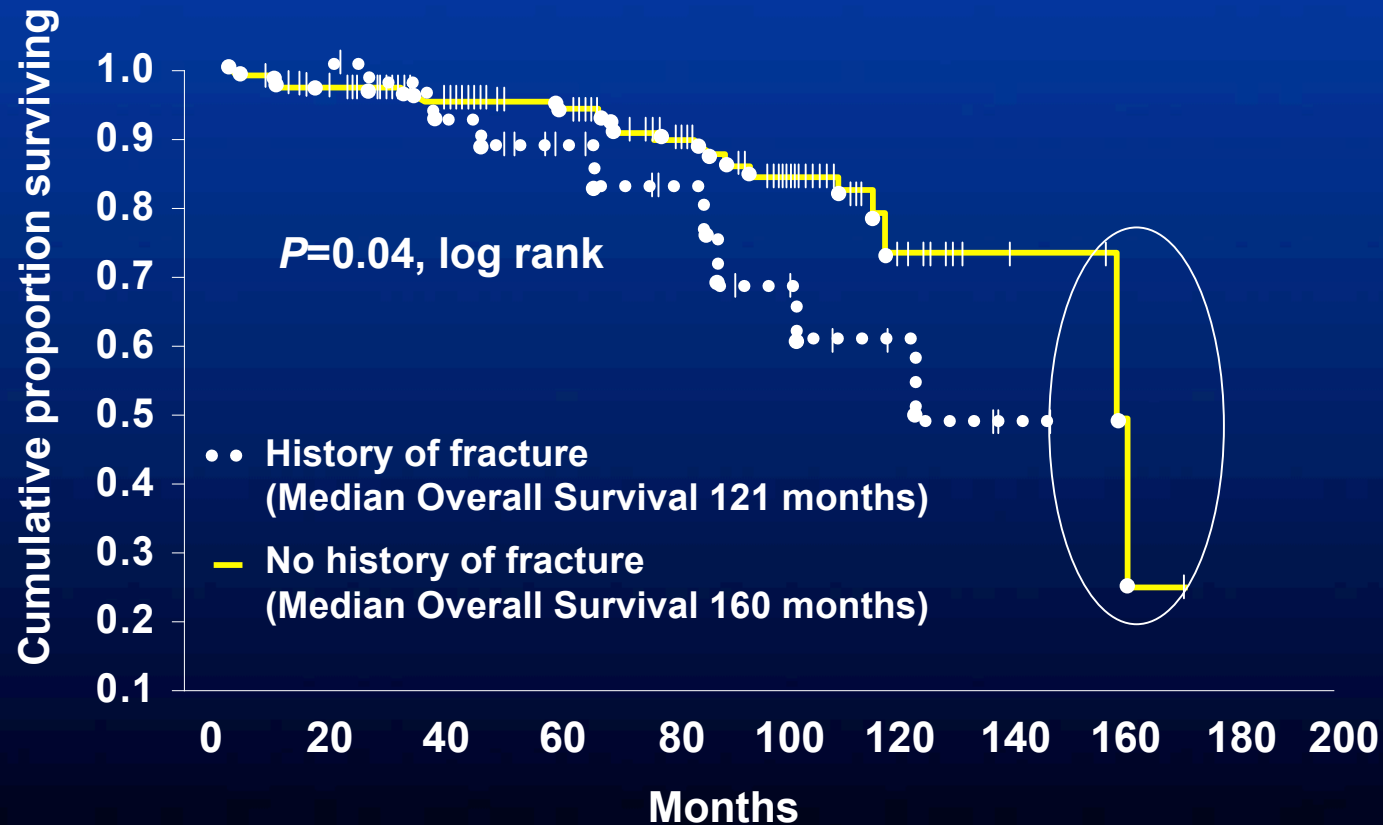


*Time after start of study drug

Skeletal Fractures and Overall Survival in Patients with Prostate Cancer



Negatively correlated with overall survival

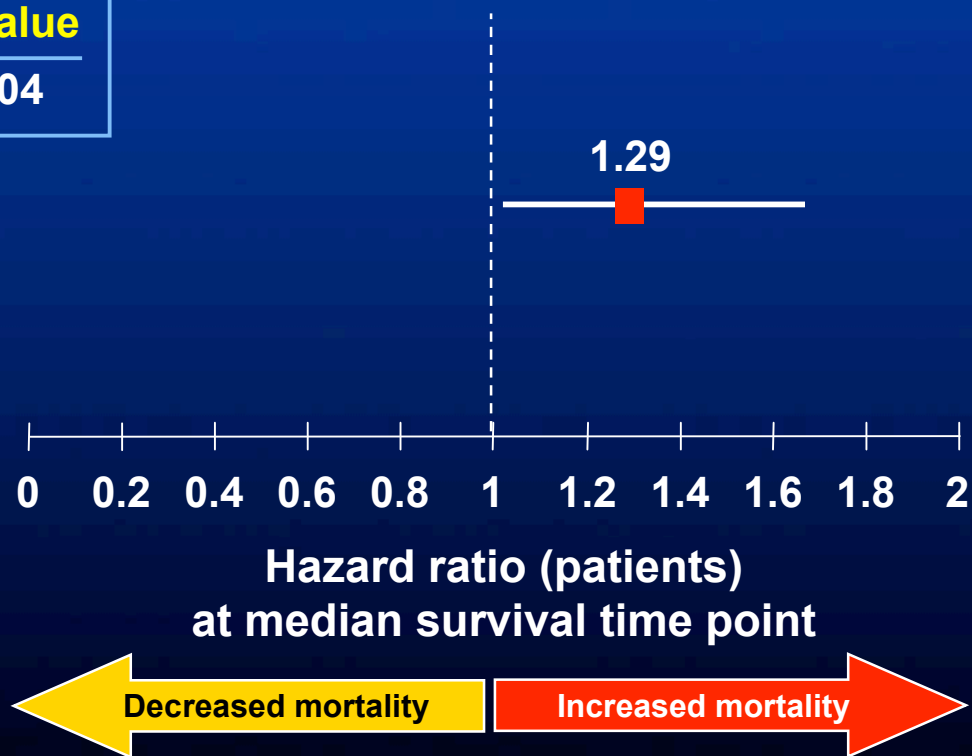


Skeletal Fractures and Risk of Mortality



Associated with increased mortality

Risk increase	<i>P</i> value
29%	0.04



Emerging Hypothesis



- **Retrospective analysis of survival based on occurrence of pathological fracture generated the following hypothesis:**
 - **Skeletal fractures caused by bone metastases can have a negative impact on patient survival**
- **This hypothesis should be further tested in a large clinical trial**

Zoledronic Acid in HRPc: Most Frequent Adverse Events

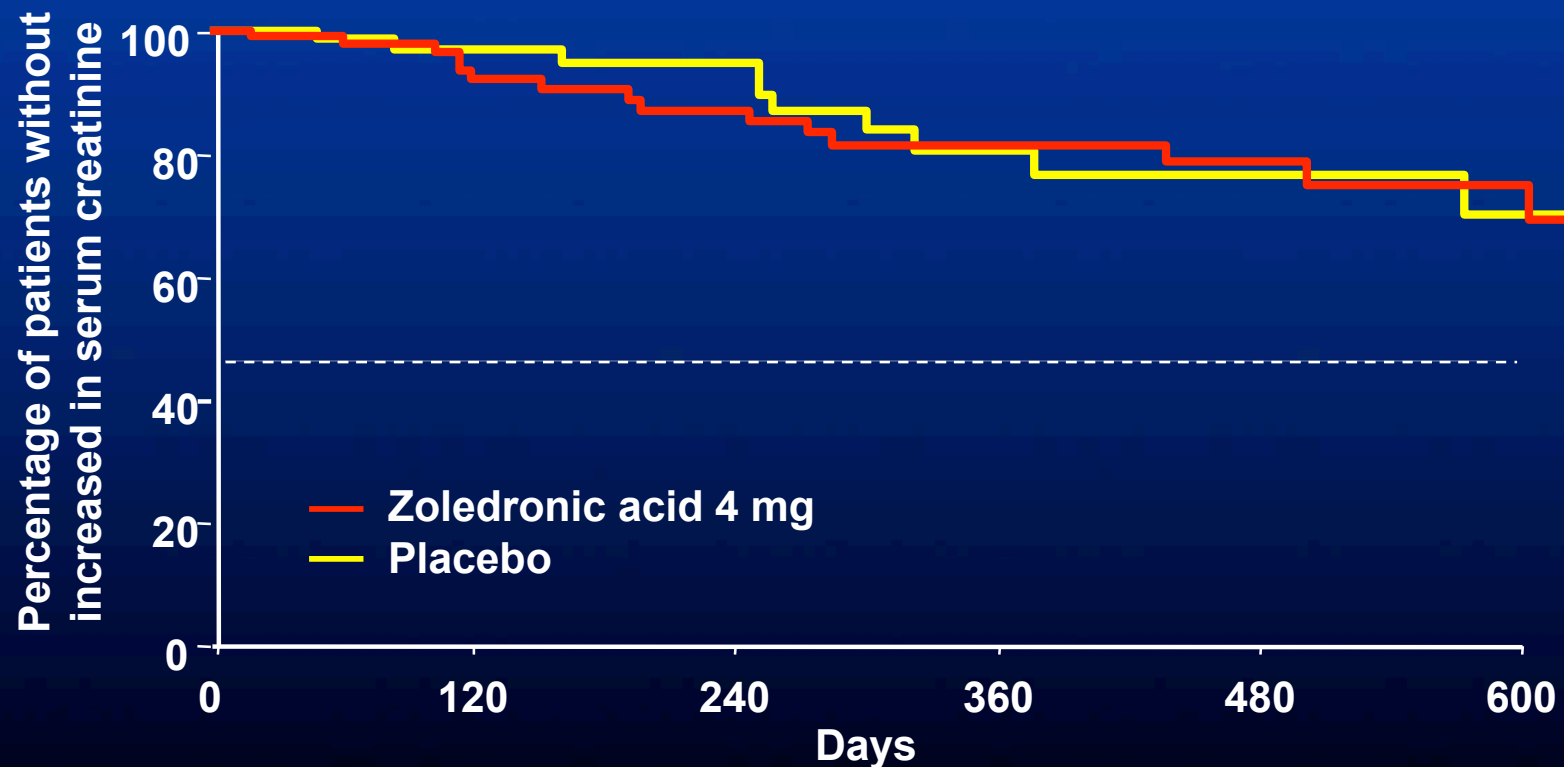


	Zoledronic acid 4 mg (%)	Zoledronic acid 8/4 mg (%)	Placebo (%)
Fatigue	32.7	30.7	25.5
Anemia	26.6	27.5	17.8
Myalgia	24.8	24.3	17.8
Fever	20.1	22	13
Edema lower limb	19.2	22	13

Zoledronic Acid in HRPC: Renal Safety*



No significant difference compared with placebo



* Increase in serum creatinine

New Dosing Recommendations for Patients with Mild-to-Moderate Renal Dysfunction



Upon initiation of zoledronic acid therapy, apply the following guideline:

Baseline creatinine clearance	Zoledronic acid recommended dose
> 60 mL/min	4.0 mg
30 – 60 mL/min	Dose should be reduced
50 – 60 mL/min	3.5 mg
40 - 49 mL/min	3.3 mg
30 - 39 mL/min	3.0 mg
< 30 mL/min	Zoledronic acid is not recommended

- Serum creatinine must be measured before each dose
- Zoledronic acid is not recommended if creatinine clearance < 30 mL/min

Recommendations to Prevent Osteonecrosis of the Jaw (ONJ)



- **Overall frequency of ONJ in cancer patients is 0.83%¹**
- **Prevalence of ONJ is higher in multiple myeloma and breast cancer patients treated with bisphosphonates¹**
- **Prior to initiation of bisphosphonate therapy:^{2,3}**
 - **A dental examination with appropriate preventive dentistry**
 - **Extraction of compromised teeth**
 - **Avoid dental implants**
 - **Eliminate sources of infection**

Recommendations to Prevent Osteonecrosis of the Jaw (ONJ)



- **During Bisphosphonate Therapy:**^{2,3}
 - Avoid invasive dental procedures
 - Maintain routine dental cleanings
 - Ensure good fit of dentures
 - Aggressively manage dental infections without surgery (effective control to a pain free state in 90.1% of patients)³

- **For patients requiring dental procedures**
 - No data to suggest discontinuation of bisphosphonate therapy reduces the risk of ONJ^{2,3}

Zoledronic Acid in HRPC with Bone Metastases: Summary



- **Zoledronic acid is the only bisphosphonate proven to reduce bone complications**
 - **Significantly decreased the risk of developing bone complications:**
 - Fewer patients experienced a bone complication
 - Extended time to first bone complication
 - Reduced incidence of radiation to bone for pain
 - **Associated with infrequent adverse events**

The Use of Bisphosphonates in HRPC Patients with Bone Metastases: Summary



- **HRPC patients are at increased risk of bone complications, which significantly increase morbidity**
 - Approximately 65% to 75% of patients will develop bone metastases¹ and are at risk of pathological fracture
- **Bisphosphonates can prevent complications associated with bone metastases**
- **Treatment has been shown to be effective in patients with asymptomatic or minimally symptomatic metastatic disease**
- **Therefore, identification of these patients may result in better patient outcomes**

Treatment Options for HRPC



- Second-line hormonal manipulations
- Radiation therapy /
Radiopharmaceuticals
- Bisphosphonates
- **Chemotherapy**
- Novel / Investigational agents

Expanding the Benefits of Chemotherapy in HRPC



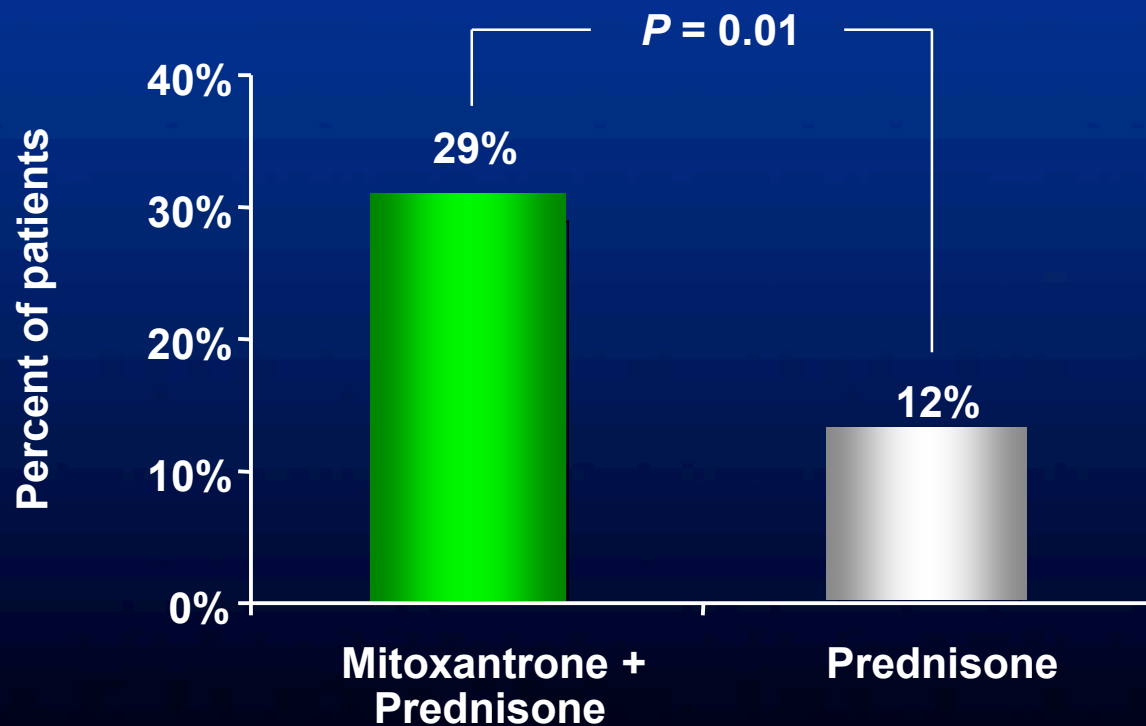
- **Mitoxantrone-based therapy**
 - Palliative response
 - No survival benefit

- **Docetaxel-based therapy**
 - Palliative response
 - Improvement in overall survival
 - Cornerstone of most evolving chemotherapy regimens

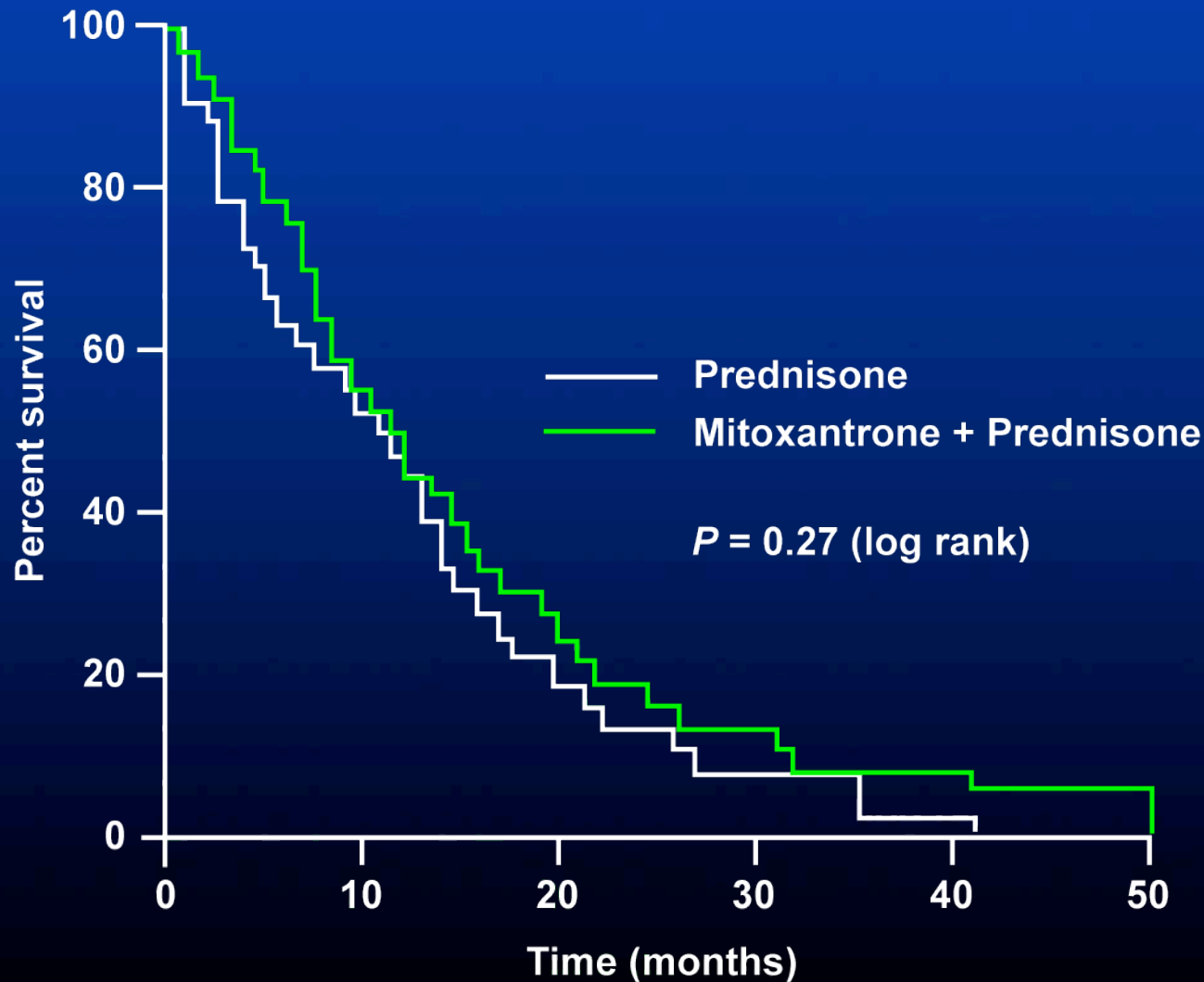
Mitoxantrone in HRPC: Palliative Response



Palliative response achieved in one-third of patients



Mitoxantrone in HRPC: No Difference in Overall Survival



Docetaxel: Phase I and II Trials



- **Results of Phase I and II docetaxel / estramustine trials have demonstrated:**
 - PSA response rates of 45% to 68%^{1,2,3}
 - Disease response rates of 20% to 50%^{1,2,3}
 - Median survival time longer than historical control groups^{1,2}

These trials provided the scientific basis for larger, randomized Phase III studies

Docetaxel: Phase III Studies



TAX 327¹

Objective:

- To compare docetaxel plus daily prednisone with mitoxantrone plus prednisone in HRPC patients

Primary End Point:

- Overall Survival

SWOG 9916²

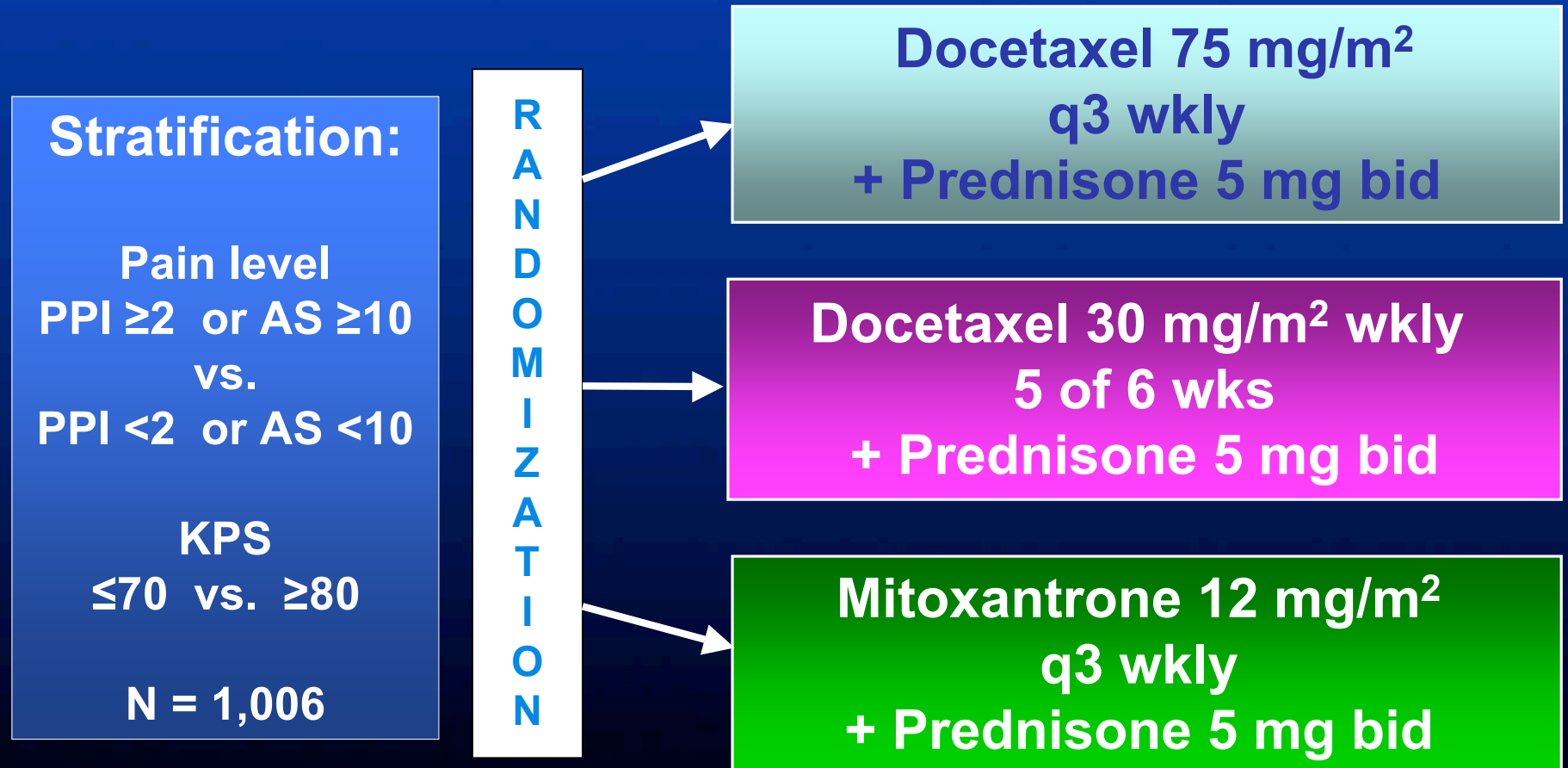
Objective:

- To compare docetaxel plus estramustine with mitoxantrone plus prednisone in HRPC patients

Primary End Point:

- Overall Survival

TAX-327: Study Design



Treatment duration in all 3 arms = 30 wks

PPI: Present Pain Intensity

AS: Analgesic Score

KPS: Karnofsky Performance-status Score

Patient Characteristics



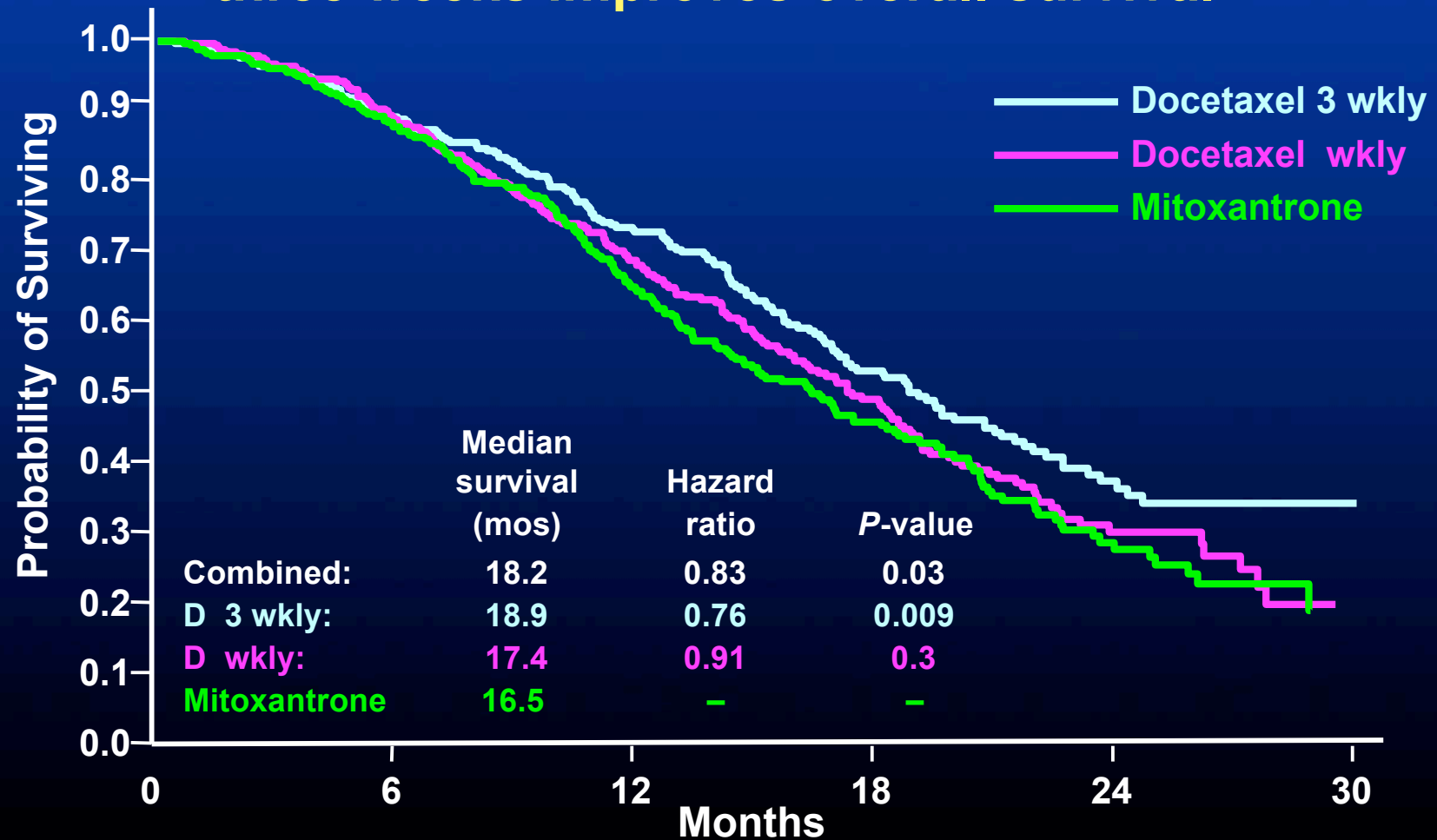
Characteristic	Docetaxel Every 3 Weeks	Docetaxel Every week	Mitoxantrone Every 3 Weeks
Number of patients randomized	335	224	337
Age			
Median (Range) (years)	68 (42-92)	69 (36-92)	68 (43-86)
Hormonal manipulations (%)+			
≤ 2	77	80	75
> 2	23	21	25
Karnofsky performance-status score ≤ 70 % (%)	13	12	14
Pain (%) PPI ≥ 2 or AS > 10	45	45	46
Serum PSA – Median (ng/mL)	114	108	123
Extent of Disease			
Bone metastases	90	91	92
Visceral disease	22	24	22

PPI: Present Pain Index
AS: Analgesic Score
KPS: Karnofsky Performance-status Score

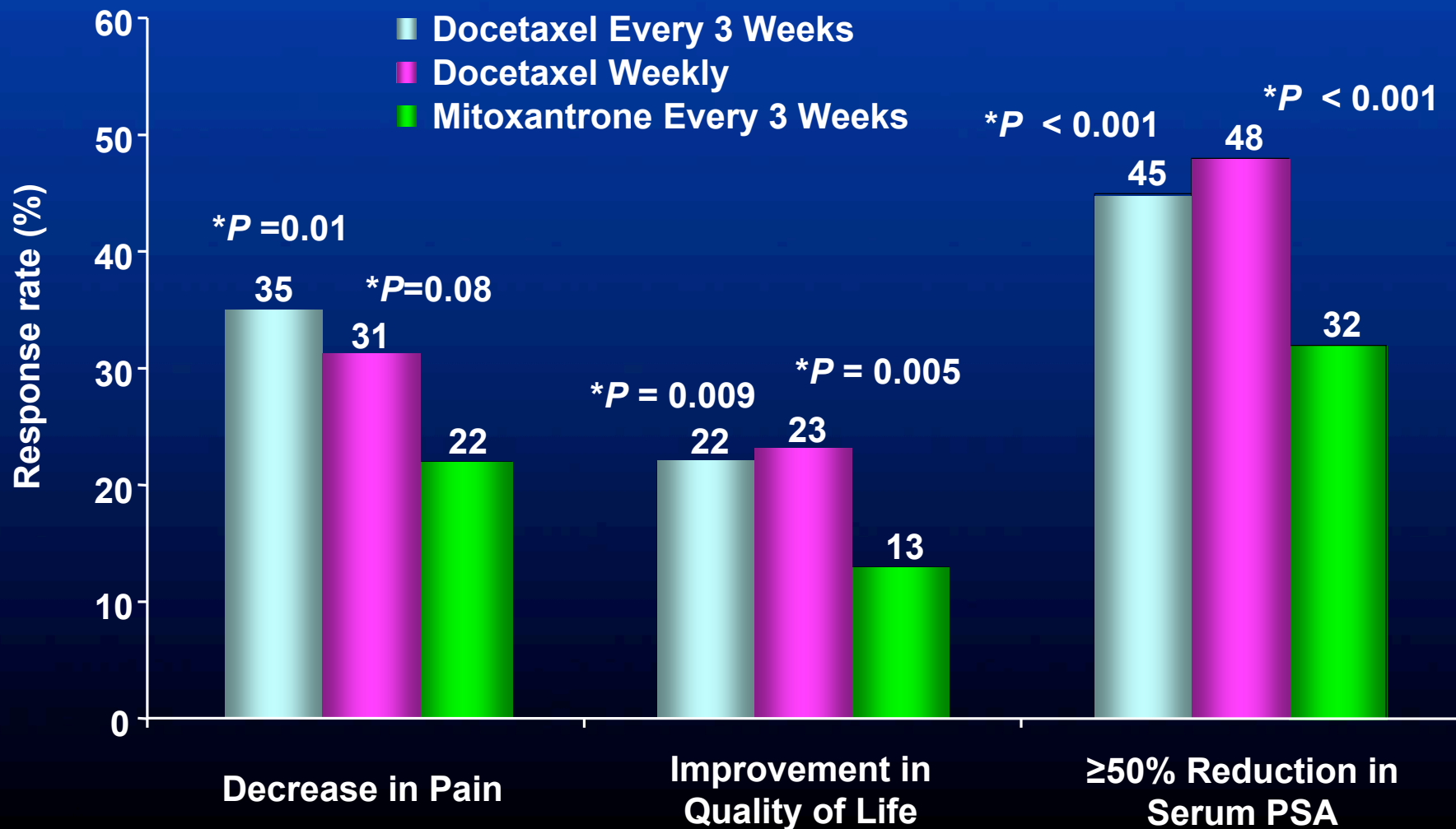
TAX-327 Study: Overall Survival



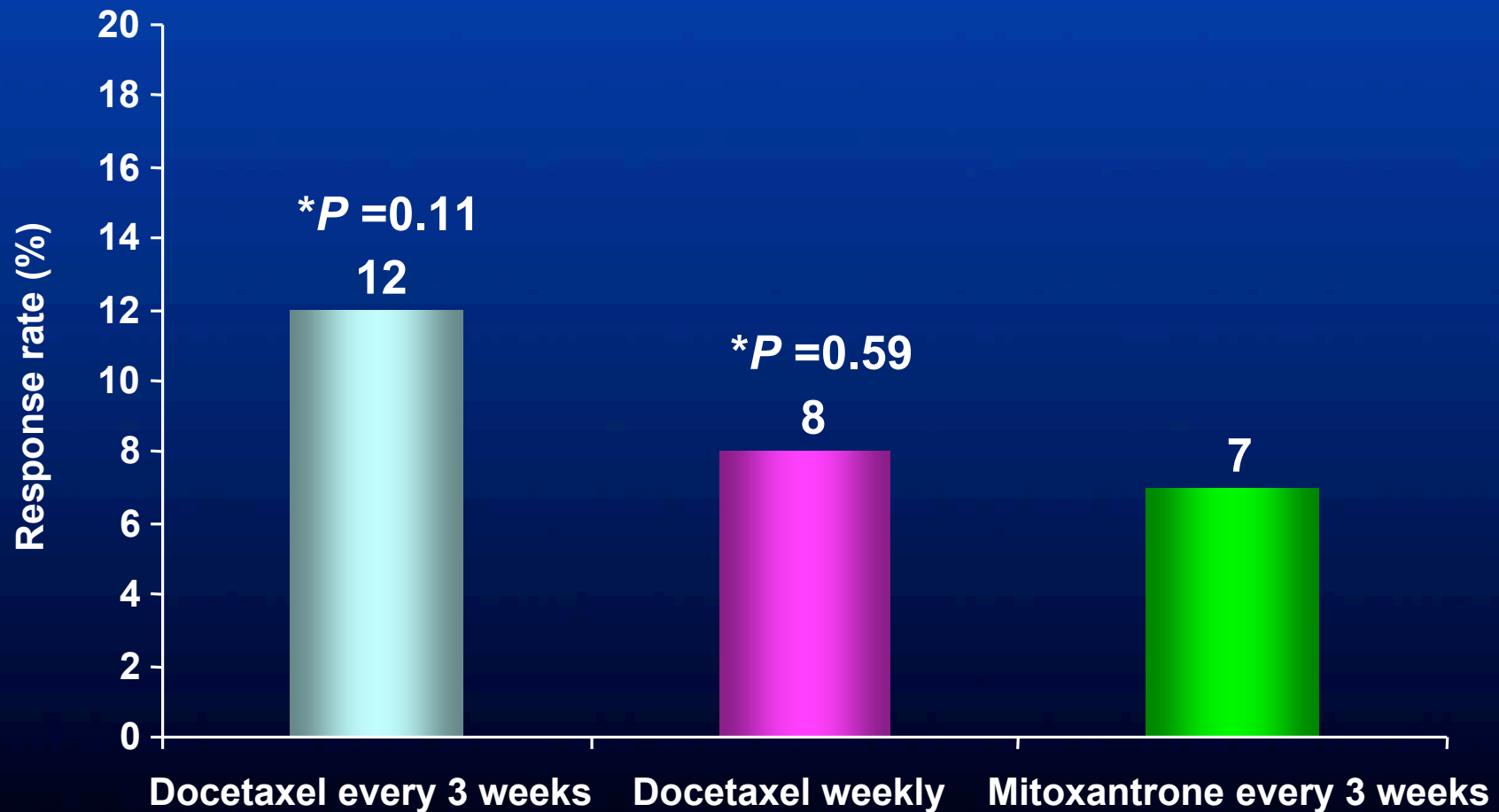
Treatment with docetaxel every three weeks improves overall survival



TAX-327 Study: Response to Treatments



TAX-327 Study: Tumour Response



TAX-327 Study: Targeted Adverse Events



% of Patients	Docetaxel Every 3 Weeks (%)	Docetaxel Weekly (%)	Mitoxantrone Every 3 Weeks (%)
Grade 3 or 4 neutropenia*	32	2	22
Impaired LVEF*	10	8	22
Fatigue*	53	49	13
Alopecia*	65	50	10
Diarrhea*	32	34	7
Nail Changes*	30	37	7
Sensory neuropathy*	30	24	14
Anorexia	17	21	7
Change in taste*	18	24	8
Stomatitis*	20	17	9
Dyspnea*	15	14	1
Tearing*	10	21	1
Peripheral edema*	19	12	2
Epistaxis	6	17	2

LVEF=Left Ventricular Ejection Fraction

* $P \leq 0.05$ for each type of event presented in comparison with the mitoxantrone group for all except epistaxis and anorexia associated with docetaxel every 3 weeks, where $P = NS$

SWOG 9916: Study Design

Hormone-Refractory
Advanced
Prostate Cancer

N = 770

R
A
N
D
O
M
I
Z
A
T
I
O
N

Docetaxel 60 mg/m² d2
(dose escalation from 60
to 70 mg/m² permitted)
+ Estramustine 280 mg tid
d1-5 q3 weekly

Mitoxantrone 12 mg/m² d1
+ Prednisone 5 mg bid
d1-21 q3 weekly

Endpoints

- Survival
- Quality of life
 - pain questionnaire and log of analgesic requirements
- Improved performance status

Patient Characteristics

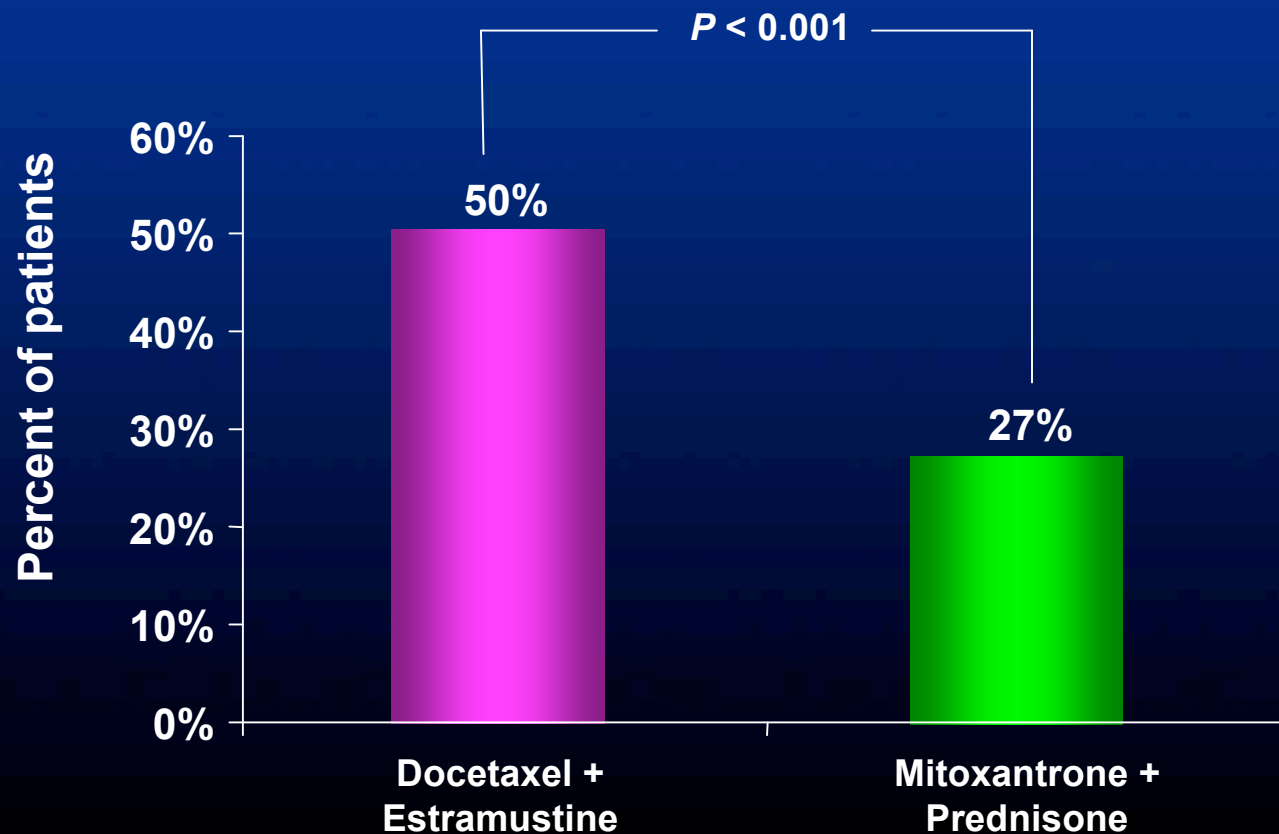


Characteristics	Docetaxel + Estramustine (N = 386)	Mitoxantrone + Prednisone (N = 384)
Age (yr)		
Median (Range)	70 (47 - 88)	70 (43 - 87)
SWOG performance-status score 0 or 1 (%)	90	88
Type of progression (%)		
Measurable or able to evaluate	81	82
Increased PSA only	19	18
PSA (ng/mL)		
Median (Range)	84 (0.1 - 10,820)	90 (0.1 - 8,378)
Sites of Disease (%)		
Bone	84	88
Soft tissue	42	45
Bone pain (%)		
Grade <2	64	64
Grade ≥ 2	36	36

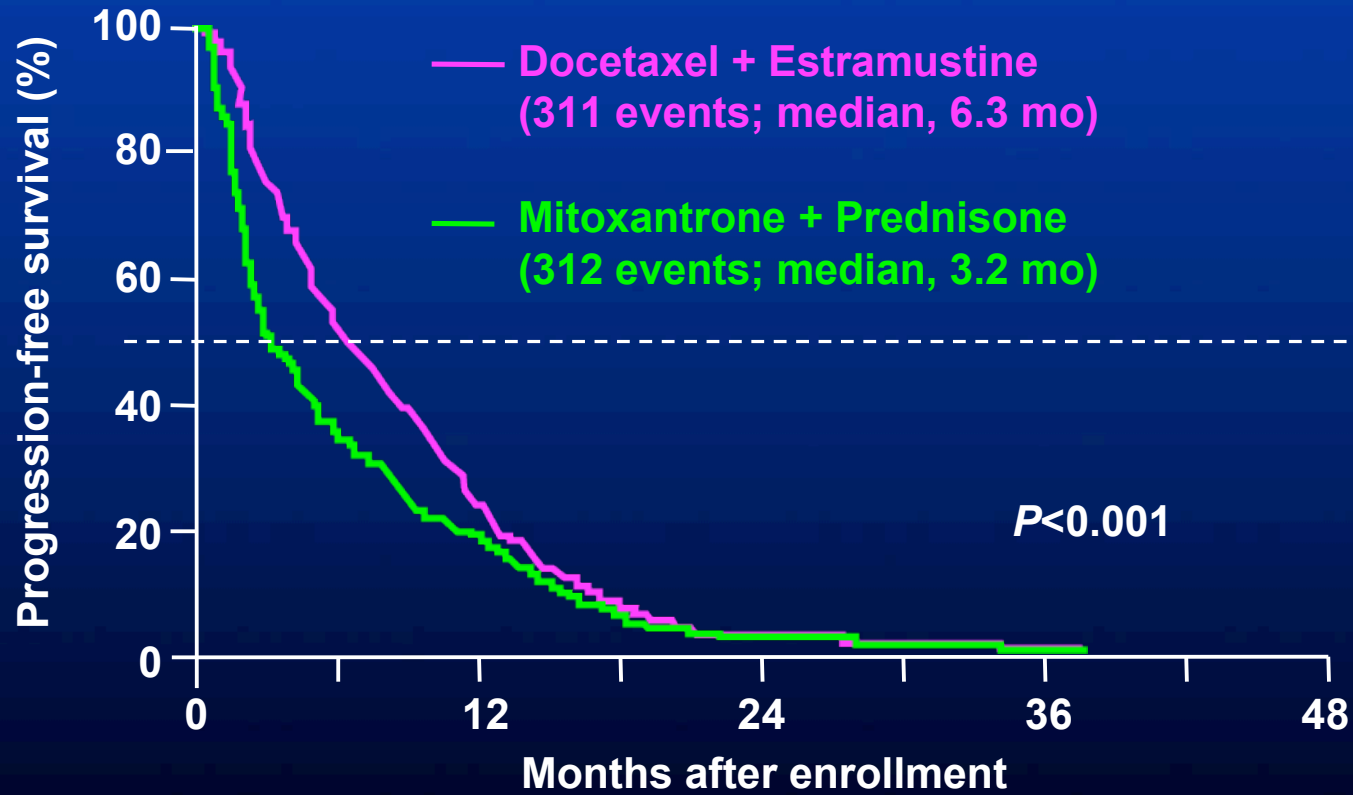
SWOG 9916: PSA Response



Decline in serum PSA at least 50% more frequent after docetaxel



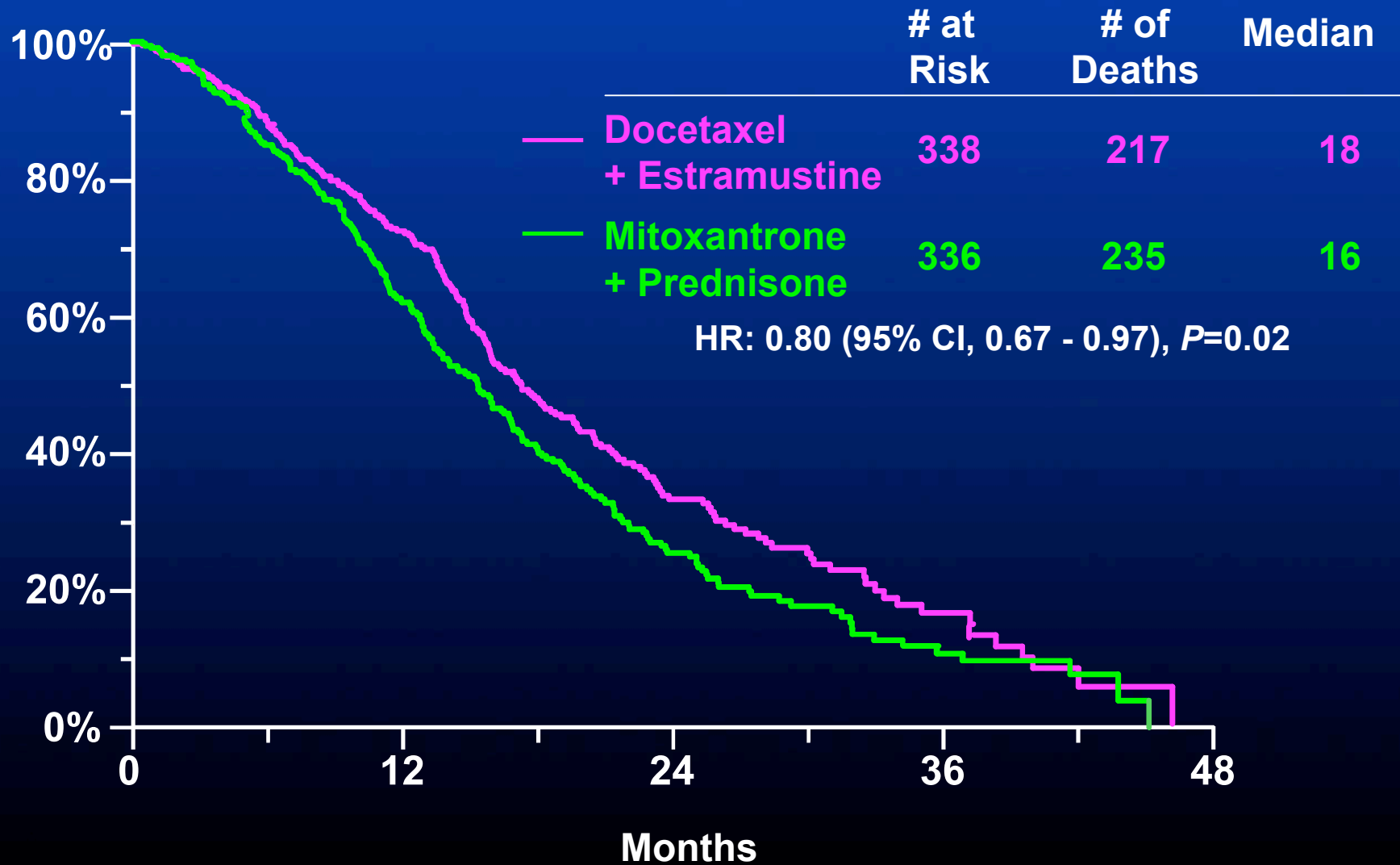
SWOG 9916: Progression-free Survival



No. at Risk

Docetaxel + Estramustine	338	176	75	20	6
Mitoxantrone + Prednisone	336	116	56	15	6

SWOG 9916: Overall Survival



SWOG 9916: Adverse Events Grade 3, 4, and 5



	Docetaxel + Estramustine (N=330)	Mitoxantrone + Prednisone (N=328)	<i>P</i>
Cardiovascular	48	22	<i>P</i> =0.001
Nausea and vomiting	66	17	<i>P</i> <0.001
Infection	45	22	<i>P</i> =0.004
Metabolic	20	2	<i>P</i> <0.001
Neurologic	23	5	<i>P</i> =0.001

Note: Adverse events are in large part due to estramustine

Conclusions Regarding SWOG 9916 and TAX-327



- **Docetaxel-based chemotherapy, given every three weeks, offers a significant improvement over mitoxantrone/prednisone in:**
 - **Survival**
 - **Decreased risk of death by 20% to 24%**
 - **Absolute increase in median survival of 2.0 to 2.5 months**
 - **Time to disease progression**
 - **Pain response**
 - **PSA response**
 - **Quality of life**

Docetaxel and Zoledronic Acid in HRPC with Bone Metastases



Should these two agents be combined?

- Currently, there is some preclinical evidence of a synergistic effect when combining docetaxel with zoledronic acid¹
- Bertelli et al.² confirmed the safety of the combination and also suggested a synergistic effect
- Clinical trials to answer this question in hormone naïve patients are just beginning (STAMPEDE trial)

1. Clézardin P. *Cancer Treat Rev* 2006;in press.

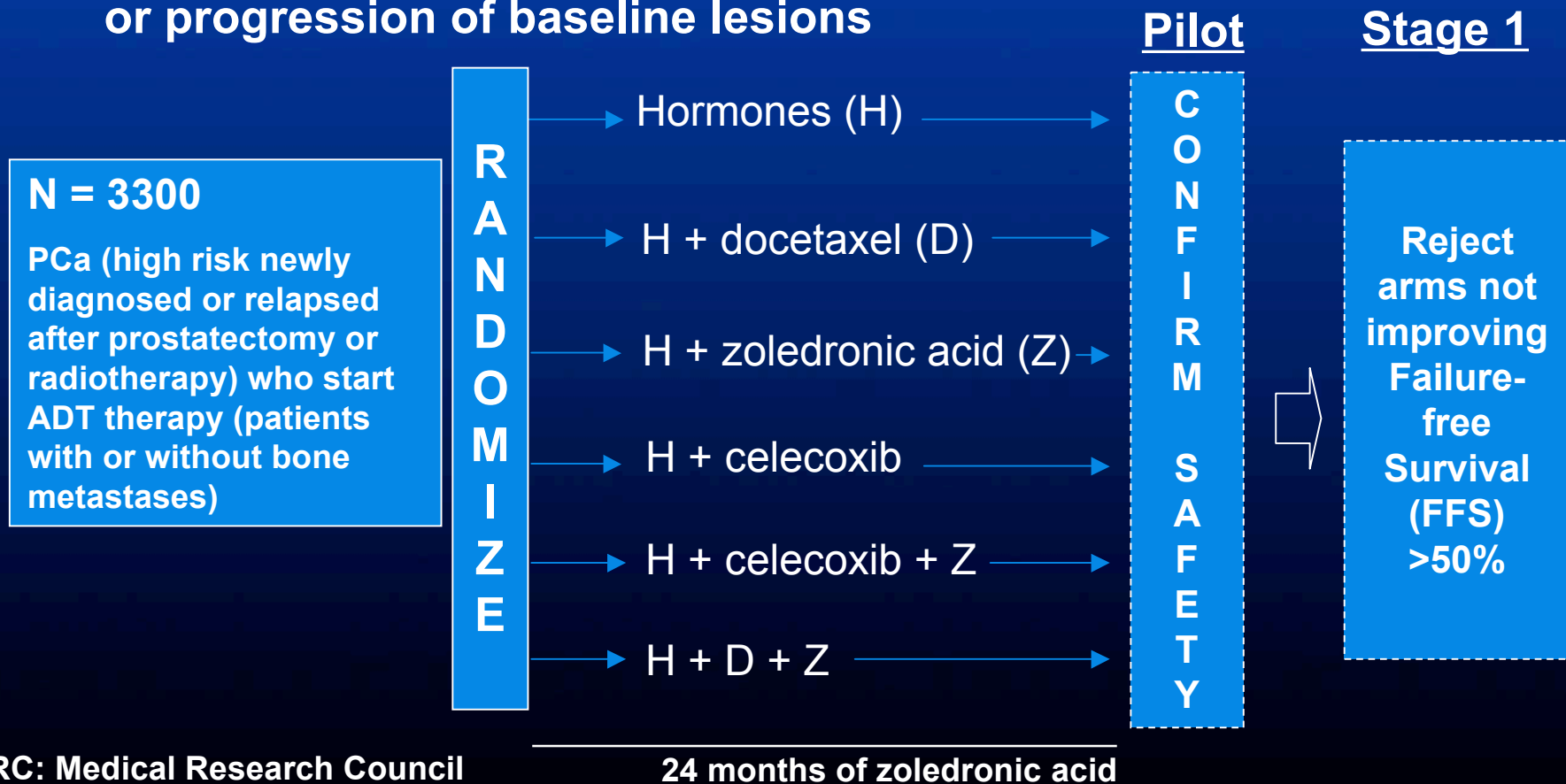
2. Bartelli G et al. *Cancer Chemother Pharmacol*. 2006;57:46-51.

2411/STAMPEDE (MRC, UK) – Hormone Naïve Patients



Endpoints:

- Safety, PSA failure-free survival, new lesions or progression of baseline lesions



MRC: Medical Research Council

PCa: Prostate Cancer

Treatment Options for HRPC



- Second-line hormonal manipulations
- Radiation therapy /
Radiopharmaceuticals
- Bisphosphonates
- Chemotherapy
- **Novel / Investigational agents**

New Agents for HRPC



- **Antiangiogenesis agents**
- **Antisense oligonucleotides**
- **Gene therapy**
- **Growth factor pathway agents**
- **Immunotherapeutic agents**
- **Proapoptotic drugs**

Overall Summary Conclusion

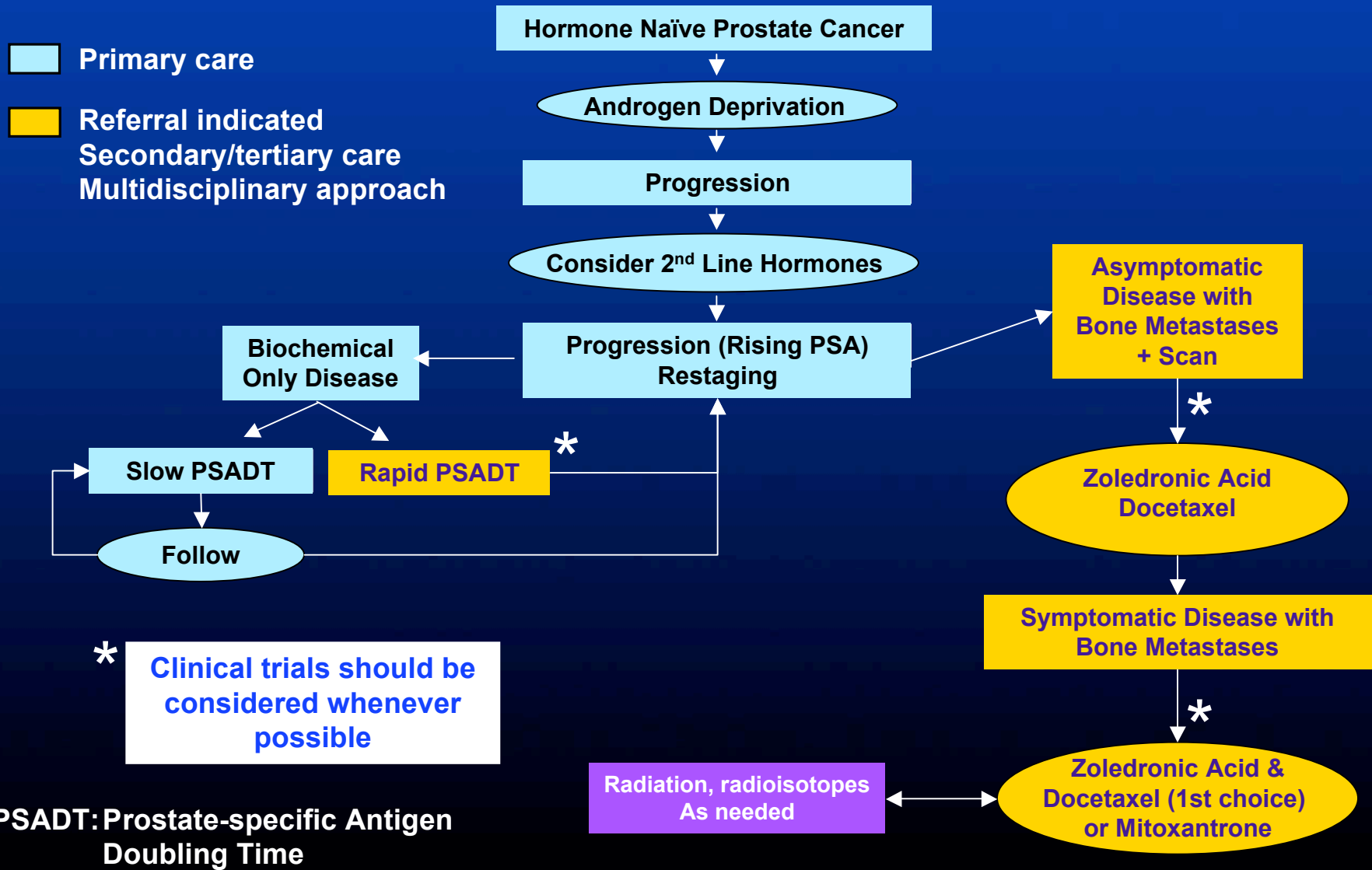


Management of HRPC: Overall Summary



- **Secondary hormonal manipulations** result in a PSA decrease, but usually have only short term value
- **Radiation therapy** provides transient pain relief and can provide effective pain relief for focal pain
- **Zoledronic acid** is proven to reduce bone complications in asymptomatic or minimally symptomatic patients
- **Docetaxel-based regimens** improve overall survival, pain, and quality of life in asymptomatic or minimally symptomatic patients

Suggested Paradigm of Current Practice Guidelines for HRPC



PSADT: Prostate-specific Antigen Doubling Time

Adapted from Pienta KJ, et al. *CA Cancer J Clin* 2005;.55:300-318; Saad et al. *Can J Urol* 2006;13 Suppl 2:52-56.