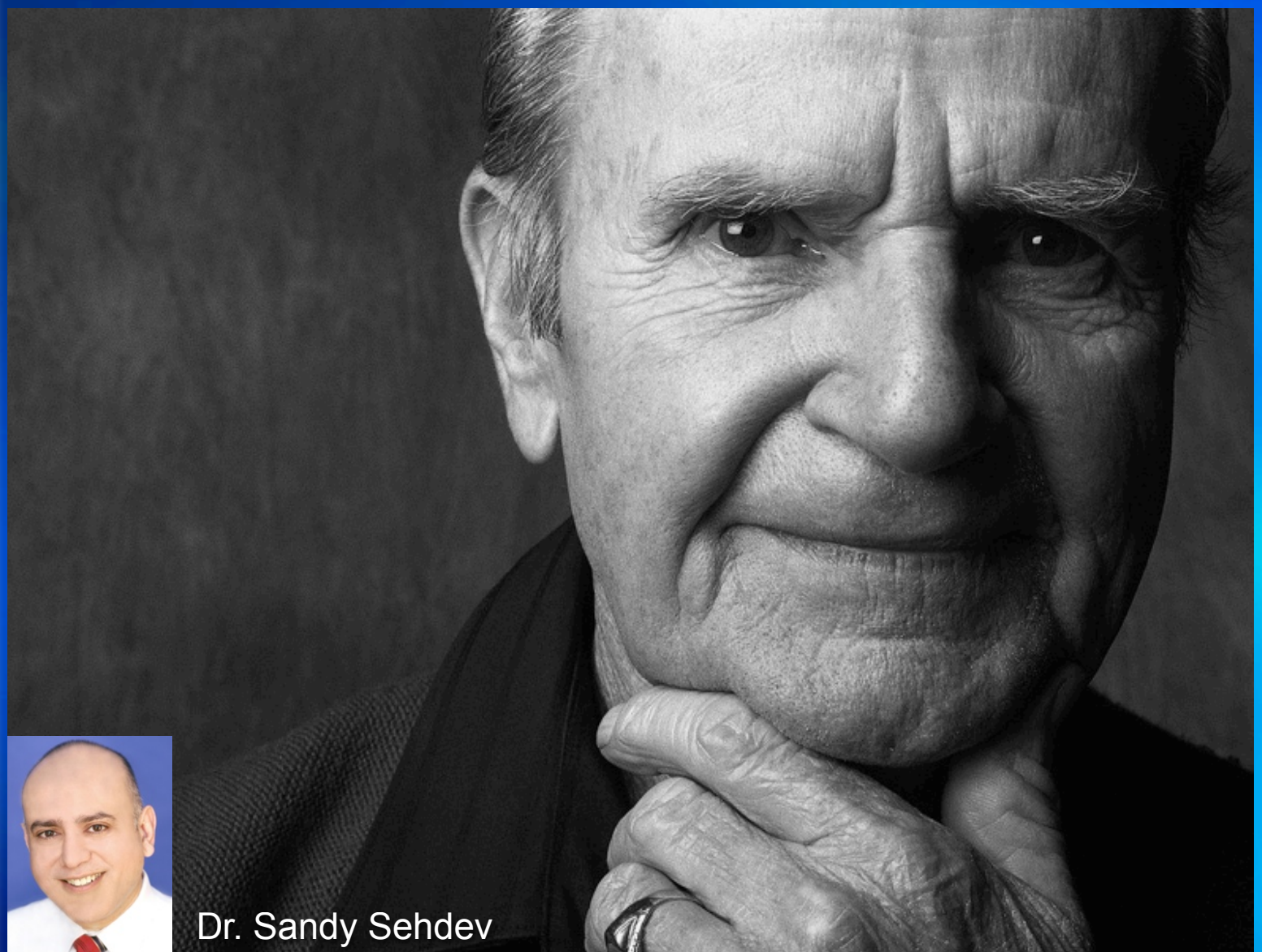
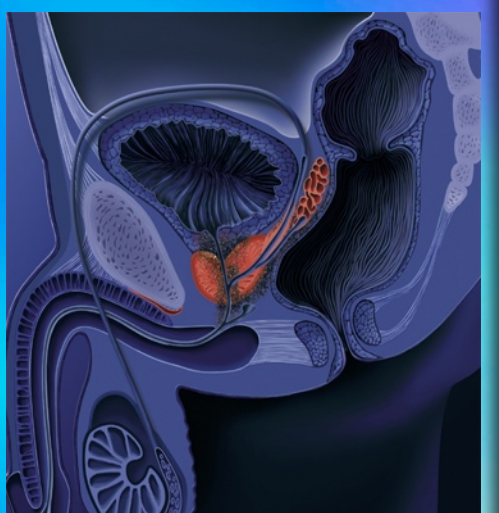
Systemic Treatment of Advanced Prostate Cancer



Dr. Sandy Sehdev

WILLIAM OSLER HEALTH CENTRE



Prostate Cancer Canada

Background

1

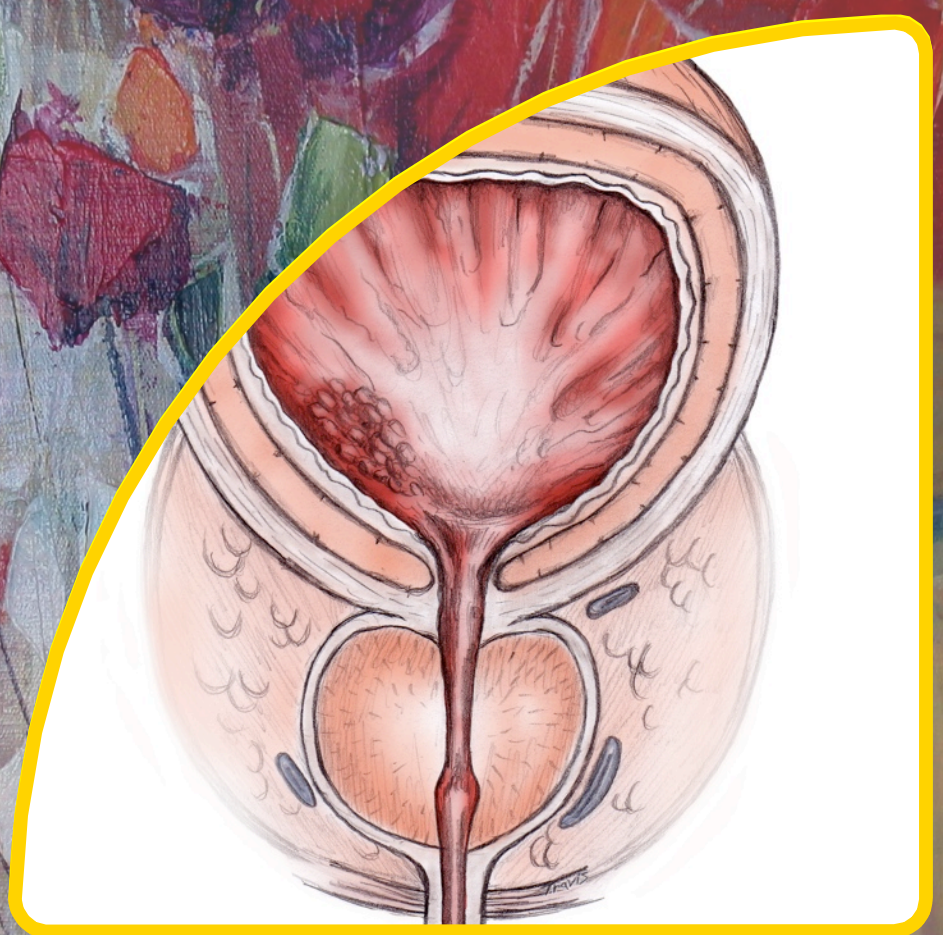
Objectives

Chemotherapy

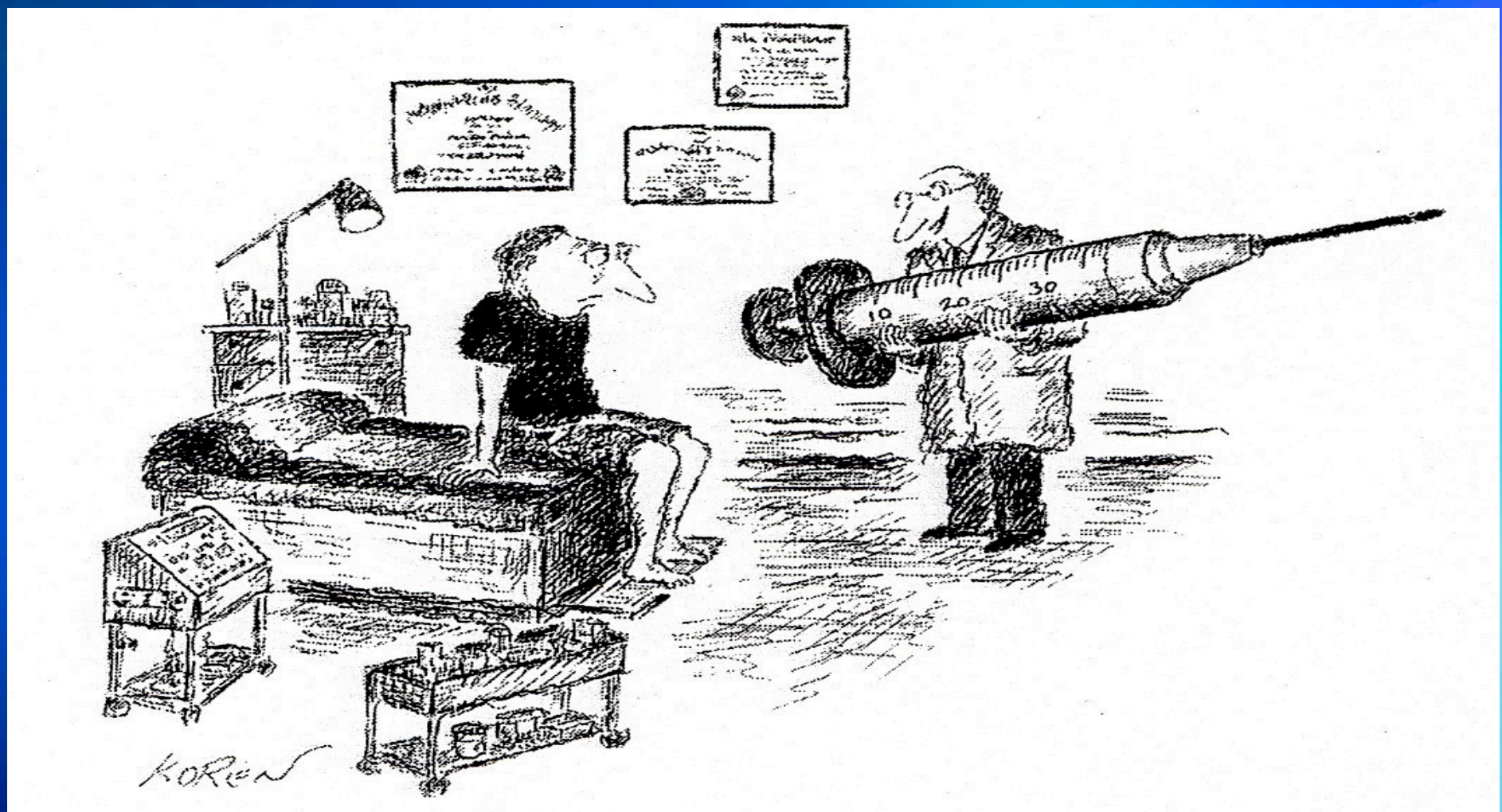
2

Bone Health

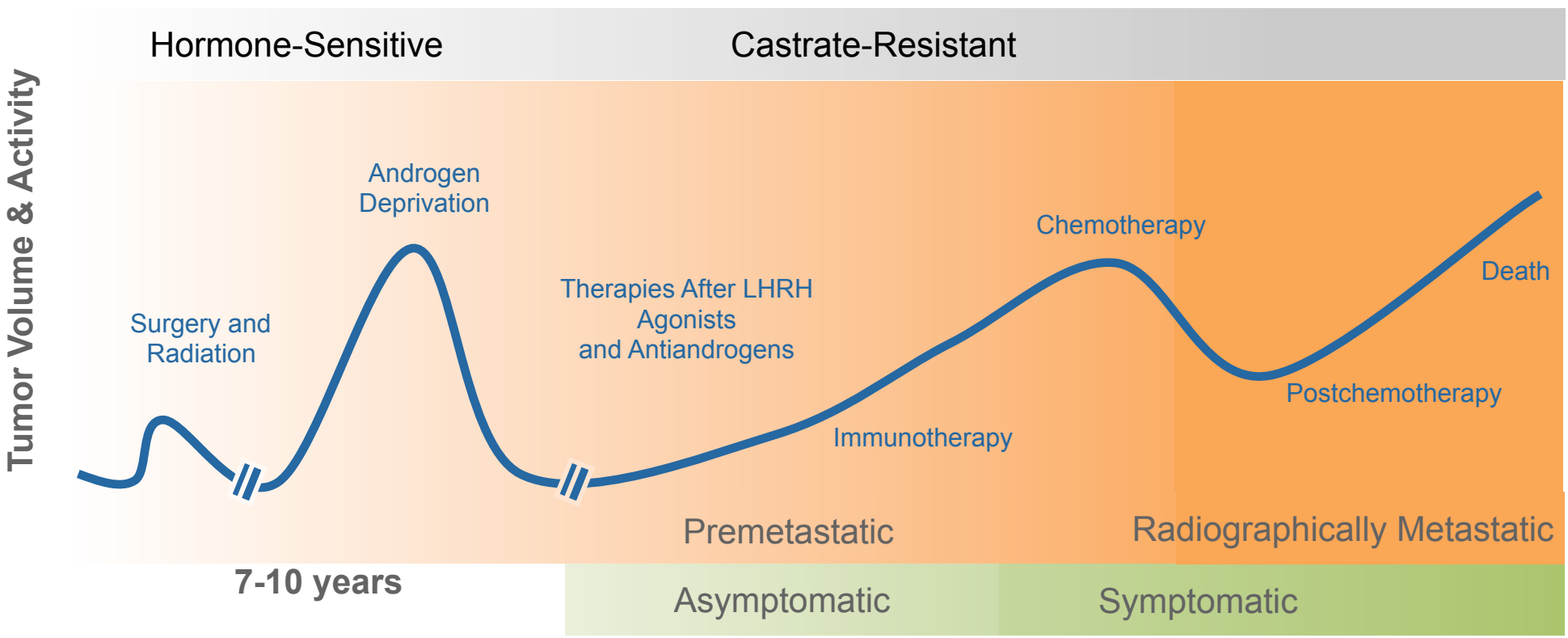
3



“This will buy you 3 months”



Natural History of Prostate Cancer



NOTE: This diagram represents *typical* disease progression. Note that some patients are metastatic at diagnoses, and are thus still hormone-sensitive.
LHRH=luteinizing hormone-releasing hormone.

1. Chen Y, et al. *Lancet Oncol.* 2009;10:981-991.
2. Hofland J, et al. *Cancer Res.* 2010;70:1256-1264.

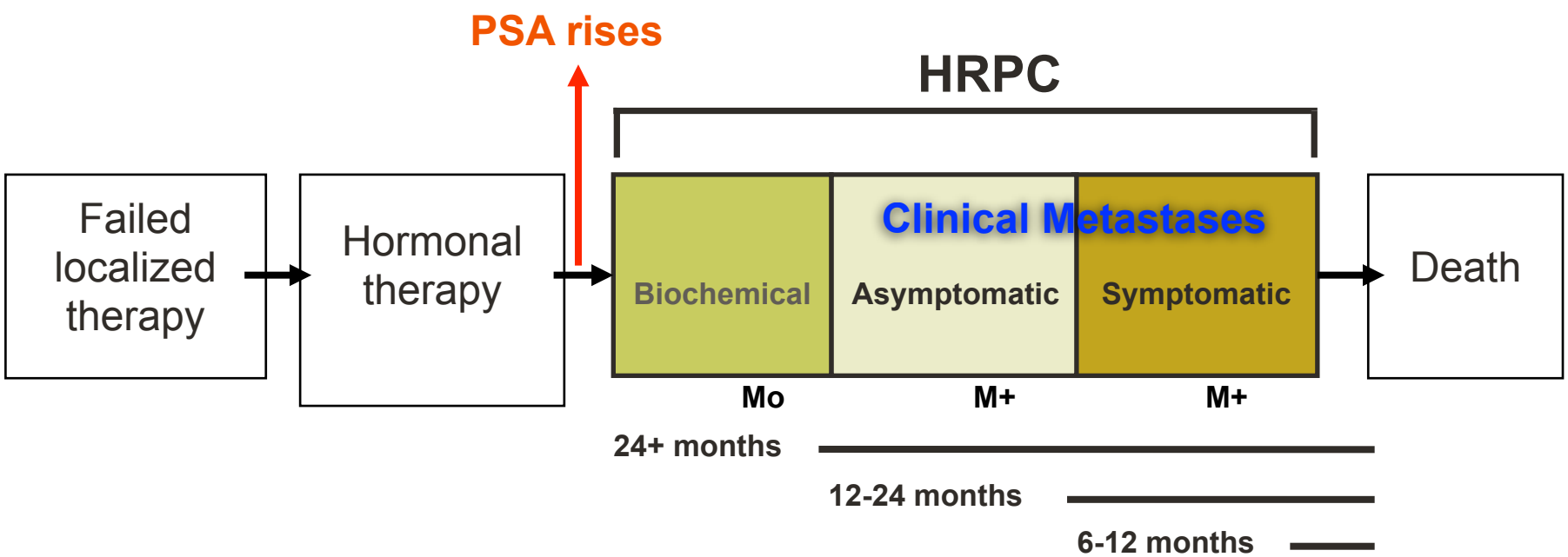
Measures of Response

- Survival (**OS**)
- Response Rates (**RR**)
- Clinical Benefit (**CB**) = RR + SD
- Time to Progression (**TTP**)
- Skeletal Related Events (**SRE**)
- Palliation of Symptoms: pain scales, Rx use
- **QoL**
- Biochemical
  - **PSA** response
  - Duration of response

CRPC – Goals of Therapy

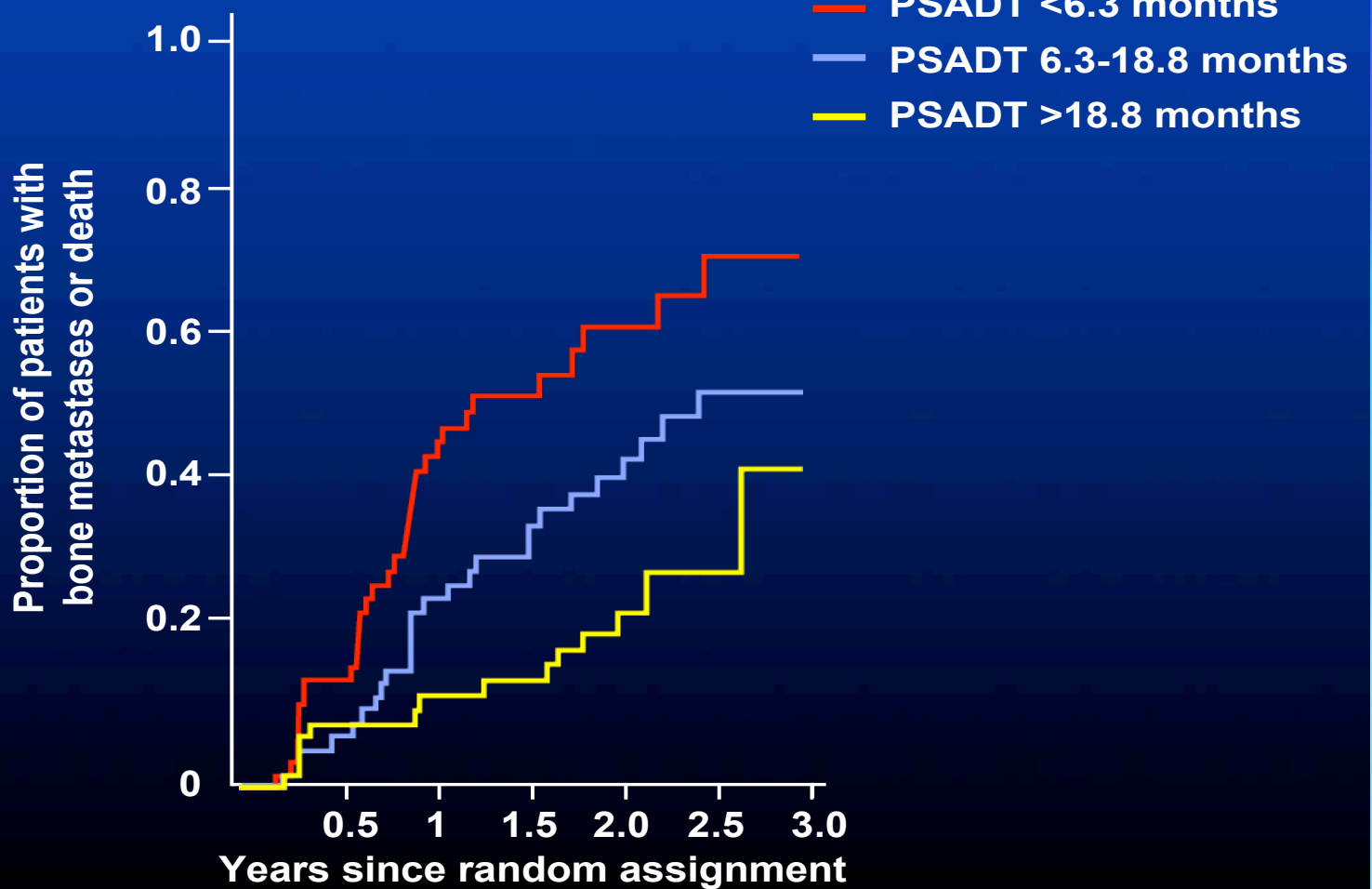
- **Improve survival**
  - no known regimen before docetaxel has been shown in phase III trials to improve overall survival
- **Improve symptoms**
  - quality of life remains a priority in treatment

Progressive Disease



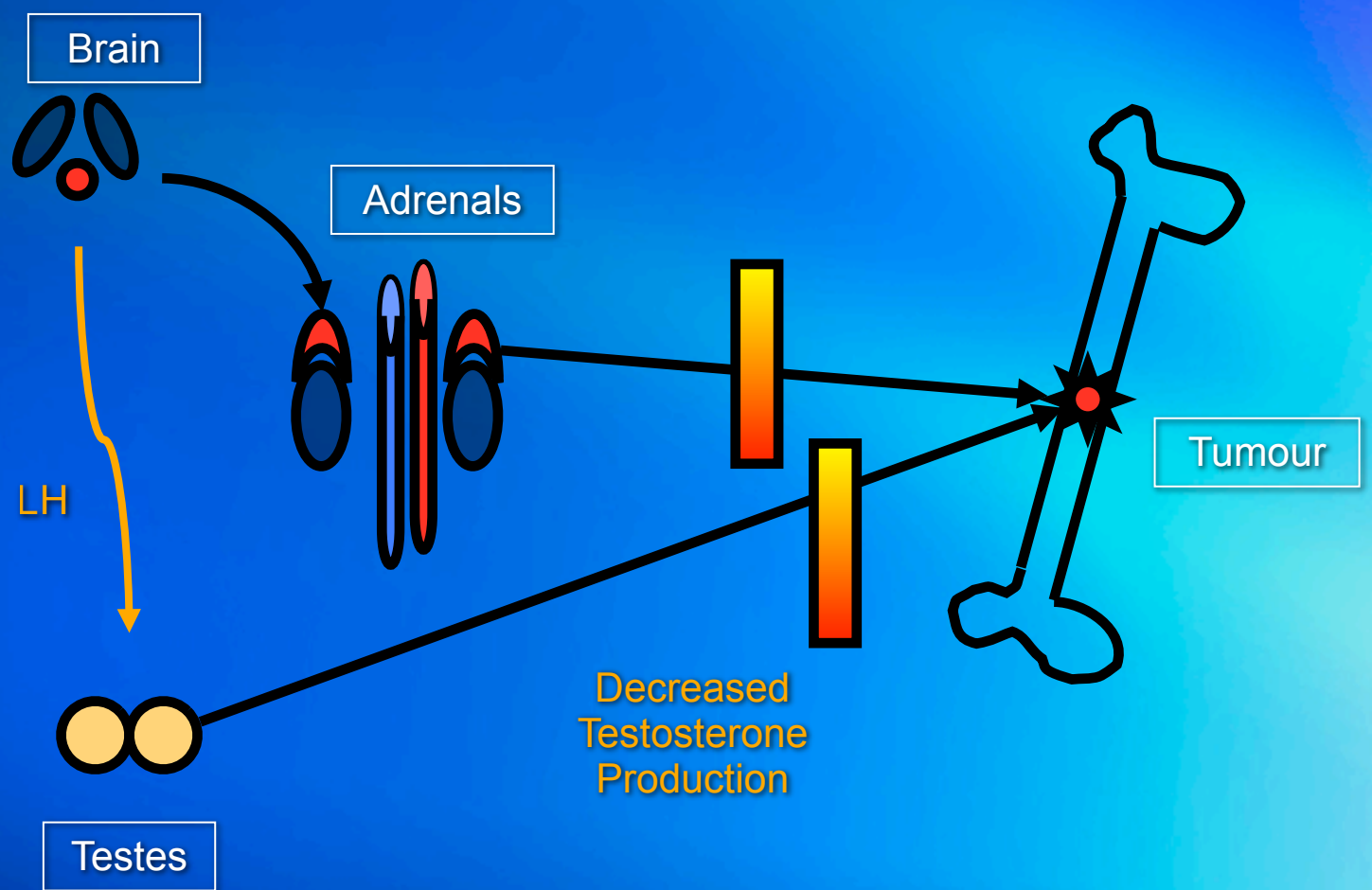
When To Treat -- When to Change Rx ??

Rising PSA in m0 CRPC
PSA Doubling Time

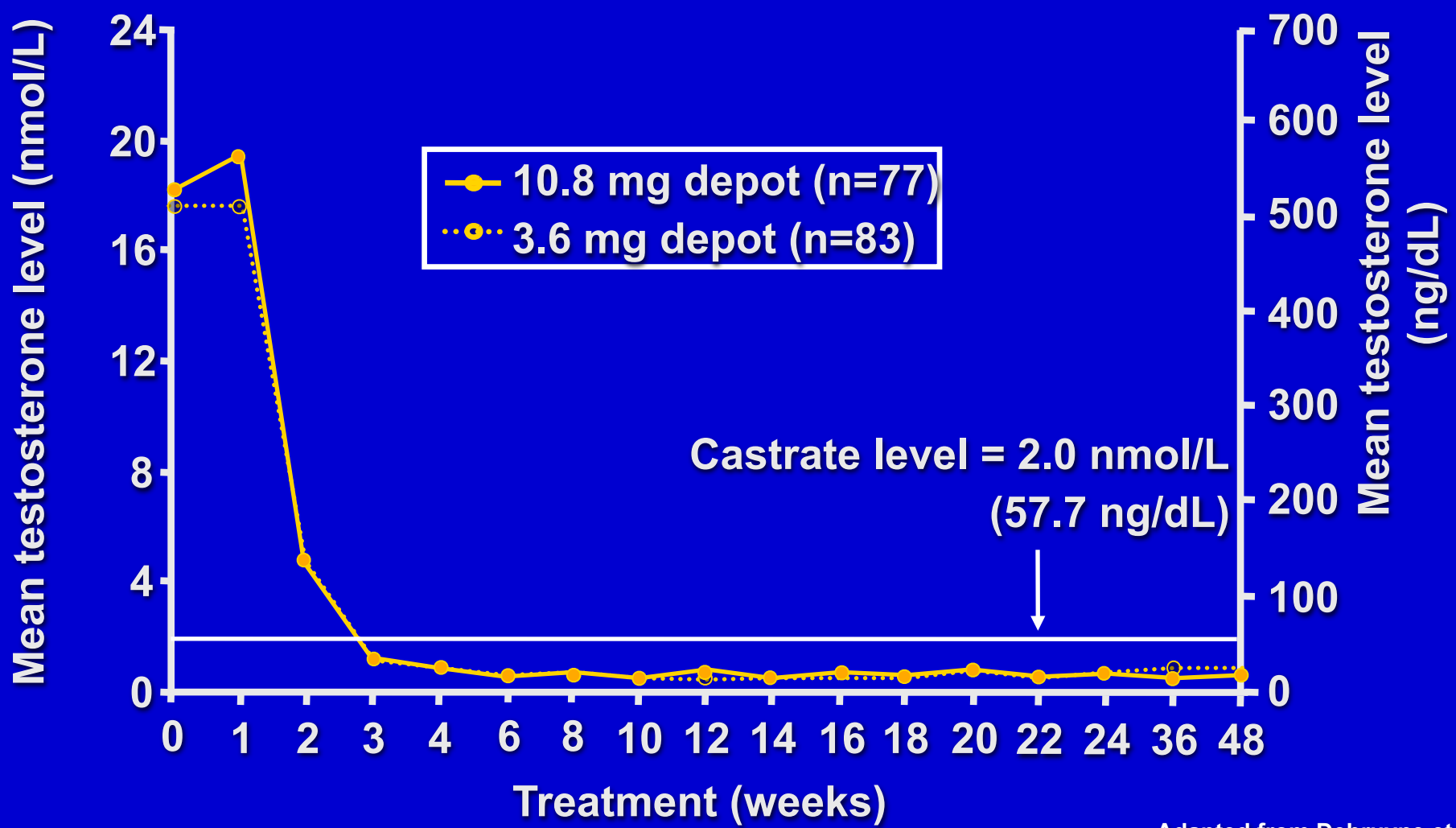


Smith MR, et al. *J Clin Oncol* 2005;23:2918-2925.

Androgen Deprivation

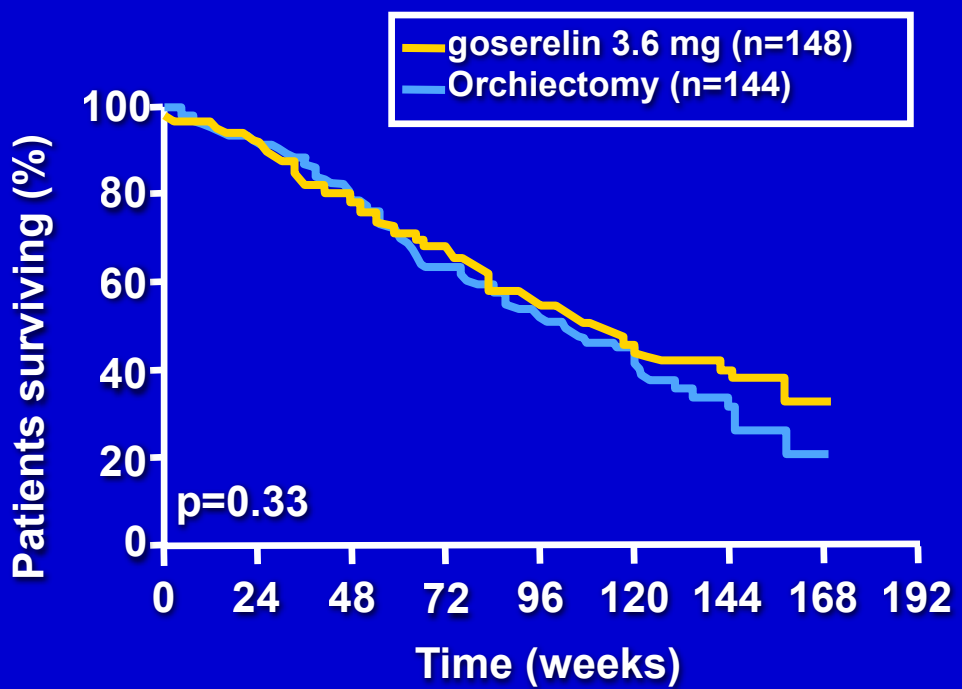


Gosarelin Suppresses Testosterone Levels to Below 20 ng/dL (0.69 nmol/L)

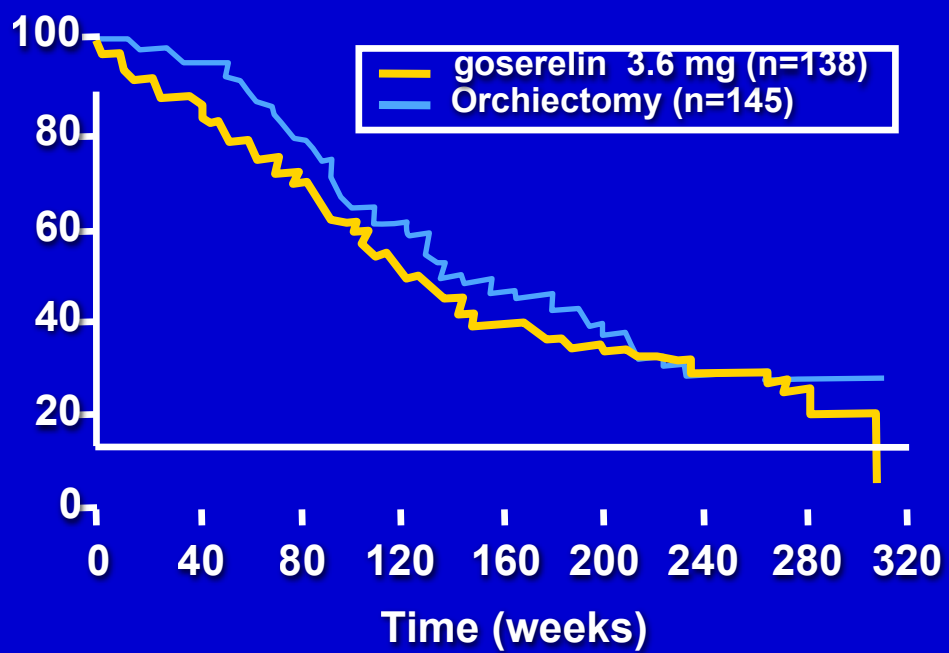


Adapted from Debruyne et al 1996

Goserelin and Orchiectomy Result in Similar OS in Metastatic Disease



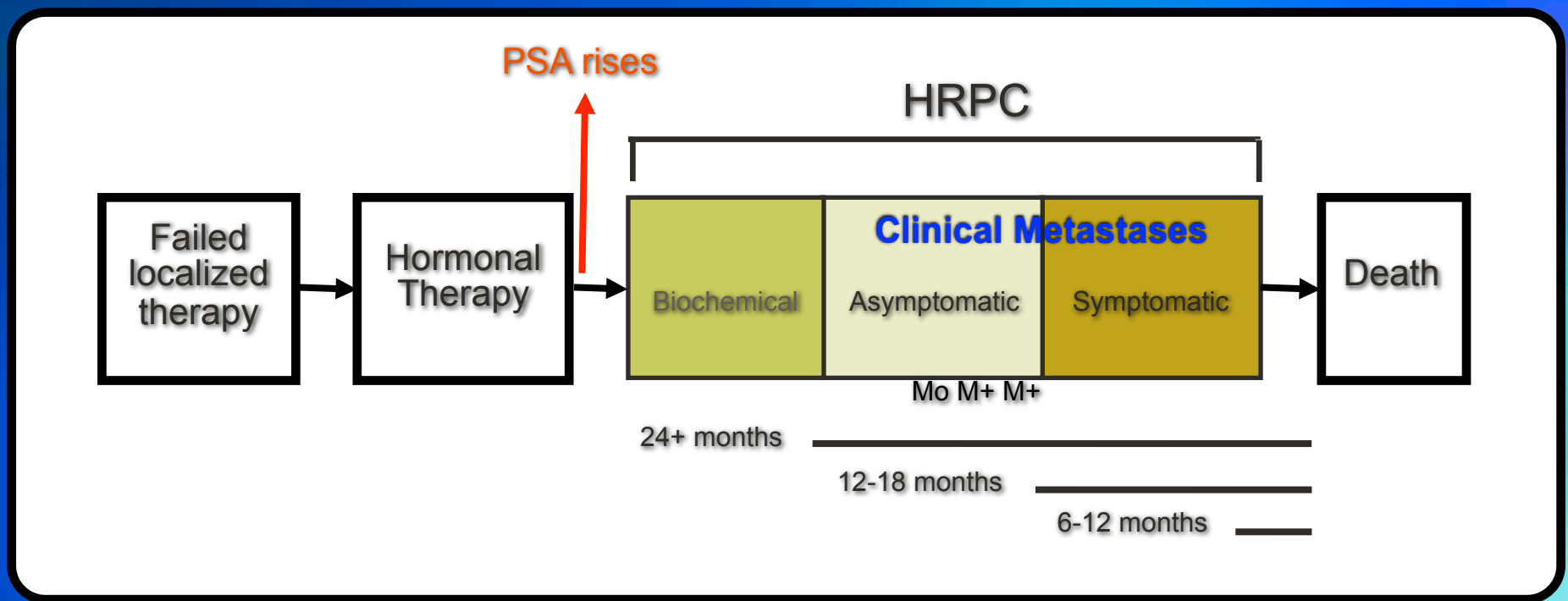
Kaisary et al (1991)



Vogelzang et al (1995)

OS, overall survival

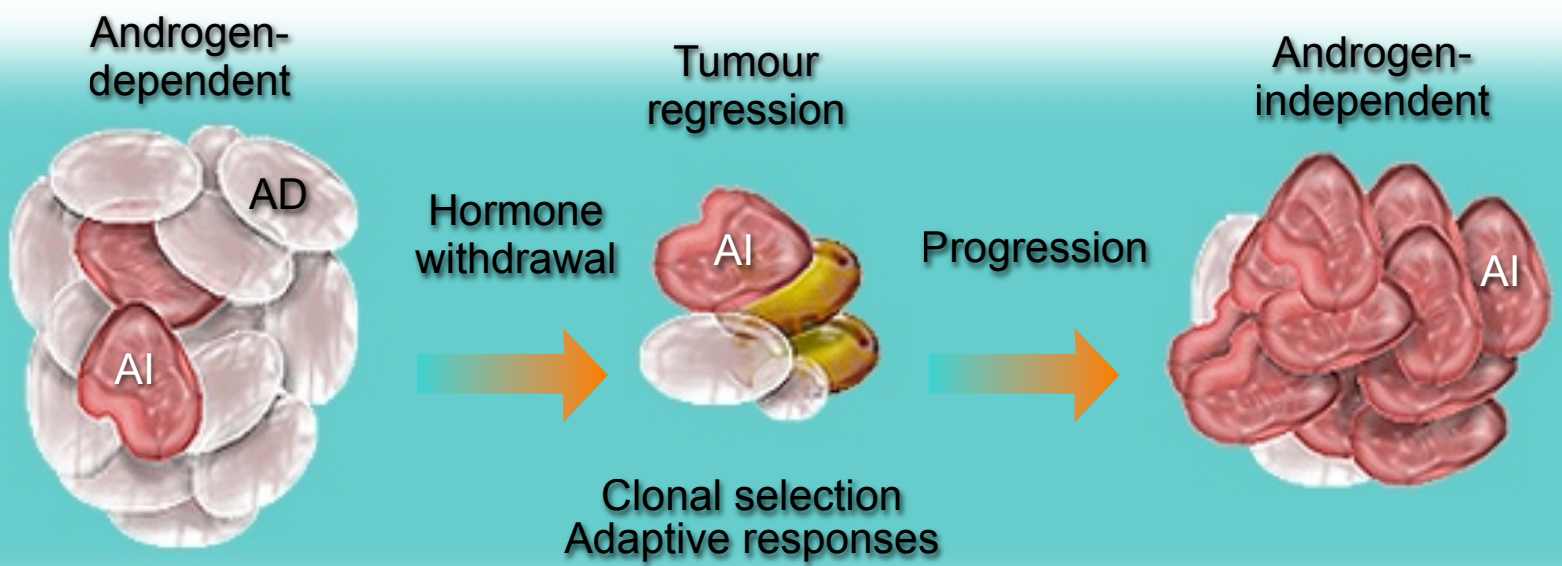
Progression



Castrate Resistant Prostate Cancer(CRPC)

- Serial rise in PSA with castrate testosterone levels
- Includes a heterogenous group of patients

Hormone Resistance



2nd Line Hormonal Rx

- Clinical and objective responses
  - PSA levels decline, patients may have symptomatic improvement
  - **Survival benefit is unknown**
- "Minimal side effects"
- Dietary: leukopenes

Antiantrogen Withdrawal

- First described with flutamide
  - can occur with other hormones
- 10% to 30% of the time
- PSA decreases within weeks
- Median duration of response: 3.5 months

Scher H. J Clin Oncol 1993;11:1566 Small E. Cancer 1995;76:1428

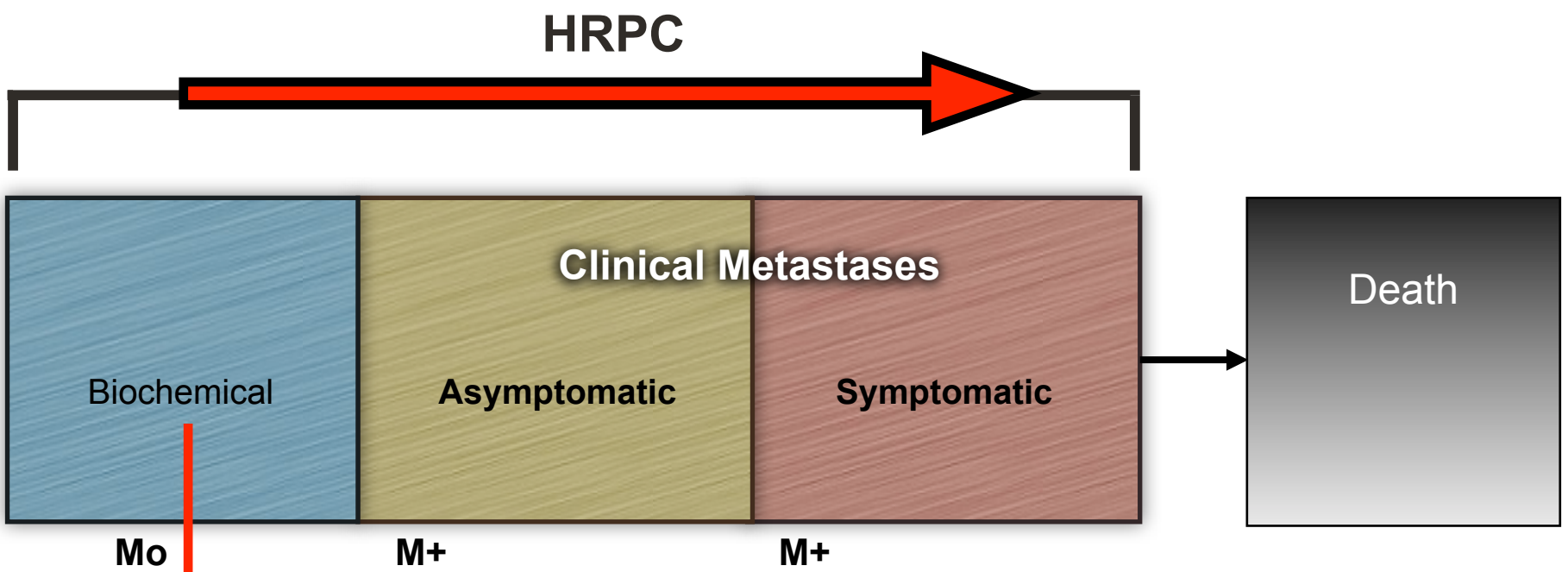
Abiraterone

From Medscape Medical News

GUCS 2009: Abiraterone Show Promise in Metastatic Prostate Cancer Patients

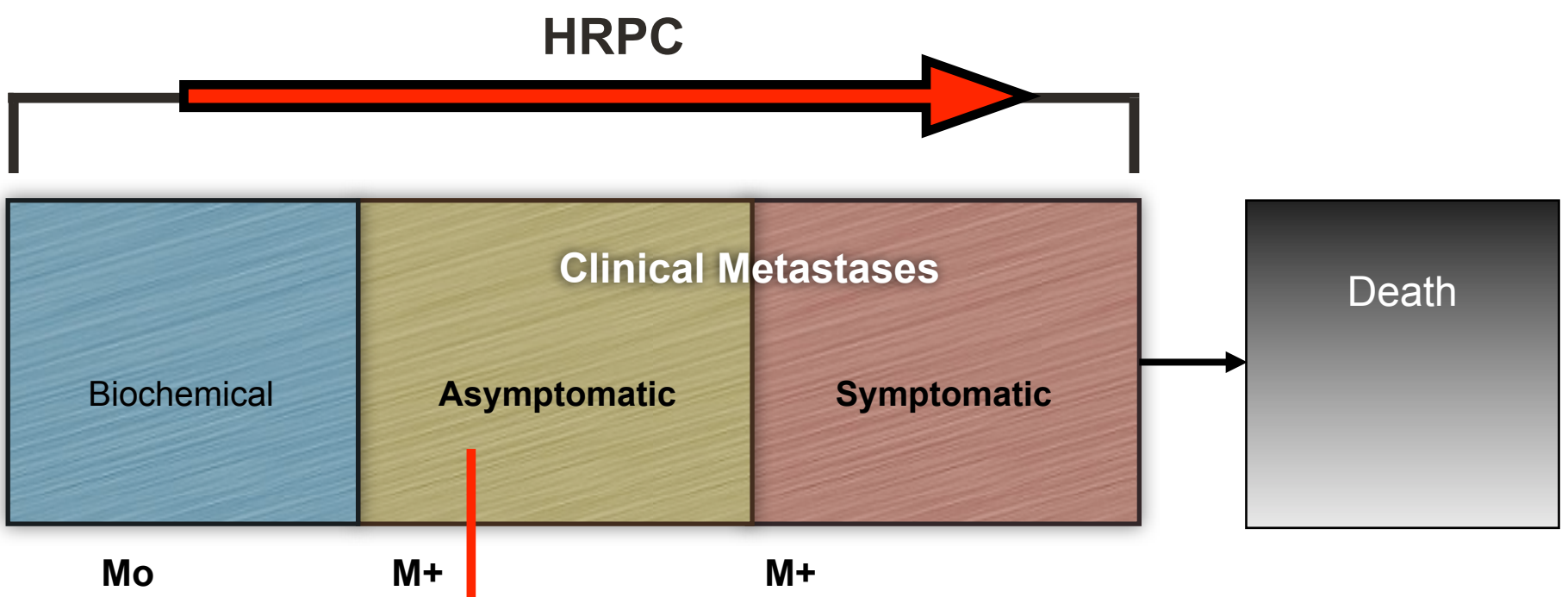
Medscape Medical News

Biochem Progression



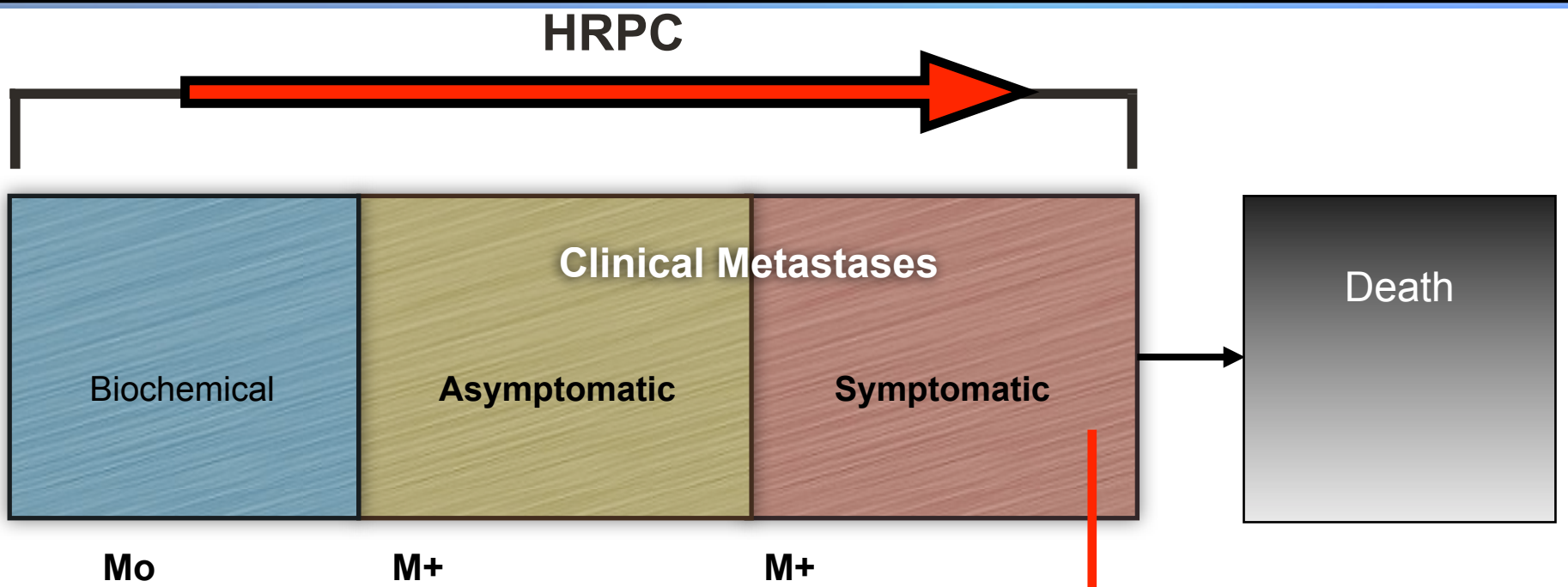
- Hormone withdrawal
- Watchful waiting
- ? Zometa™ -- if bone mets
- Chemotherapy

Asymptomatic



- Antiandrogens
- ? Zometa (US vs Canada)
- Chemotherapy

Symptomatic

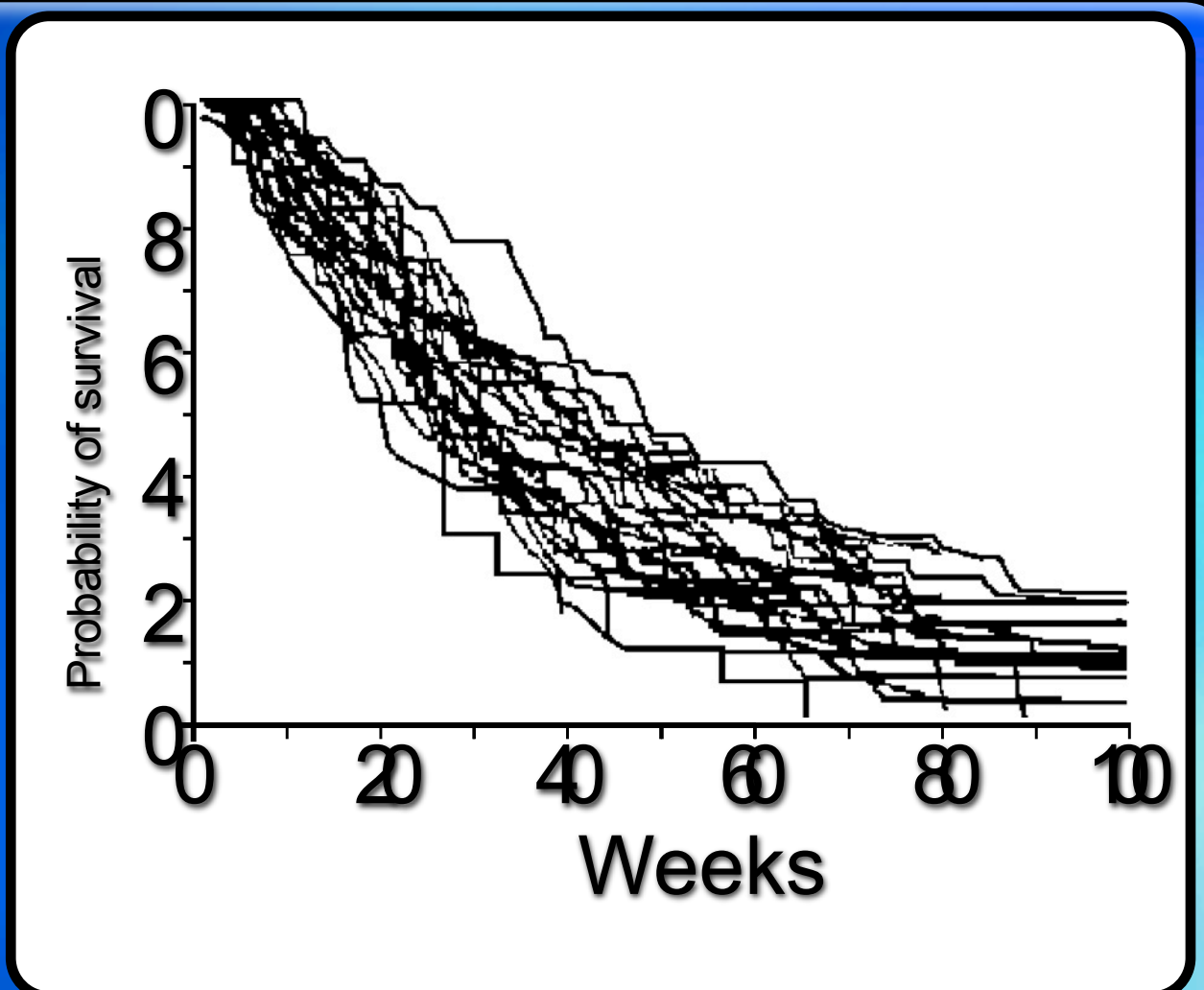


- Analgesia
- XRT
- Zometa™
- Prednisone
- Chemotherapy

Chemotherapy

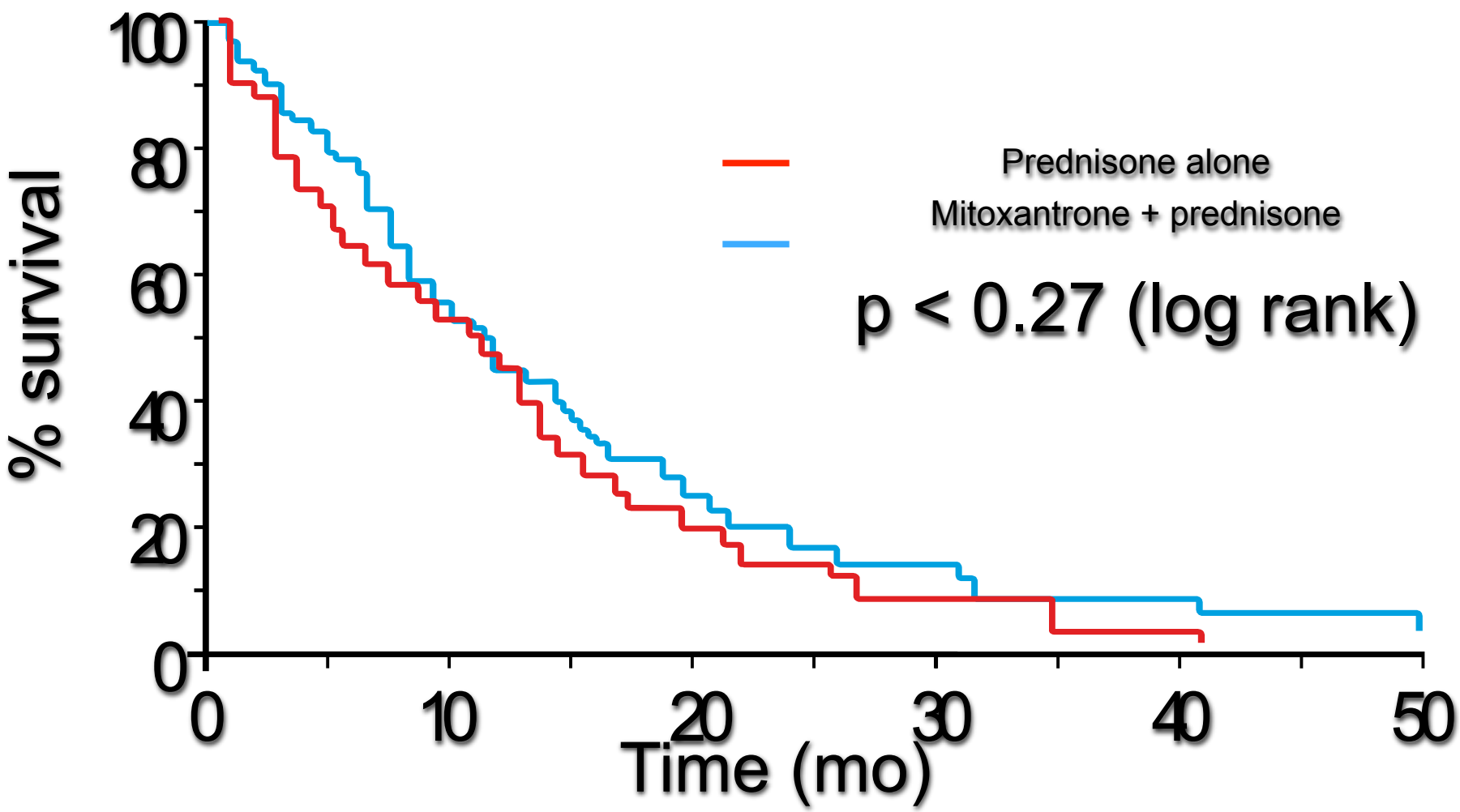
Early Results

- Prior to 1985
  - Eisenberger et al
  - 17 trials (n = 1,464)
  - response rate – 4.5%
- "Spaghetti curves"
  – all drugs equally ineffective
- 1987-1991
- Yagoda and Petrylak
- 26 trials (n = 3,184)
  - overall response rate – 8.7%



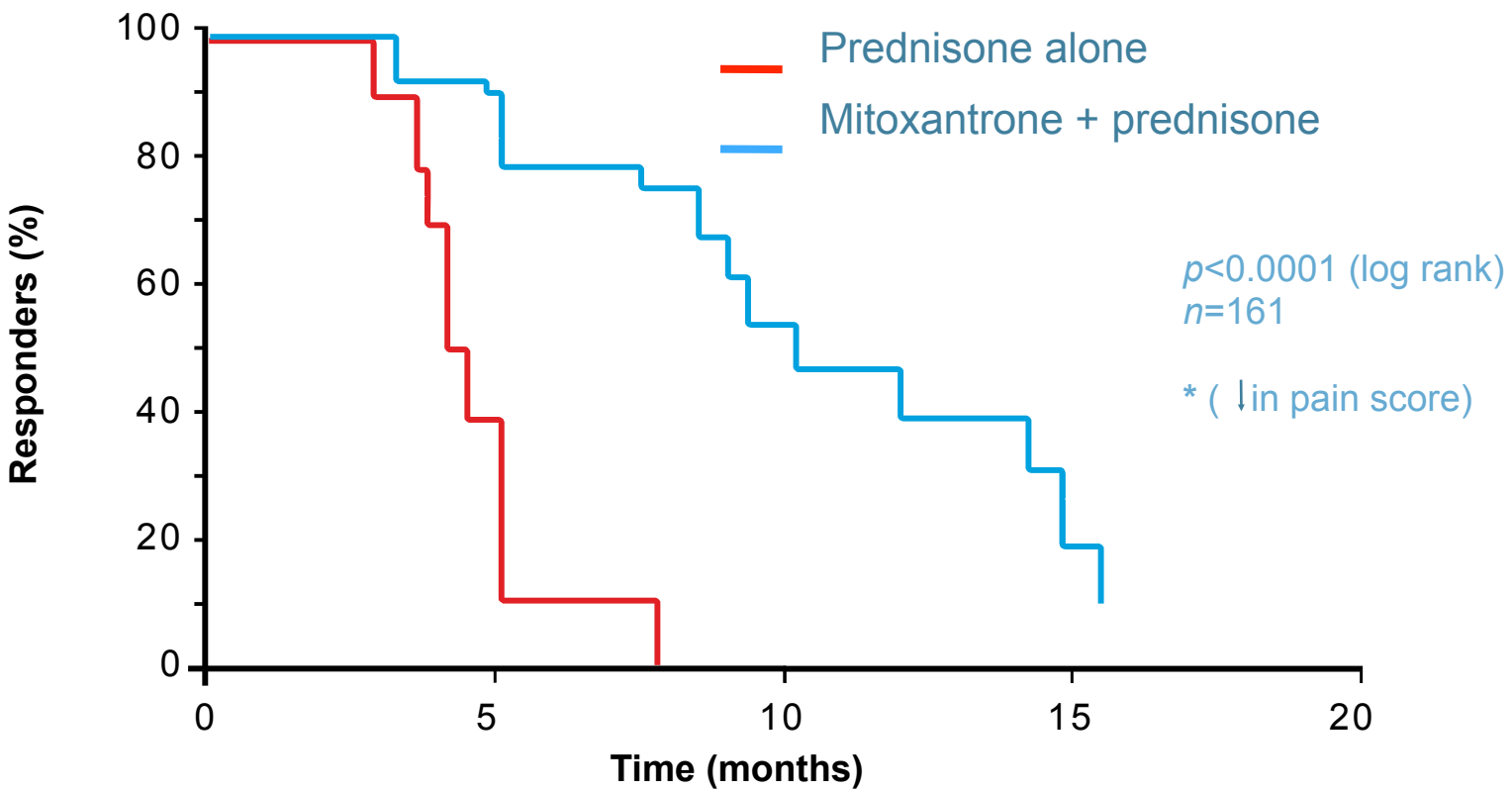
Eisenberger M. J Clin Oncol 1985;3:827 Yagoda A. Cancer 1993;71(3 Suppl):1098

Mitoxantrone: OS



Tannock I. J Clin Oncol 1996;14:1756 Kantoff P. J Clin Oncol 1999;17:2506

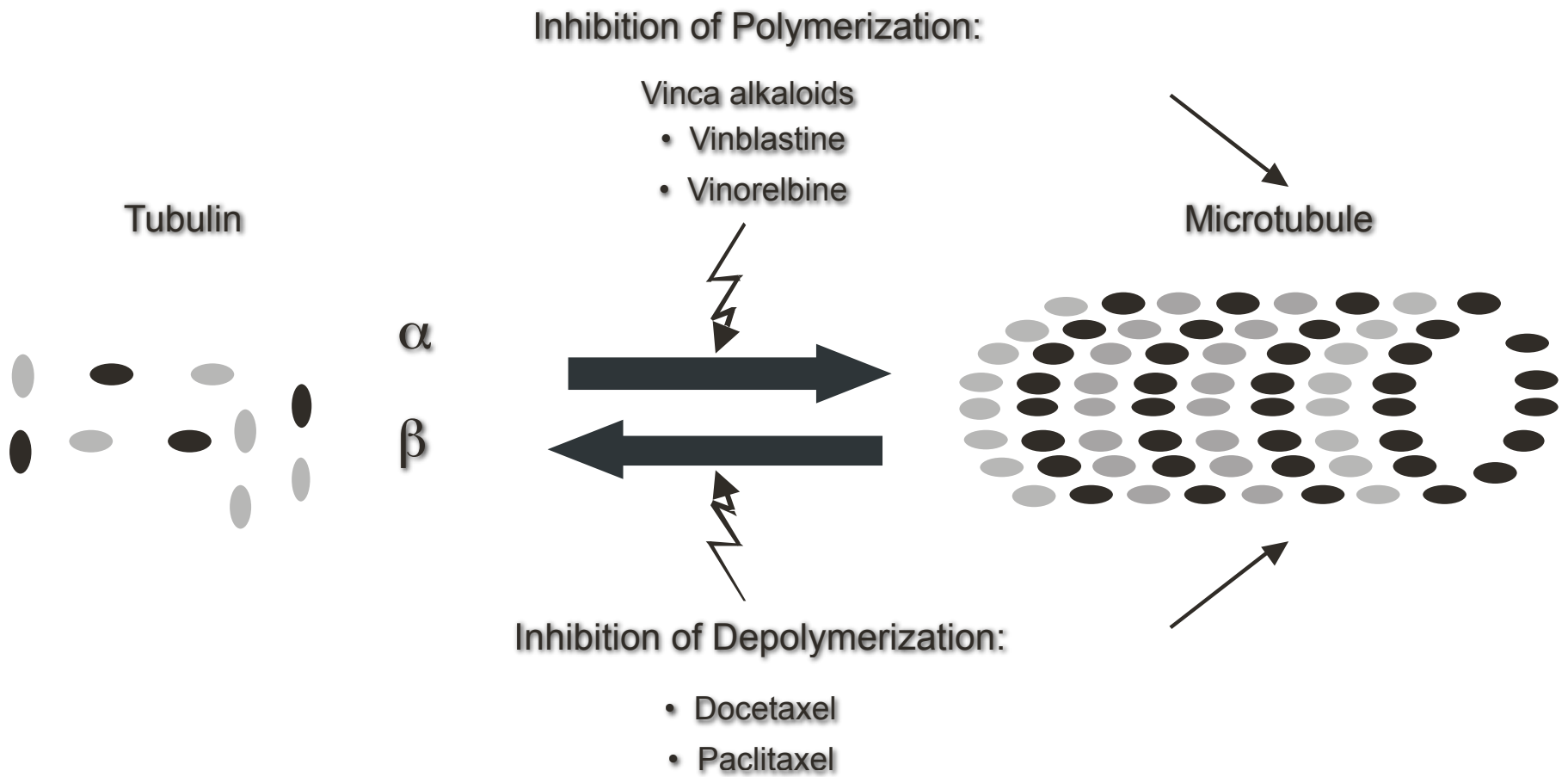
Mitoxantrone: Palliative Response*



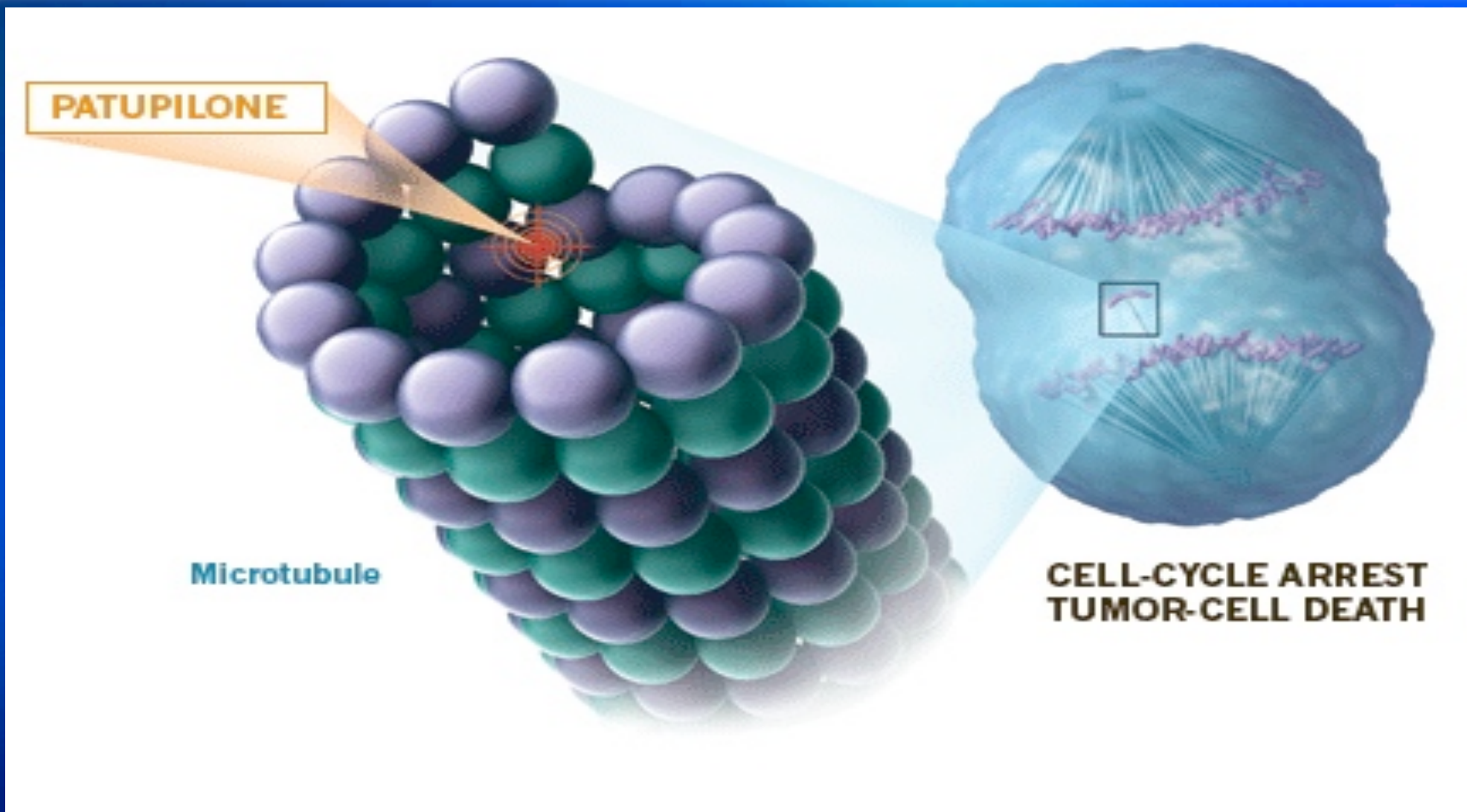
- 29% vs. 12% palliative response for mitoxantrone + prednisone vs. prednisone alone
- Improved QOL

Tannock IF et al. *J Clin Oncol* 1996;14:1756-1764.

Microtubule Agents



Microtubule Agents



A multicentre comparison of docetaxel given weekly or every three weeks + prednisone with mitoxantrone + prednisone in patients with hormone-refractory prostate cancer: Study TAX-327

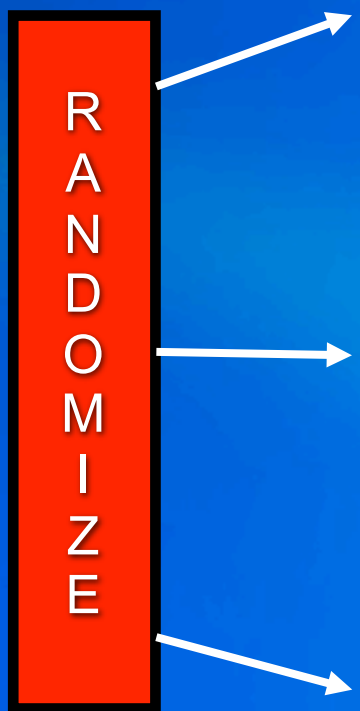
Ronald De Wit, M.D. PhD
Mario A. Eisenberger, M.D.
Ian Tannock, M.D. PhD
and
TAX-327 investigators

TAX327 Study Design

Stratification:

Pain level

KPS
≤70 vs. ≥ 80



Docetaxel 75 mg/m^2 q3 wk + Prednisone 5 mg bid

Docetaxel 30 mg/m^2 wkly 5 of 6 wks + Prednisone 5 mg bid

Mitoxantrone 12 mg/m^2 q3 wks + Prednisone 5 mg bid

Treatment duration in all 3 arms = 30 wks

TAX 327 Update: Survival

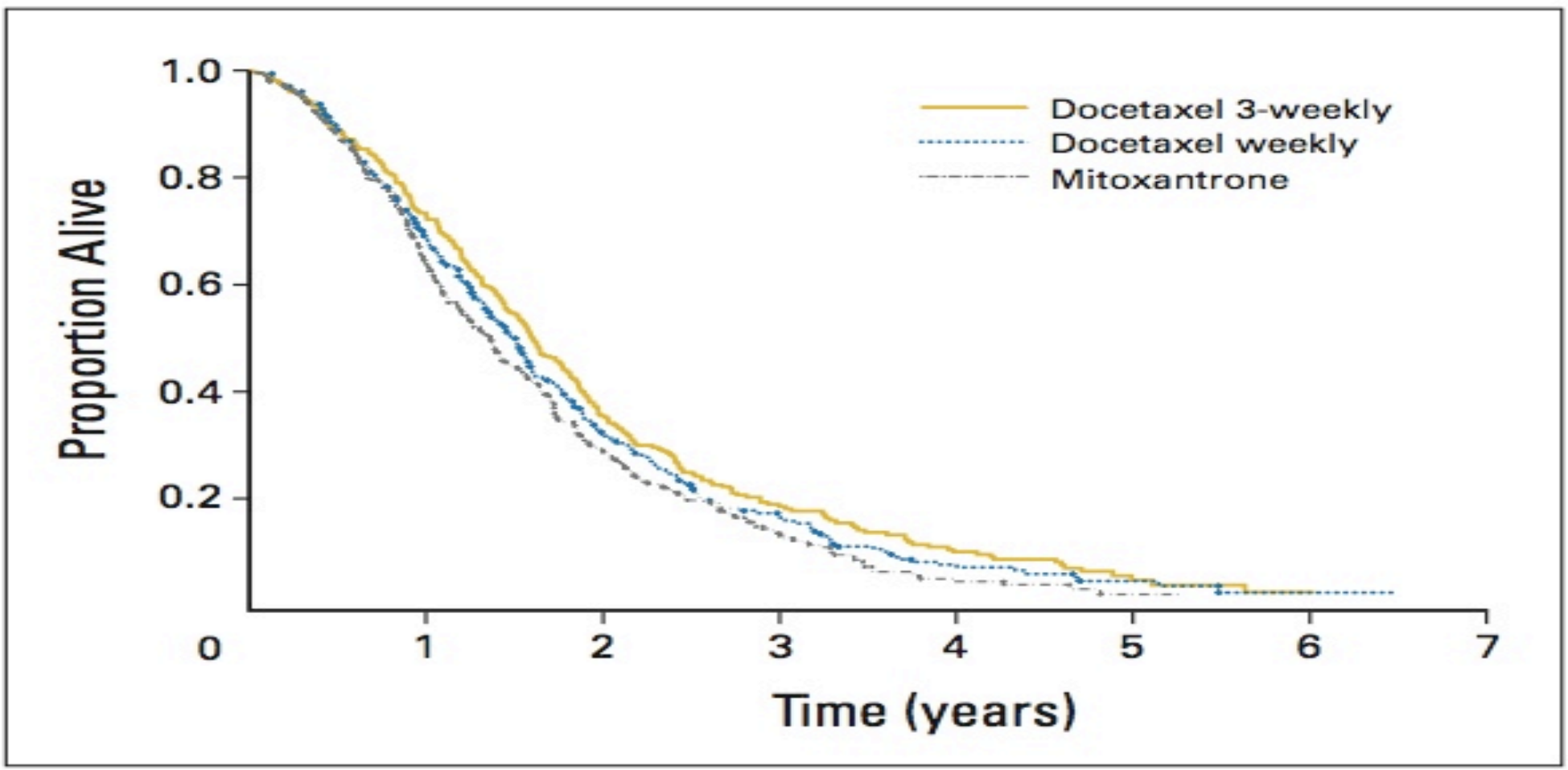
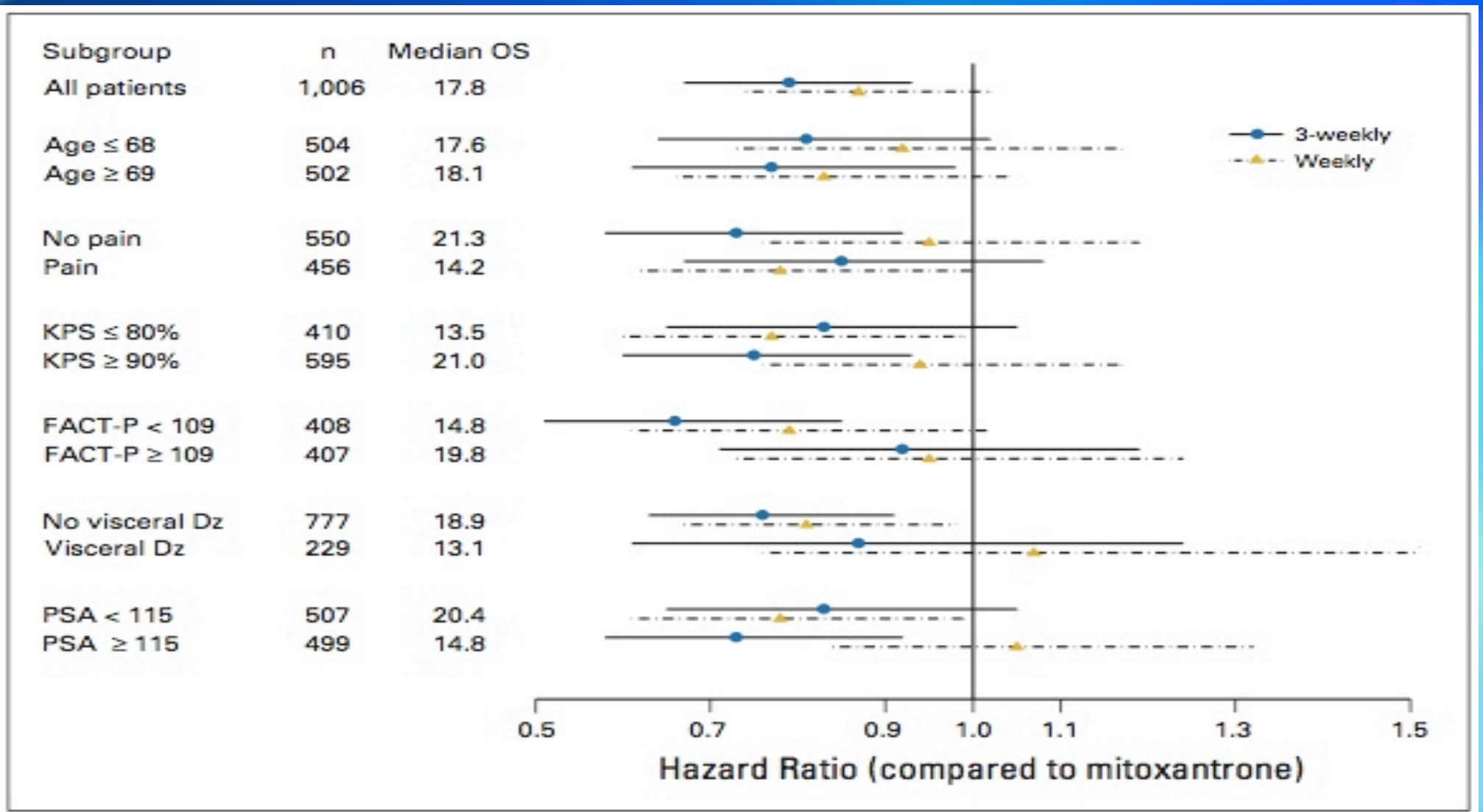


Fig 1. Overall survival data from March 2007, with 867 deaths among 1,006 randomly assigned patients.

TAX 327 Update: Survival



Response Rates

	Docetaxel 3 wkly	Docetaxel wkly	Mitoxantrone
Pain Response Rate*			
n, evaluable	153	154	157
Response rate (%)	35	31	22
P-value (vs. mitoxantrone)	0.01	0.07	–
PSA Response Rate*			
n, evaluable	291	282	300
PSA response rate (%)	45	48	32
P-value (vs. mitoxantrone)	0.0005	<0.0001	–
Tumor Response Rate*			
n, evaluable	141	134	137
Response rate (%)	12	8	7
P-value (vs. mitoxantrone)	0.1	0.5	–

* Determined only for patients with pain or PSA ≥20 or measurable disease at baseline, respectively

Quality of Life Response

> 16 points FACT-P score compared to baseline

	Docetaxel 3-wkly	Docetaxel wkly	Mitoxantrone
Evaluable patients	278	270	267
Response (%) (95% CI)	22 (17-27)	23 (18-28)	13 (9-18)
P-value*	0.009	0.005	

*Compared to mitoxantrone

Caveats

- **Side Effects**:
  - Asthenia 53% (all grades)
    - Very important issue
  - Anemia (gr 3-4 5%)
  - Infections / febrile neutropenia -- 5-6%
  - Withdrawal rates -- only 46% completed Rx
  - Toxic deaths -- few

Side Effects: Blood
(mod severe - severe)

	Docetaxel 3 wkly	Docetaxel wkly	Mitoxantrone
Treated (N)	332	330	335
Anemia	5.0	5.0	2.0
Neutropenia	32.0	1.5	22.0
Neutropenic infection	3.0	0.0	0.9
Febrile neutropenia	2.7	0.0	1.8
Septic death	0.0	0.3	0.3

Side Effects: Other

	Docetaxel 3 wkly		Docetaxel wkly		Mitoxantrone	
Toxicity	All grades	3/4	All grades	3/4	All grades	3/4
Alopecia	65	NA	50	NA	13	NA
Fatigue	53	4.5	49	5.5	35	5.1
Nausea	41	2.7	36	2.4	36	1.5
Diarrhea	32	2.1	34	4.8	10	1.2
Neuro-Sensory	30	1.8	24	0.9	7	0.3
Nail change	30	NA	37	NA	7	NA
Constipation	25	2.1	17	1.5	17	0.6

Side Effects: Other

	Docetaxel 3 wkly		Docetaxel wkly		Mitoxantrone	
Toxicity	All grades	3/4	All grades	3/4	All grades	3/4
Stomatitis	20	0.9	17	0.3	8	0.0
Tearing	10	0.6	21	0.3	1	0.0
Peripheral edema	19	0.6	12	0.6	1	0.0
Vomiting	17	1.5	22	2.1	14	1.5
Anorexia	17	1.2	21	0.3	14	0.3
Dyspnea	15	2.7	14	1.5	9	0.9
Epistaxis	6	0.3	17	0.6	2	0.0

Chemo Issues

- **Pt factors: personal**
  - Does he (or family) want chemo?
  - Misgivings / myths
  - Education
- **Pt factors: medical**
  - Performance status (KPS, ECOG)
  - Organ function, other concurrent diseases
  - Survival expectation

Chemo Issues

- **Tempo of disease -- speed**
  - indolent
  - aggressive
- **Gleason grade** (?predictive of behaviour)
- **Symptoms**

Karnofsky PS

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

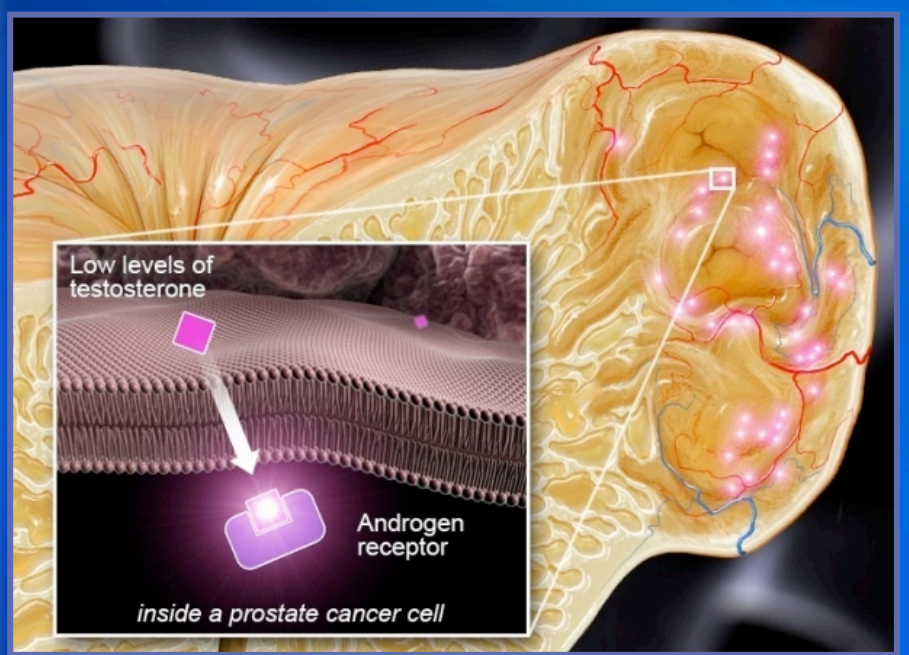
ECOG PS

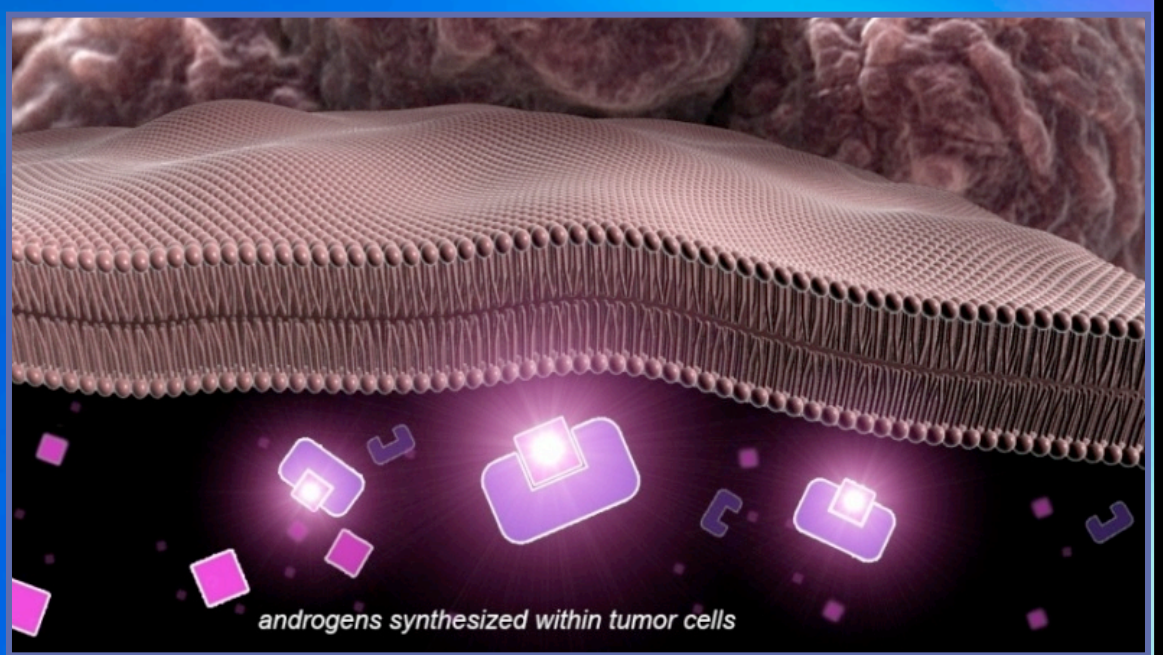
ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

How Does the Tumour Progress Despite Castrate Levels of Testosterone?

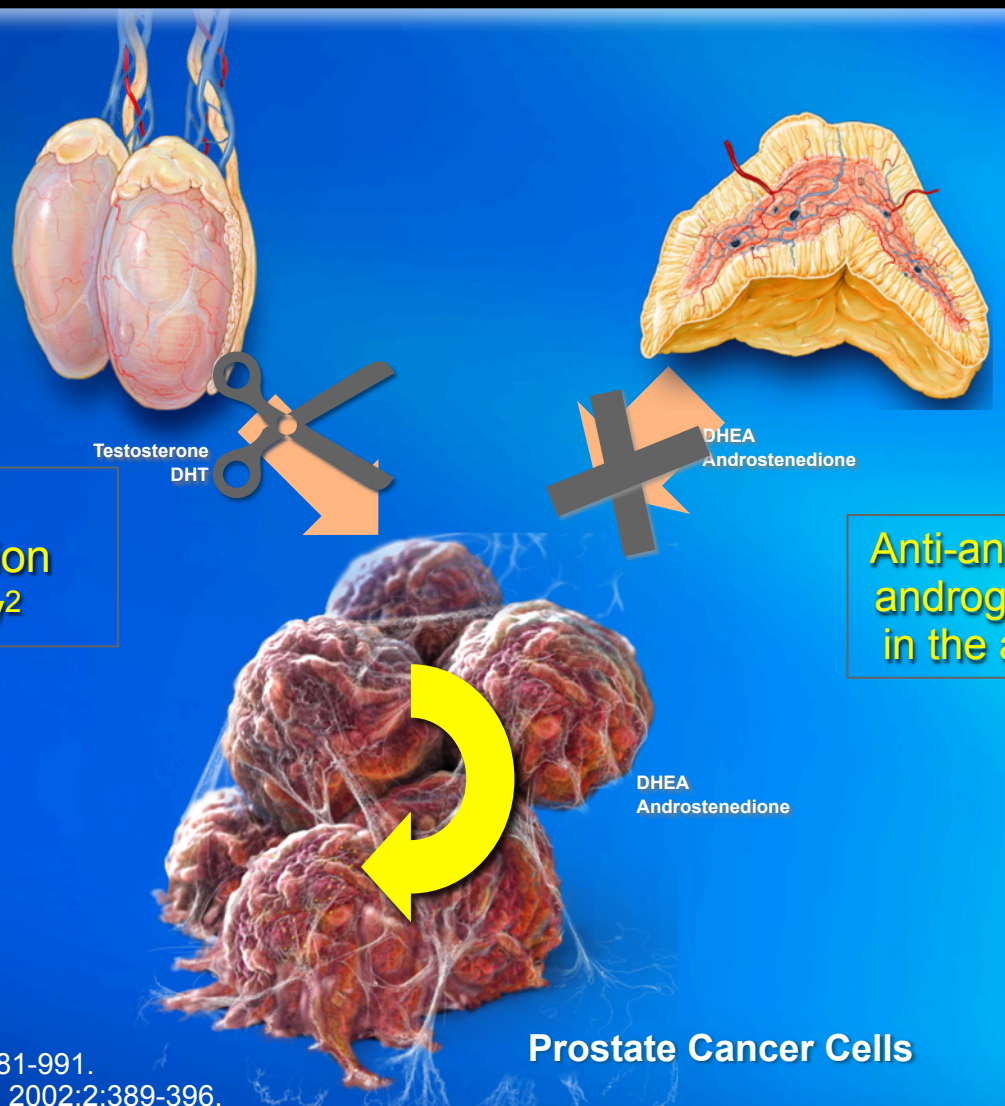
Postulated: increase local synthesis of androgens within tumours





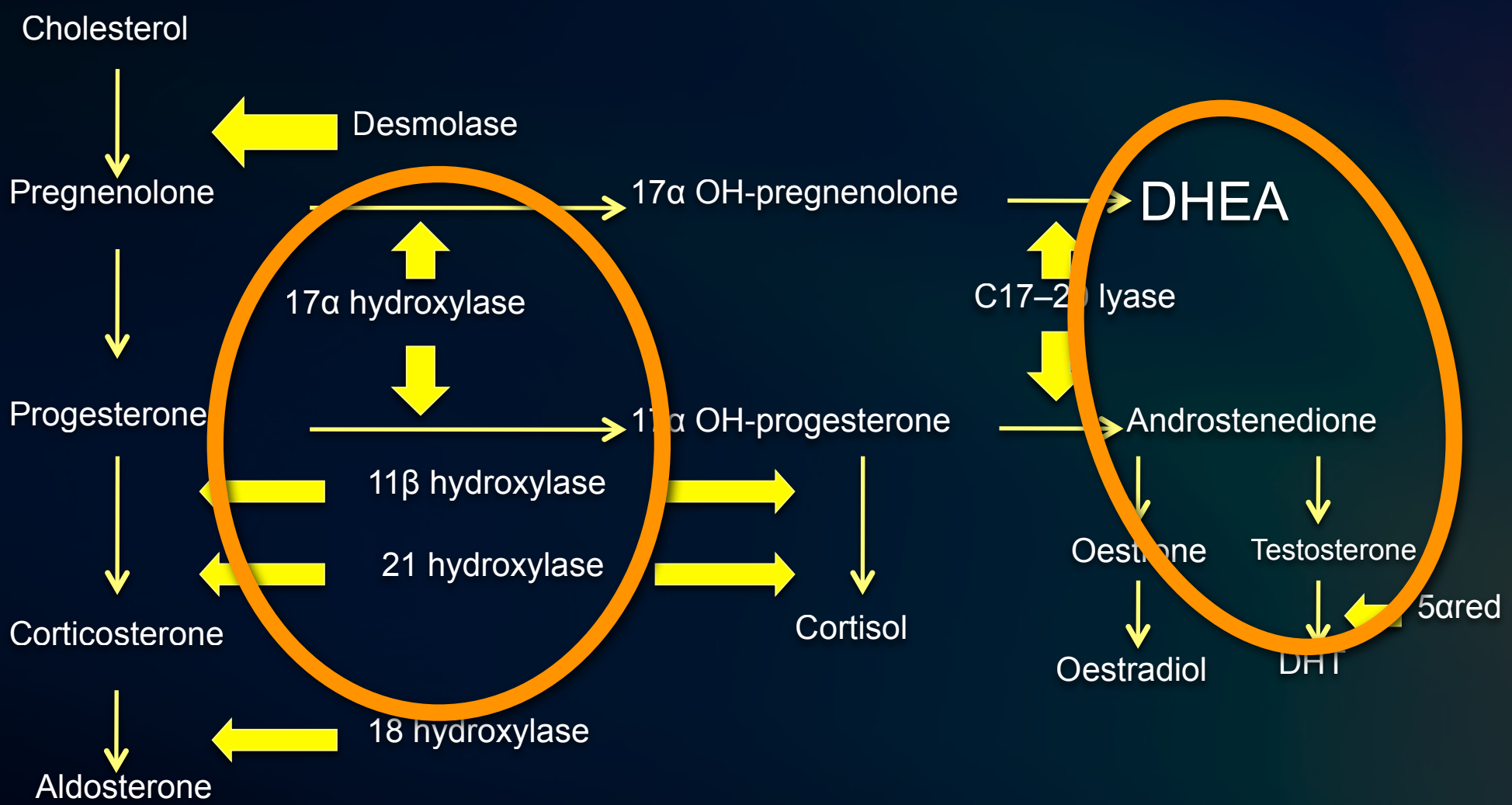
Chen Y et al. Current Options in Pharmacology. 2008, 8:440-448

Recent Research Has Shown That the Tumour is a Third Source



1. Chen Y, et al. *Lancet Oncol.* 2009;10:981-991.
Denmeade SR, et al. *Nature Rev Cancer*. 2002;2:389-396.

Abiraterone: Potent Inhibitor of 17-20 Lyase and 17-Alpha Hydroxylase

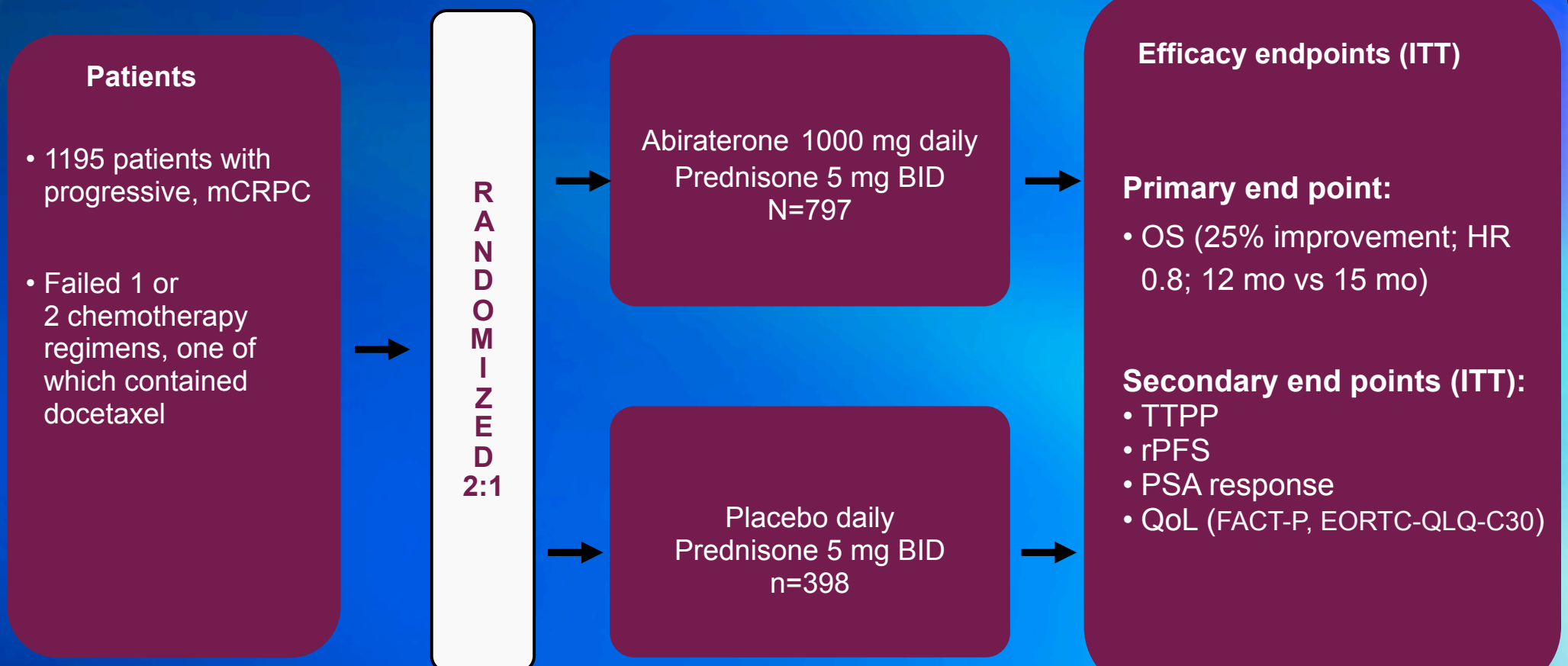


Abiraterone acetate plus low dose prednisone improves overall survival in patients with metastatic castration-resistant prostate cancer (CRPC) who have progressed after docetaxel-based chemotherapy: Results of COU-AA-301, a randomized double-blind placebo-controlled phase 3 study

JS de Bono[1], C Logothetis[2], K Fizazi[3], S North[4], L Chu[5], KN Chi[6], T Kheoh[7], CM Haqq[7], A Molina[7], and HI Scher[8]
on behalf of the COU-AA-301 Investigators

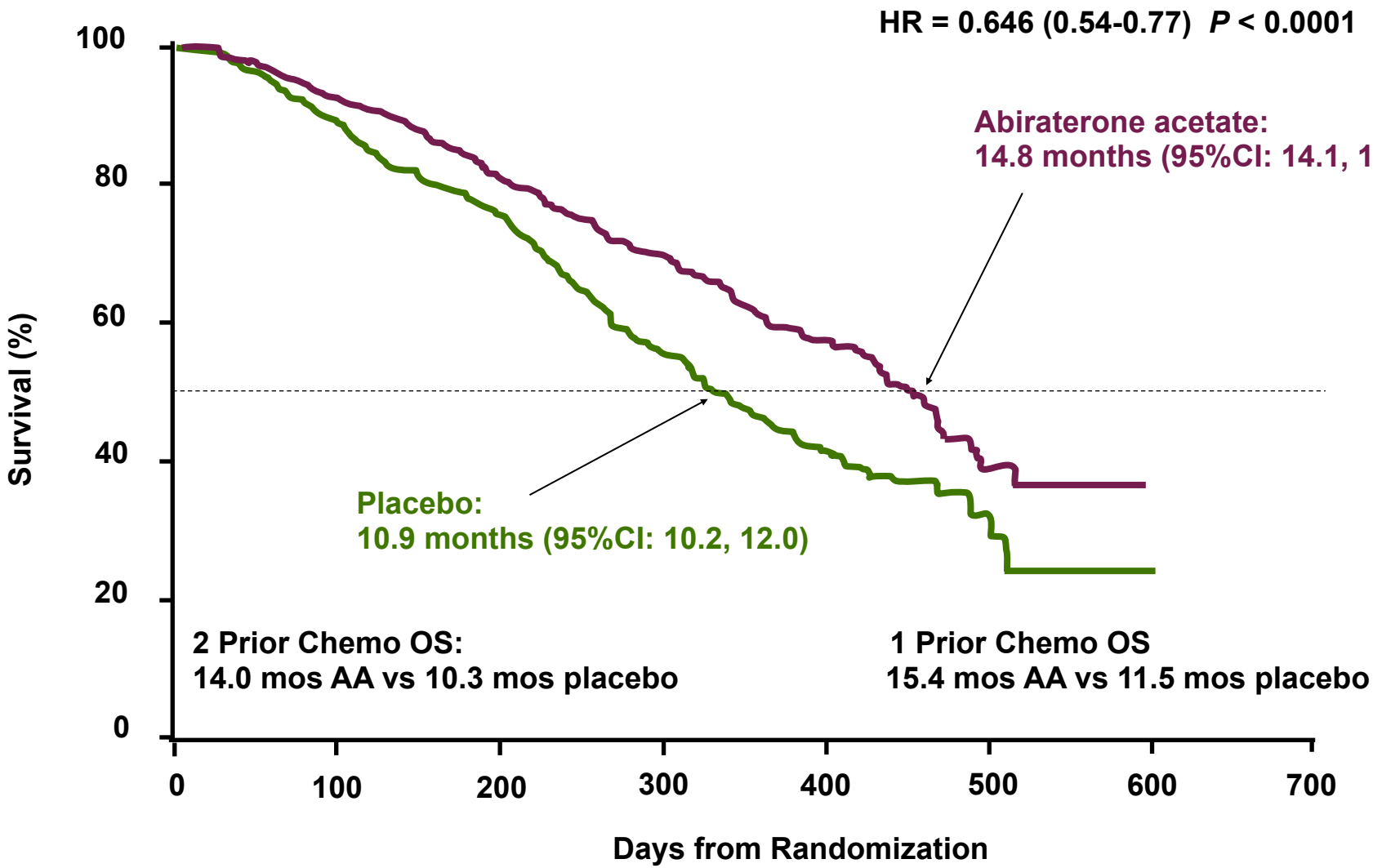
[1]Royal Marsden Foundation Trust/Institute of Cancer Research, Sutton, Surrey, United Kingdom; [2]M. D. Anderson Cancer Center, Houston, TX, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Cross Cancer Institute, University of Alberta, Edmonton, Alberta, CA; [5]Oncology Hematology Consultants, Sarasota, FL, USA; [6]BC Cancer Agency, Vancouver, BC, CA; [7]Ortho Biotech ORD, Unit of Cougar Biotechnology, Los Angeles, CA, USA; [8]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

COU-AA-301 Study Design



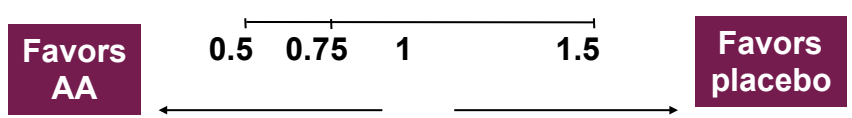
Phase III, multinational, multicenter, randomized, DB, PC study (147 sites/13 countries)

Survival

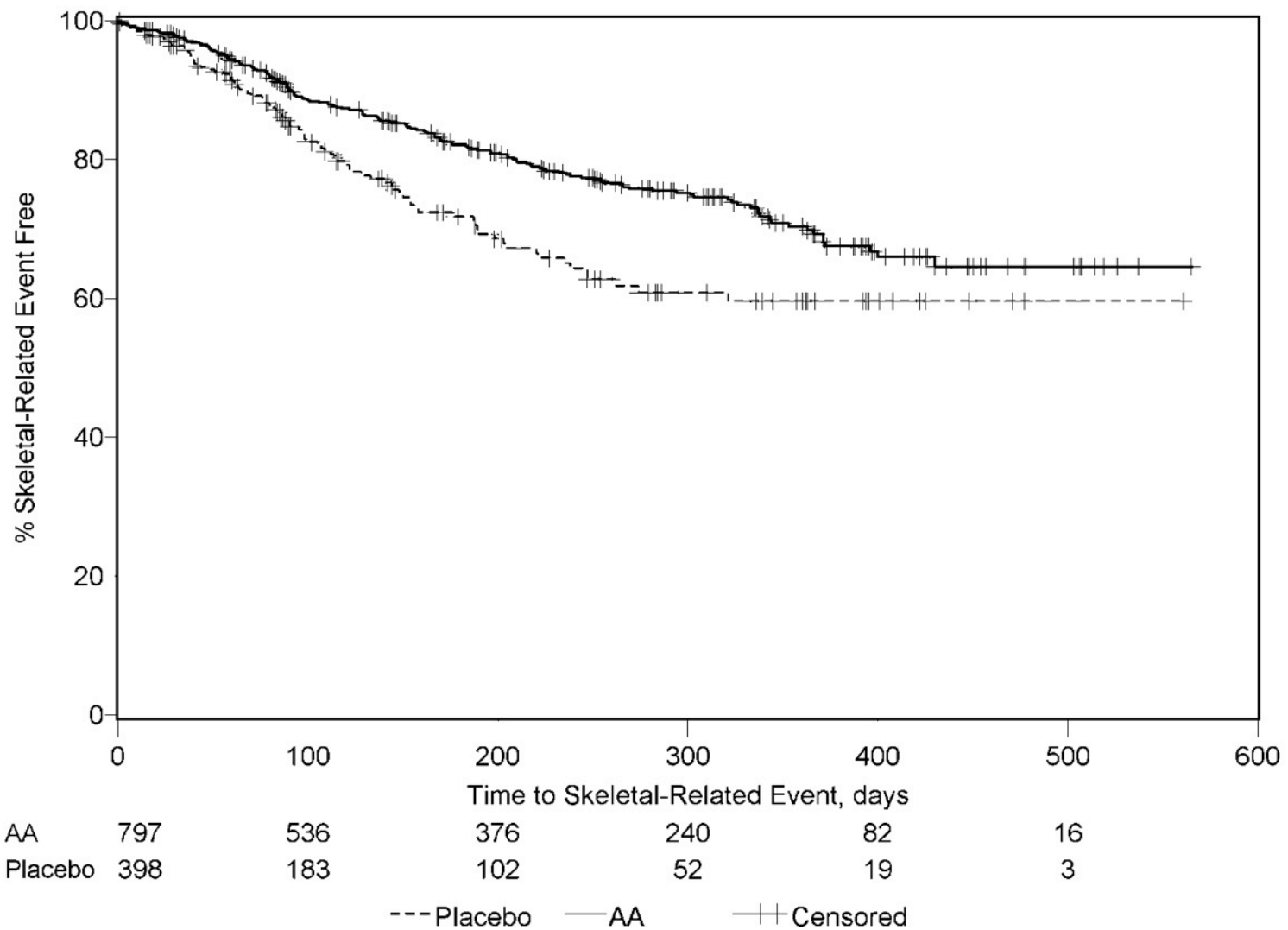

HR = 0.646 (0.54-0.77) P < 0.0001
Abiraterone acetate:
14.8 months (95%CI: 14.1, 15.4)
Placebo:
10.9 months (95%CI: 10.2, 12.0)
2 Prior Chemo OS:
14.0 mos AA vs 10.3 mos placebo
1 Prior Chemo OS
15.4 mos AA vs 11.5 mos placebo
Survival (%)
100
80
60
40
20
0
0
100
200
300
400
500
600
700
Days from Randomization

Subgroups

Variable	Subgroup	N	HR	95% CI
All subjects	All	1195	0.66	0.56-0.79
Baseline ECOG	0-1	1068	0.64	0.53-0.78
	2	127	0.81	0.53-1.24
Baseline BPI	< 4	659	0.64	0.50-0.82
	≥ 4	536	0.68	0.53-0.85
No. of prior chemo regimens	1	833	0.63	0.51-0.78
	2	362	0.74	0.55-0.99
Type of progression	PSA only	363	0.59	0.42-0.82
	Radiographic	832	0.69	0.56-0.84
Baseline PSA above median	YES	591	0.65	0.52-0.81
Visceral disease at entry	YES	709	0.60	0.48-0.74
Baseline LDH above median	YES	581	0.71	0.58-0.88
Baseline ALK-P above median	YES	587	0.60	0.48-0.74
Region	North America	652	0.64	0.51-0.80
	Other	543	0.69	0.54-0.90



Time to Skeletal Events



Pain

Pain palliation defined as: 30% reduction in pain intensity score without an increase in analgesic score; assessed in patients with a BPI-SF ≥4 at baseline

	Abiraterone + Prednisone	Prednisone + Placebo
Evaluable for pain response	**394**	**163**
Responder	**155 (44.4%)**	**44 (27.0%)**
Relative Risk	**1.65 (1.25, 2.17)**	
p-value	**0.0002**	

Side Effects

	AA (n = 791)		Placebo (n = 394)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Fluid retention	30.5%	2.3%	22.3%	1.0%
Hypokalaemia	17.1%	3.8%	8.4%	0.8%
LFT abnormalities	10.4%	3.5%	8.1%	3.0%
Hypertension	9.7%	1.3%	7.9%	0.3%
Cardiac disorders	13.3%	4.1%	10.4%	2.3%

Time to Disease-Related Pain after Sipuleucel-T in Asymptomatic Patients with Metastatic Castrate Resistant Prostate Cancer (mCRPC): Results from Three Randomized Phase 3 Trials

Eric J. Small[1], Celestia S. Higano[2], Philip W. Kantoff[3], James B. Whitmore[4], Mark W. Frohlich[4], Daniel P. Petrylak[5]

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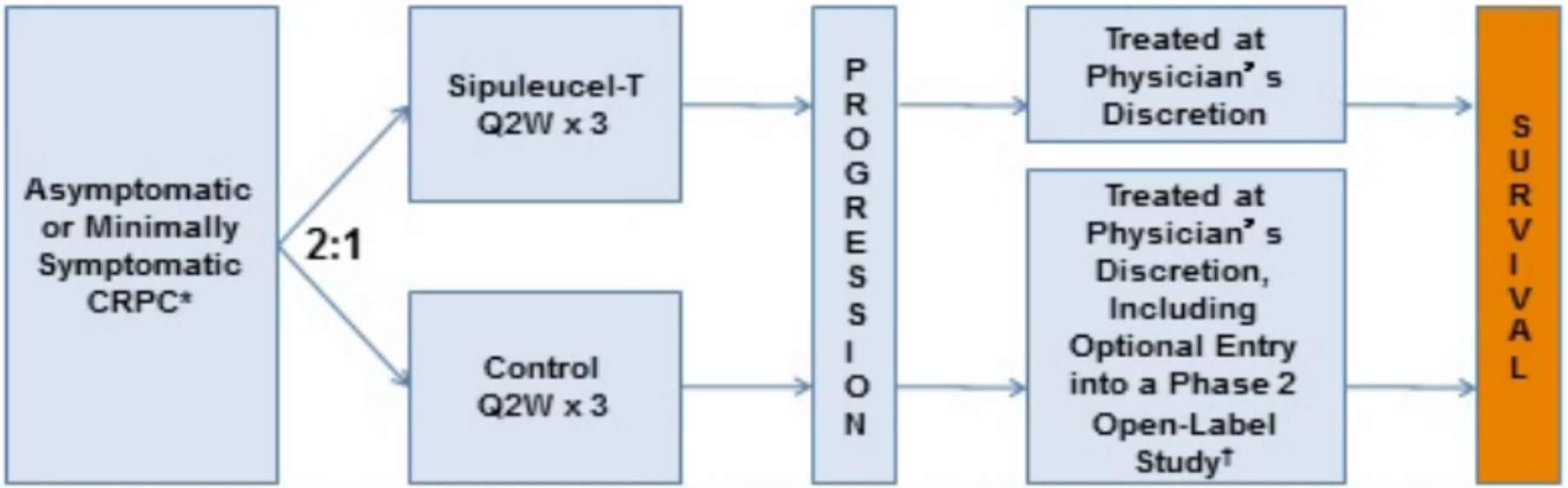
Background: Phase 3 Trial Design (D9901, D9902A and IMPACT)



*Studies D9901 and D9902A enrolled only asymptomatic subjects. †The phase 2, open-label study involved treatment with a product manufactured according to the same specifications as sipuleucel-T but from cells cryopreserved at the time the control was prepared.

Endpoints

IMPACT (N=512)

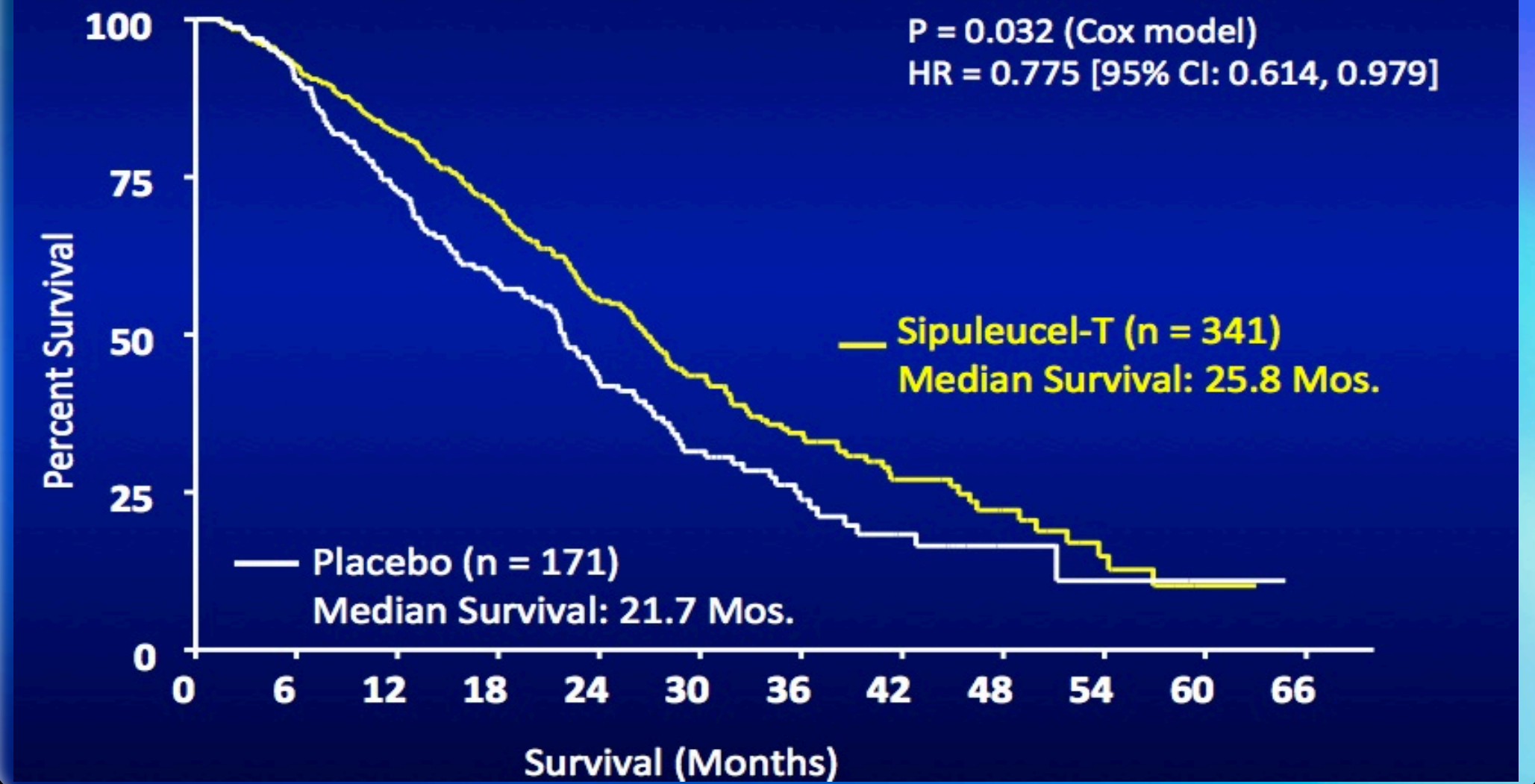
- Primary: Overall Survival
- Secondary: Time to Objective Disease Progression

D9901 (N=127) and D9902A (N=98)

- Primary: Time to Disease Progression
- Planned Analysis: Overall Survival

Small E et al. J Clin Oncol. 2006;24:3089-94; Higano CS et al. Cancer 2009;115:3670-9; Kantoff PW et al. N Engl J Med. 2010;363:411-22

Survival


P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.
Placebo (n = 171)
Median Survival: 21.7 Mos.
Percent Survival
100
75
50
25
0
0
6
12
18
24
30
36
42
48
54
60
66
Survival (Months)

New Chemotherapy Agents

Cabazitaxel (Jevtana™)

Targeting Microtubules Again

TROPIC: Phase 3 Study: 146 Sites, 26 Countries

De Bono et al. Lancet 2010, volume 9747, 1147 -1154

Hormone Resistant Metastatic Prostate Cancer Patients Previously Treated With A Taxotere Containing Regimen

Randomization (1:1)
Stratified for Measurability of Disease and ECOG PS

cabazitaxel 25 mg/m² q3w + Prednisone*

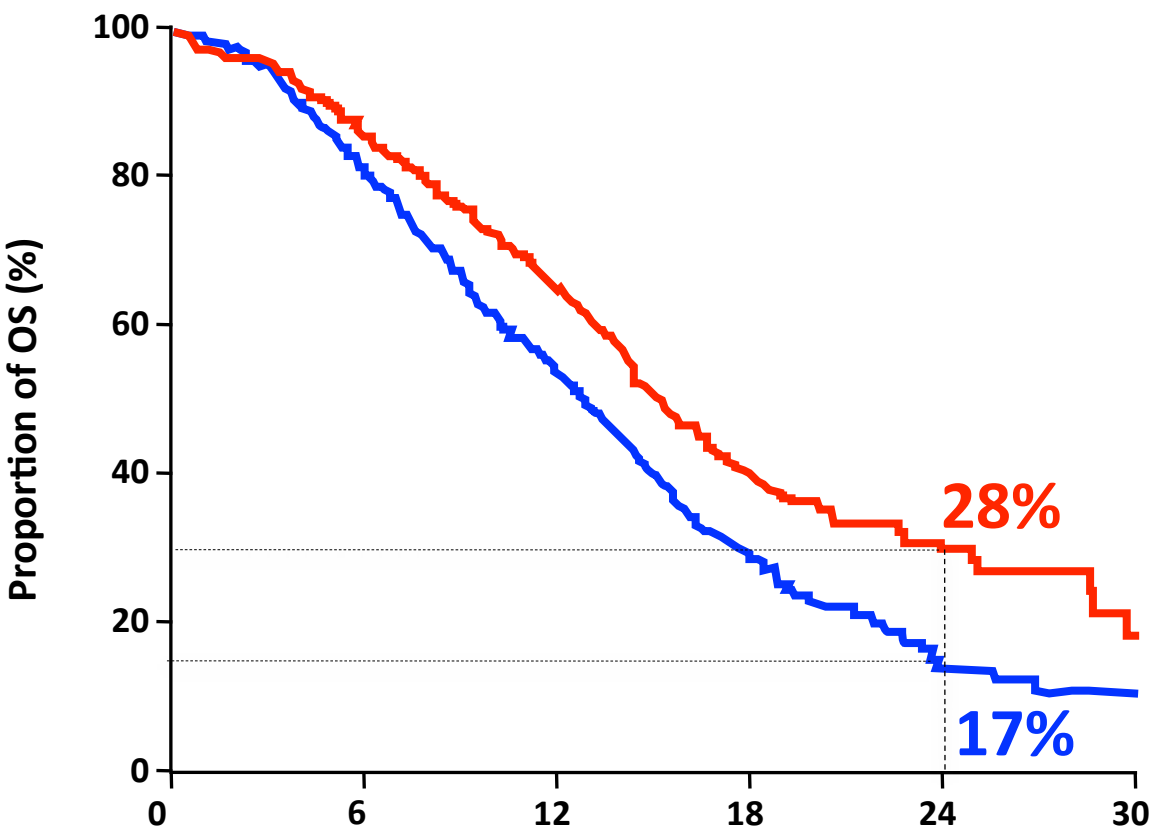
mitoxantrone 12 mg/m² q3w + Prednisone*

755 patients, Maximum treatment duration 10 cycles, planned 511 events to detect 25% reduction in hazard ratio, 90% power, 2 sided 5% alpha level

Primary endpoint = Overall Survival, Secondary endpoint = PFS, response rate and safety, interim (futility) PFS based analysis after 225 events

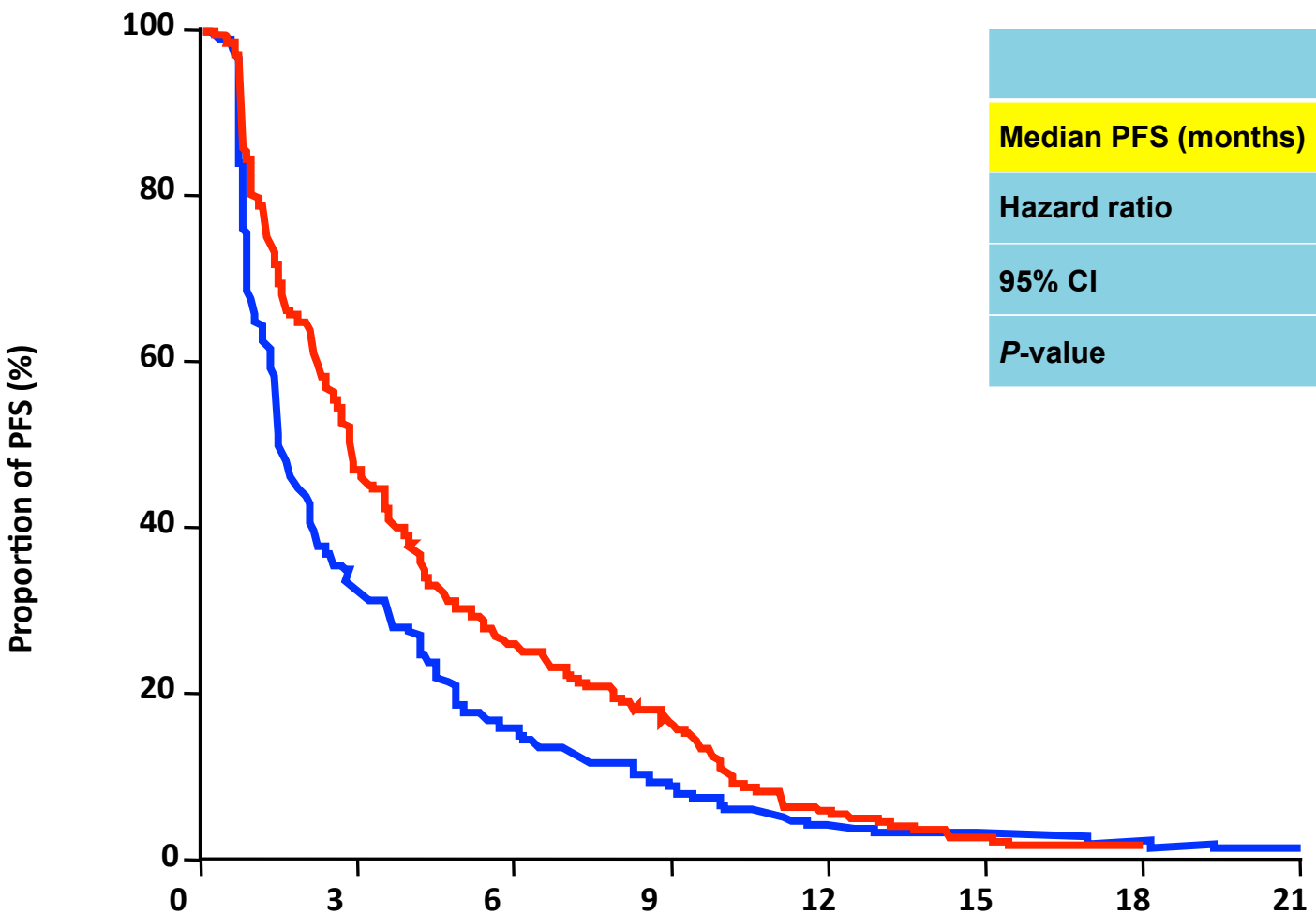
* Or prednisolone – 10 mg given orally daily

Survival



	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.70	
95% CI	0.59–0.83	
P value	<0.0001	

Progression Free



	MP	CBZP
Median PFS (months)	1.4	2.8
Hazard ratio	0.74	
95% CI	0.64–0.86	
P-value	<0.0001	

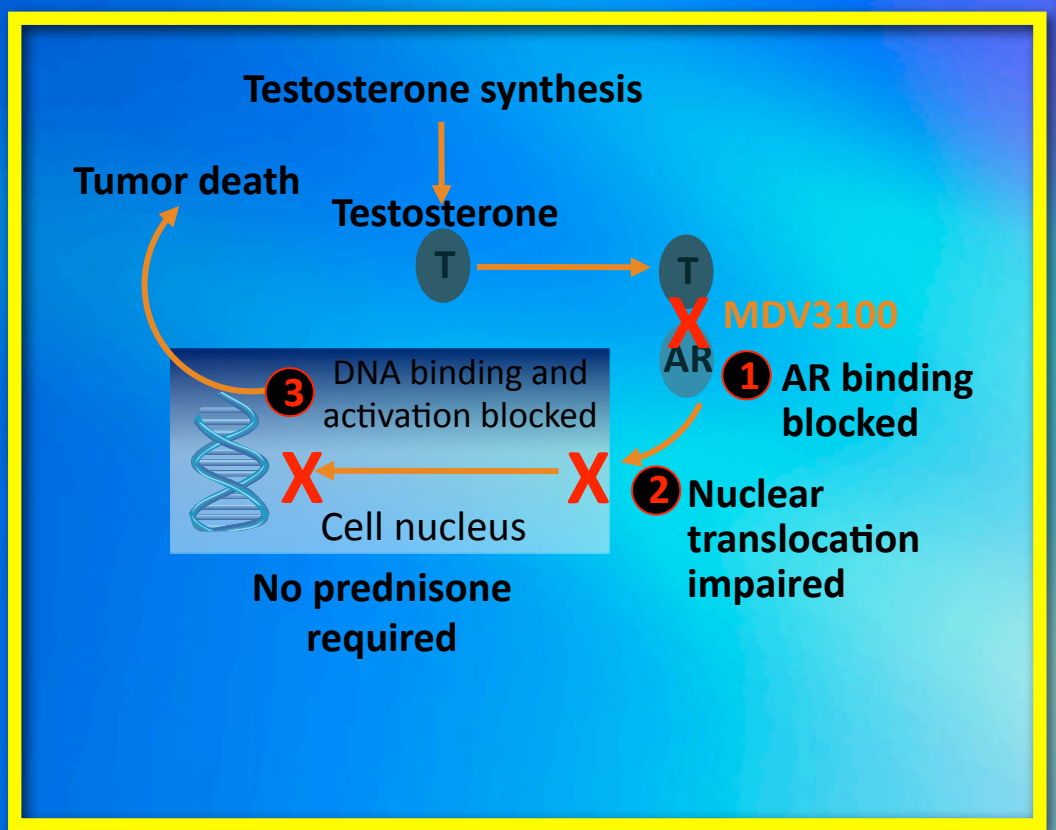
Side Effects

	MP (n=371)		CBZP (n=371)	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Any adverse event	88	39	96	57
Febrile neutropenia	1	1	8	8
Diarrhea	11	<1	47	6
Fatigue	27	3	37	5
Back pain	12	3	16	4
Nausea	23	<1	34	2
Vomiting	10	0	23	2
Hematuria	4	1	17	2
Abdominal pain	4	0	12	2

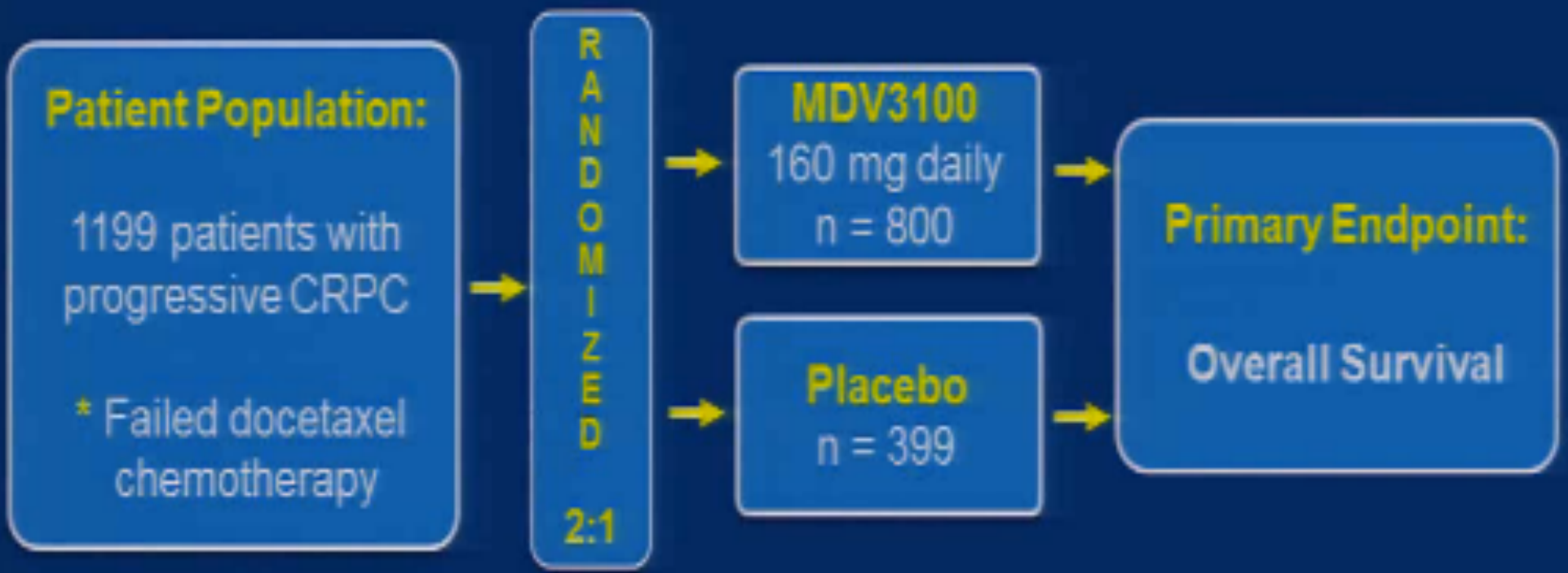
MDV3100

Antiandrogen with three effects on Androgen Receptor:

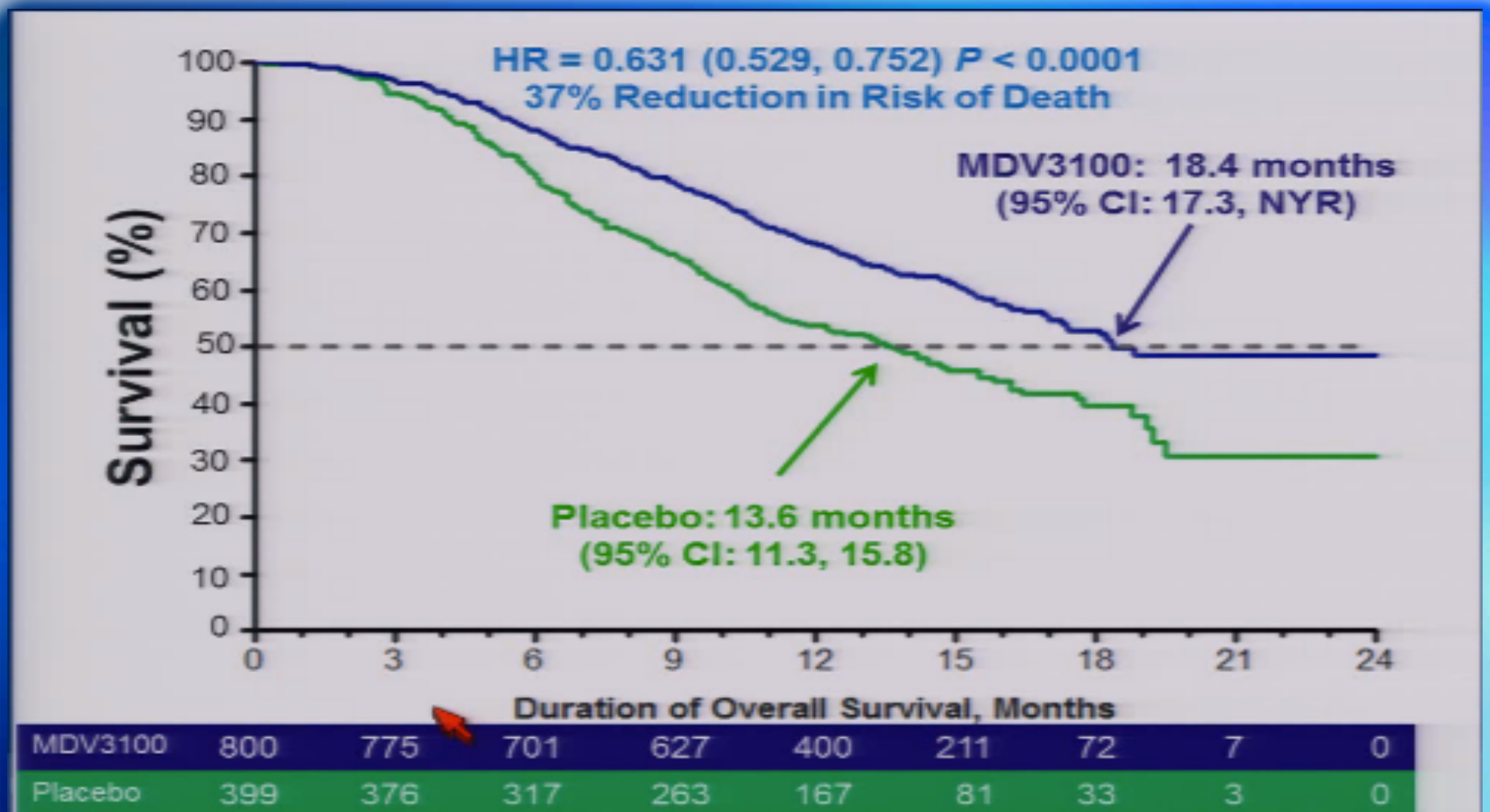
- AR inhibition
- AR degradation
- Inhibition of AR transport into prostate cancer cell nucleus



AFFIRM: A Phase 3 Trial of MDV3100 vs. Placebo in *Post*-Chemotherapy Treated Castration-Resistant Prostate Cancer (CRPC)



Survival: 4.8 mo +

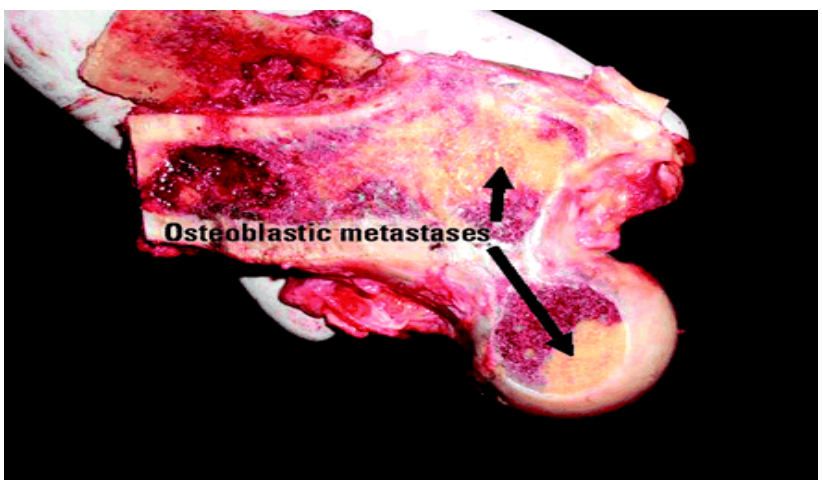


Radiation: "Internal"
Alpharadin: Radium-223

For Bone Metastases

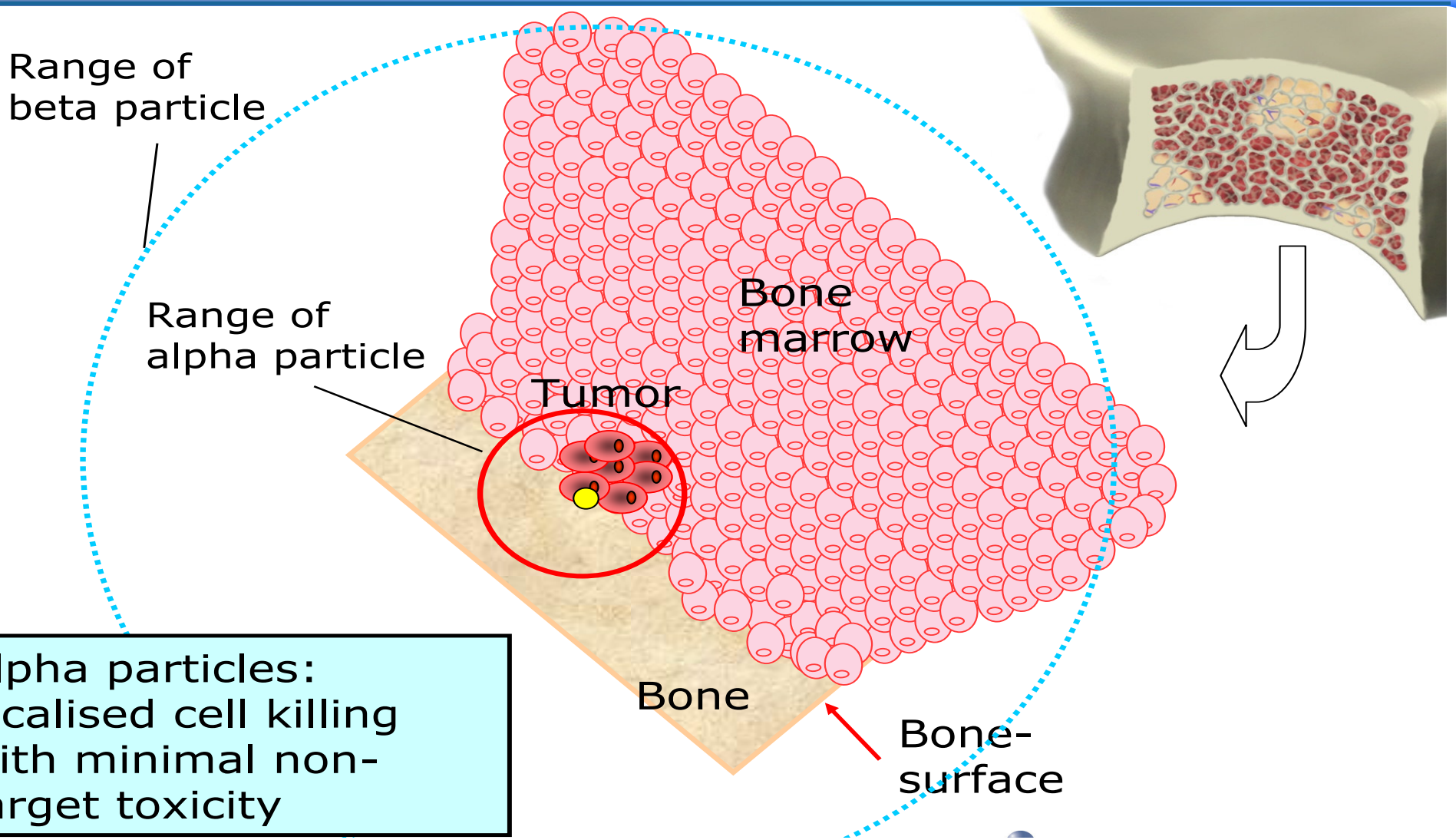
Mechanism

- **Acts as a calcium mimic:**
  - a natural bone-seeker – 11.4 days half-life
  - targets areas of new bone growth accompanying metastases
  - incorporated into bony matrix (metabolic targeting)
- **Emits alpha-particles that induce primarily non-reparable, double strand DNA breaks in adjacent tumour cells**



Surgical sample showing deposition of new bone within skeletal metastasis

Mechanism

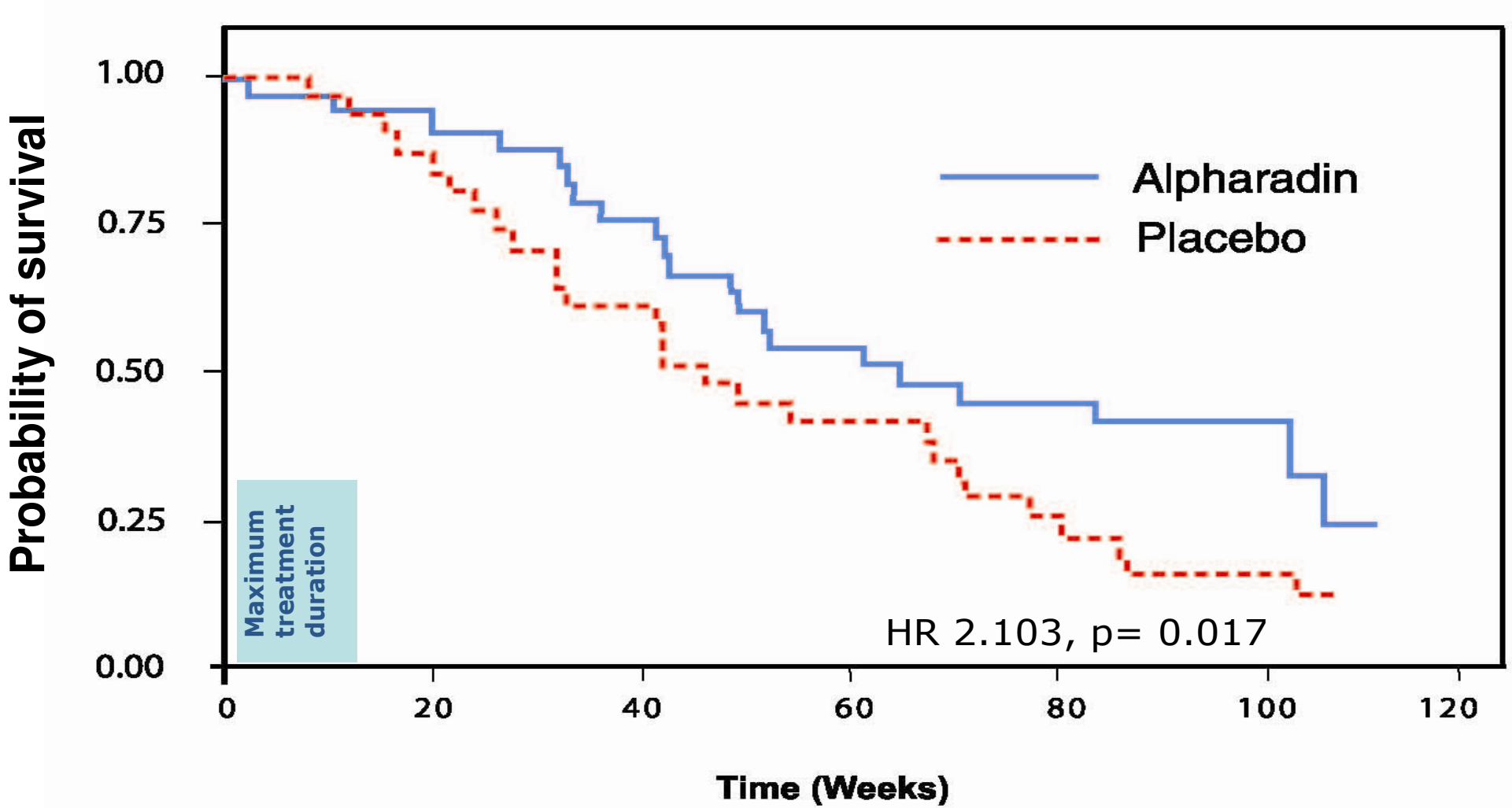


Alpha particles: localised cell killing with minimal non-target toxicity

Mechanism

Limited side effects due to short range

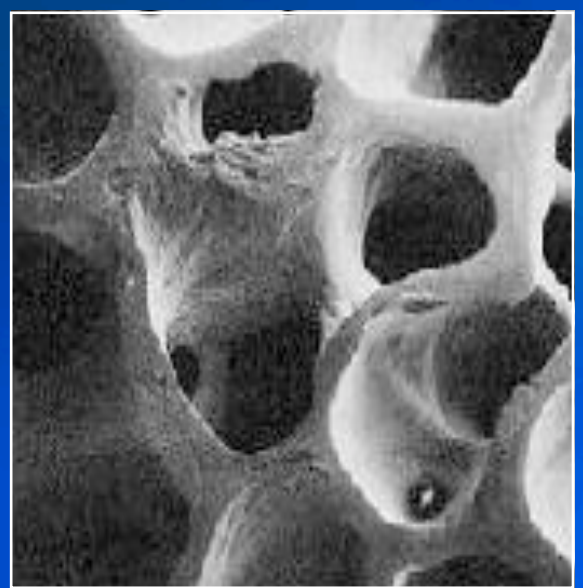
Survival


Probability of survival
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
Time (Weeks)
Alpharadin
Placebo
Maximum treatment duration
HR 2.103, p= 0.017

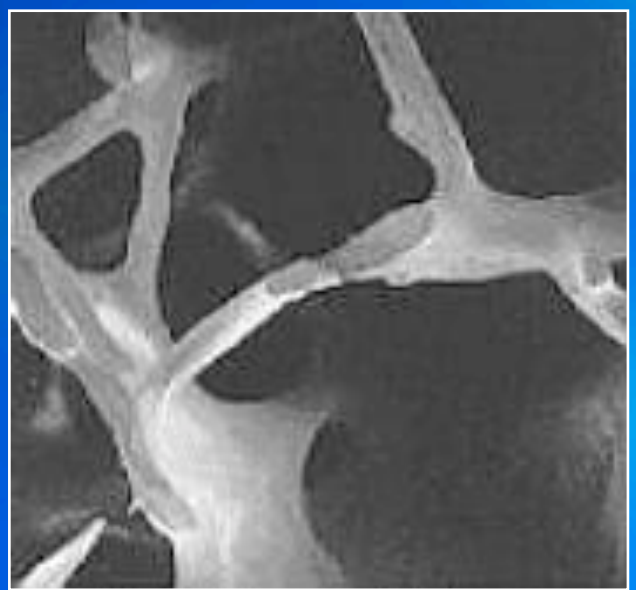
Rad223: Summary

- Improved overall survival from 46.4 to 65.3 weeks (41% increase)
- In *per protocol* population (2 or more injections), the median survival was 71.0 weeks (53% increase)
- At 24 months, 10/33 (30%) patients were alive in Alpharadin arm versus 4/31 (13%) in placebo arm
- Benign side effect profile – similar to placebo

Bone Mets



Normal



Osteoporosis

Mets

Dempster D. J Bone Miner Res 1986;1:15

Skeletal Related Events (SREs) in Cancer Have Potentially Severe Consequences

Pain
50-90% of patients with bone metastases[1]

Pathologic fracture[3]

22%[2]

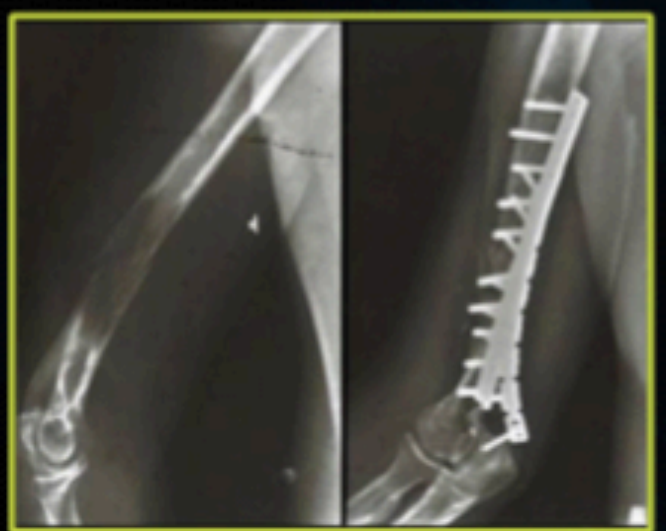
Radiotherapy to bone[4]

29%[2]

Spinal cord compression[5]

7%[2]

Surgery to bone[6]

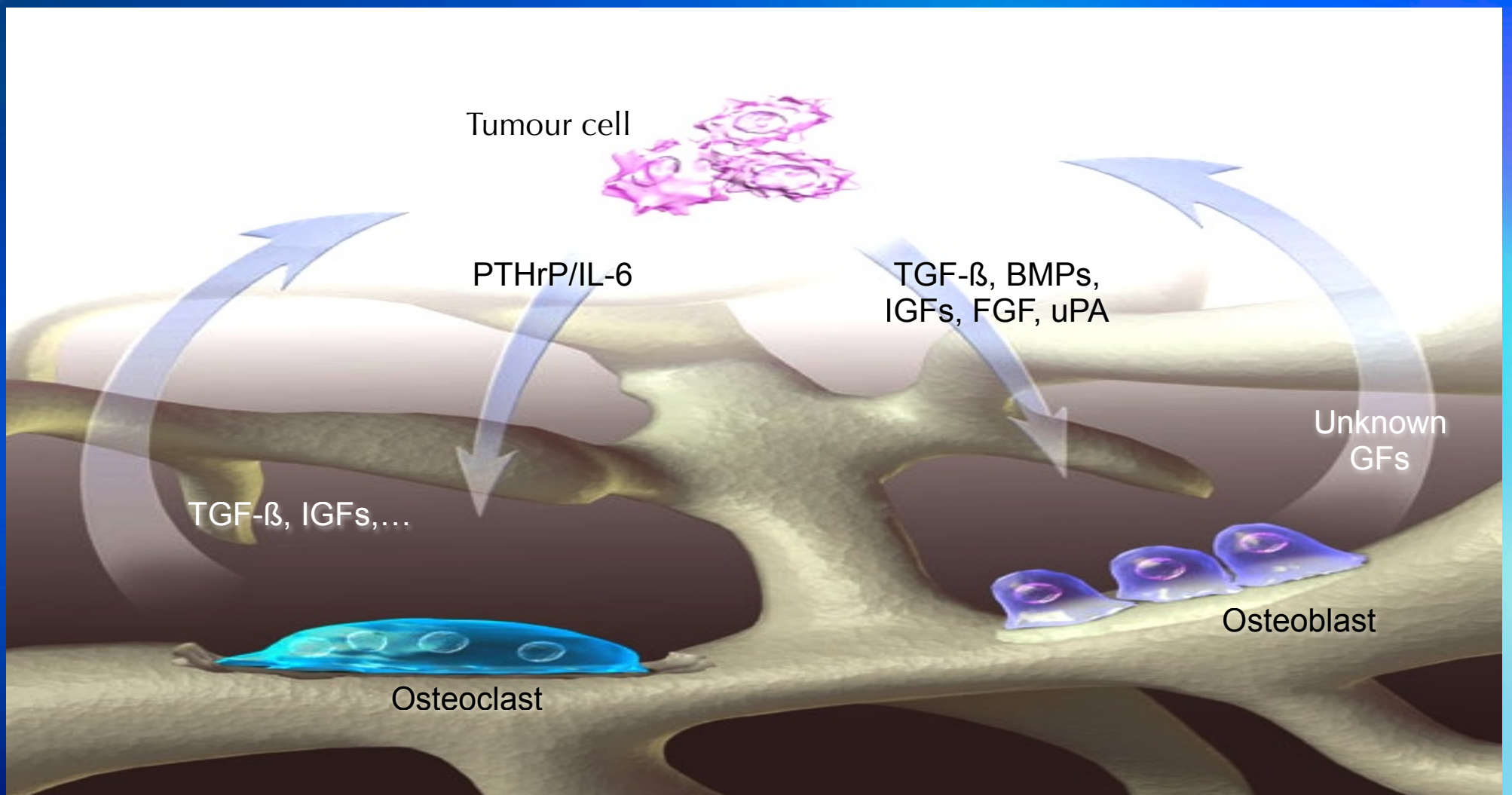


3%[2]

1. Clemons et al. *Oncologist* 2006;11:227-33. 2. Saad et al. *J Natl Cancer Inst* 2002;94:1458-68.

Images: 3. Wheeless' Textbook of Orthopaedics. www.wheelessonline.com ©2007 Data Trace Publishing Company. All rights reserved. 4. This image is licensed under the GNU Free Documentation License. 5. Higdon et al. *Am Fam Physician* 2006;74: 1873-80. Permission obtained. 6. Weber. http://www.hopkins-arthritis.org. Accessed Oct. 15, 2007. Provided by John Hopkins Arthritis Center at John Hopkins University.

Bone Metabolism



Impact of Bone Mets

Bone pain
Pathologic #
Surgery to bone
Spinal cord compression
XRT to bone

= SREs

Impaired mobility + ↓ QOL

↑ $

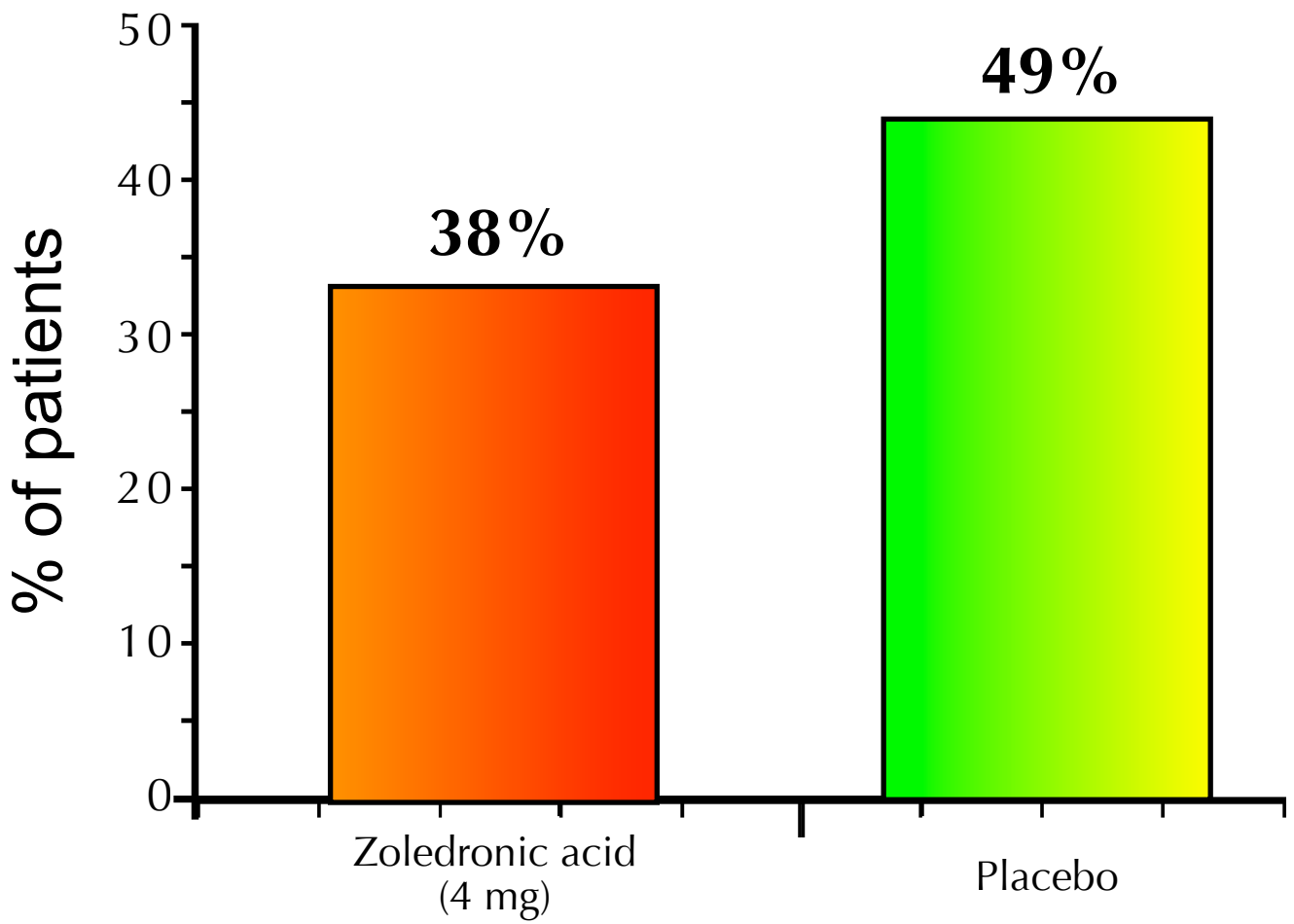
↓ Survival

Early intervention may avoid SRE and improve QOL

Zometa in met PC

Saad F. *J Natl Cancer Inst* 2004;96(11):879-882.

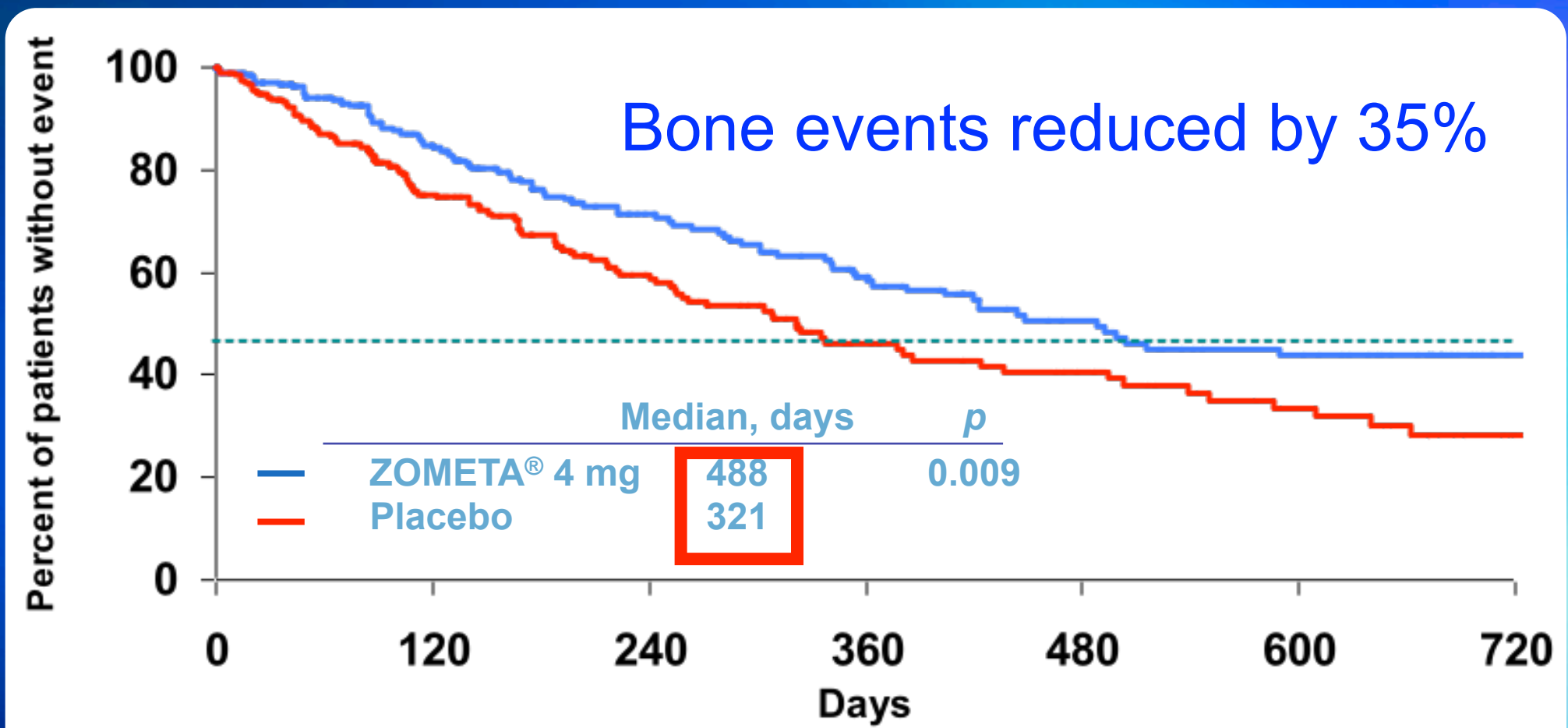
SREs



n = 643
* (11% absolute reduction;

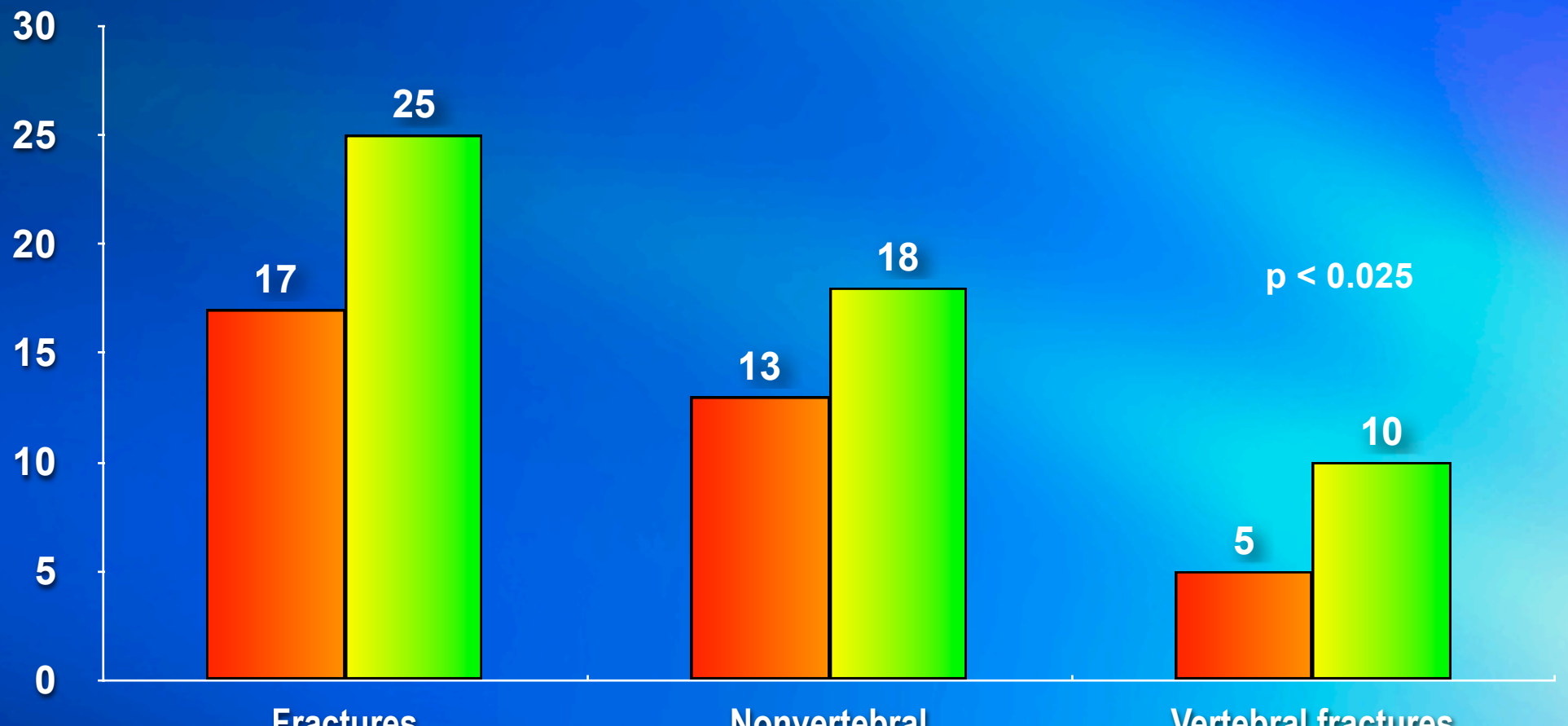
p = 0.021)

Time to 1st SRE



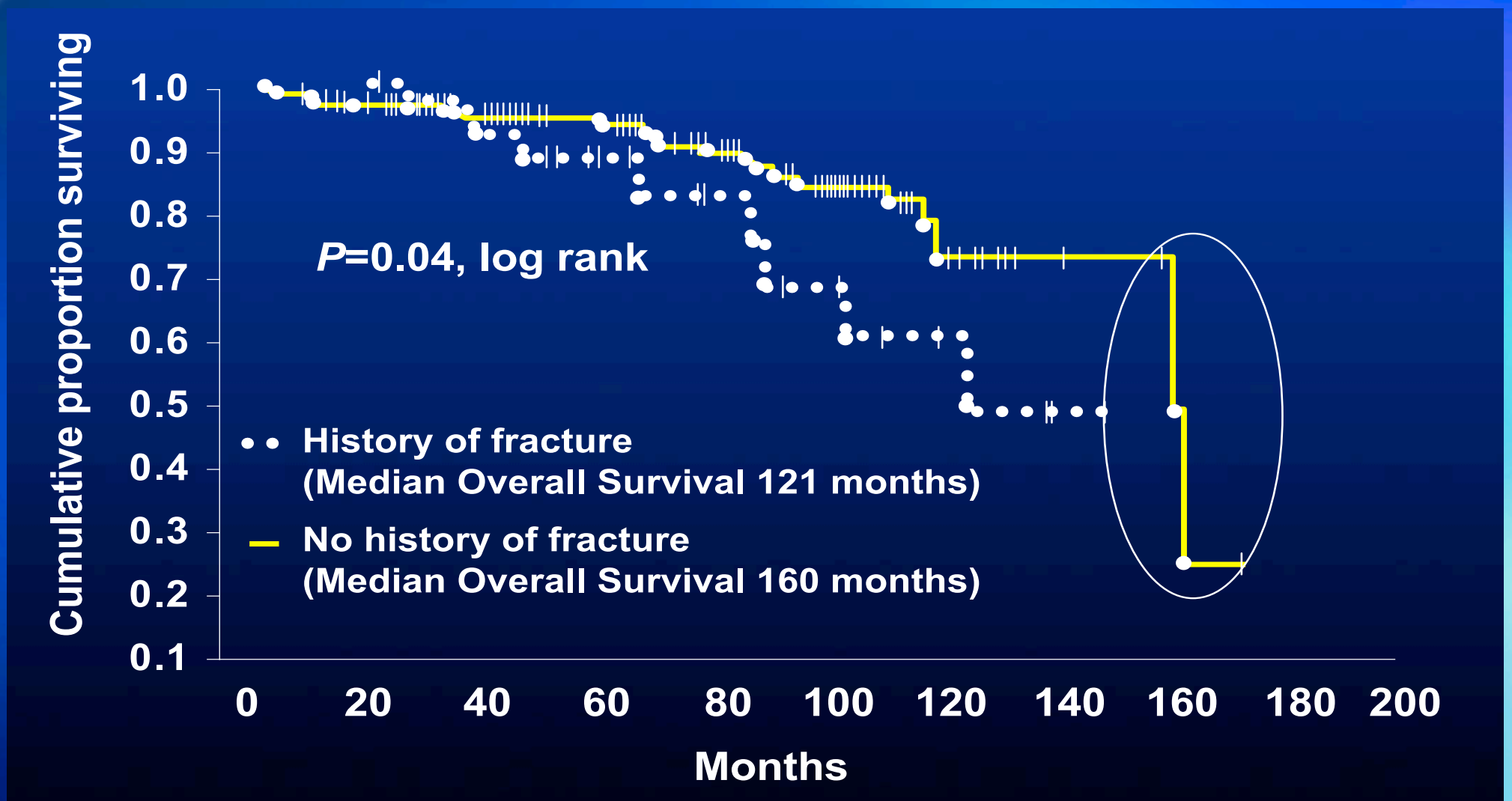
Saad F. J Natl Cancer Inst 2002;94:1458

Fractures

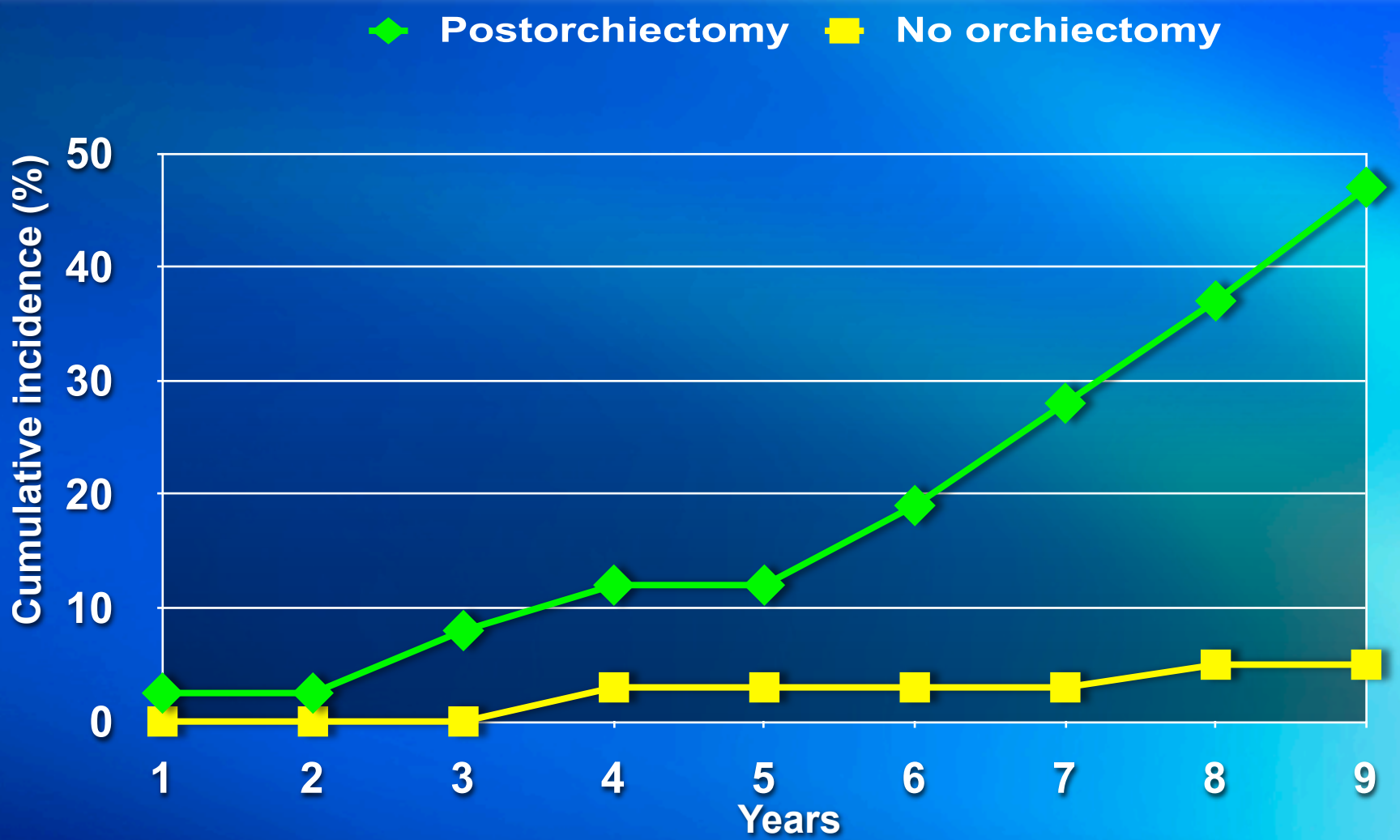


Saad F. J Natl Cancer Inst 2004;96:879

Skeletal Fractures and OS

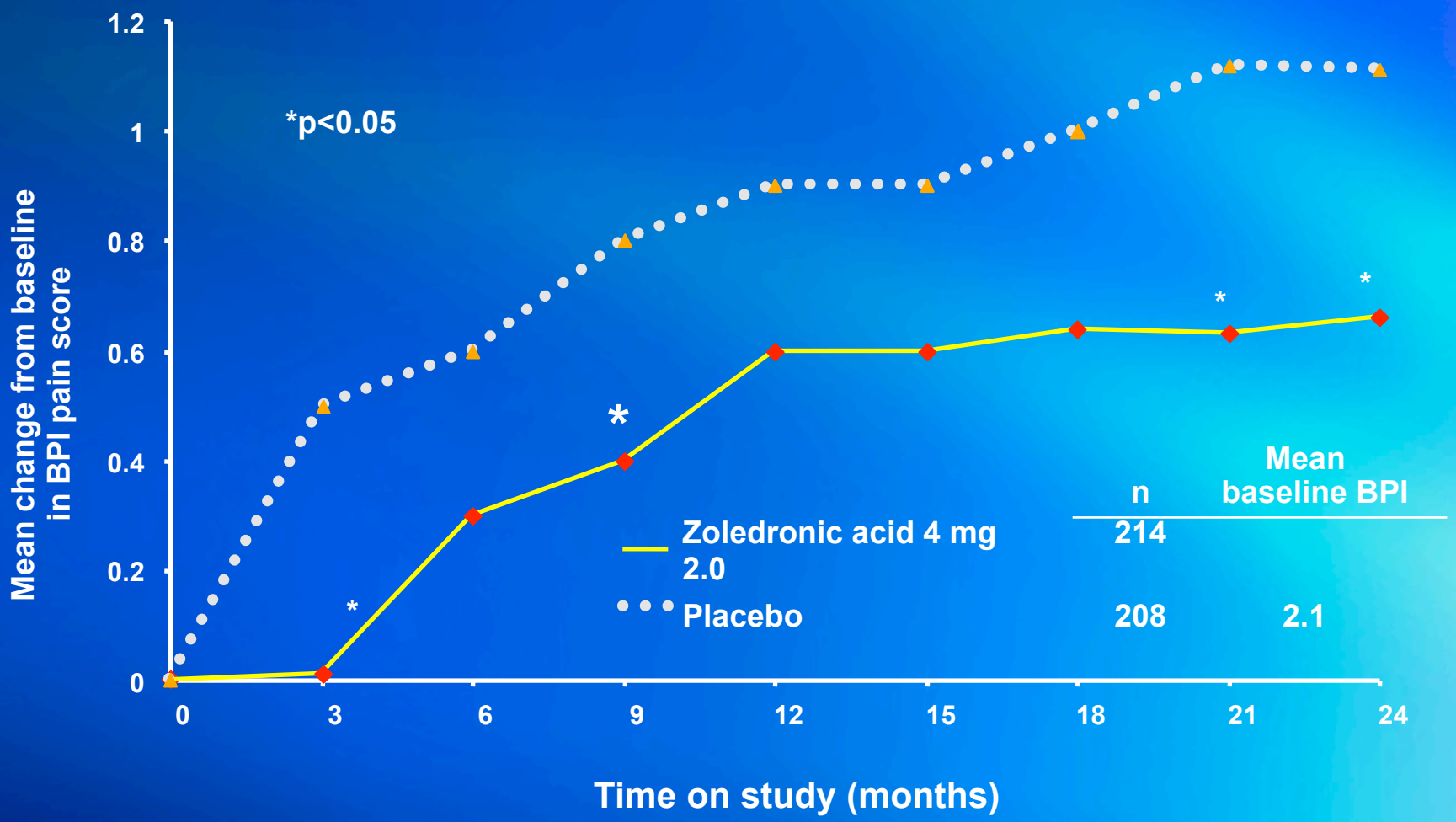


ADT Increases Fracture Risk



Daniell H. J Urol 1997;157:439

Change from Baseline Pain Score



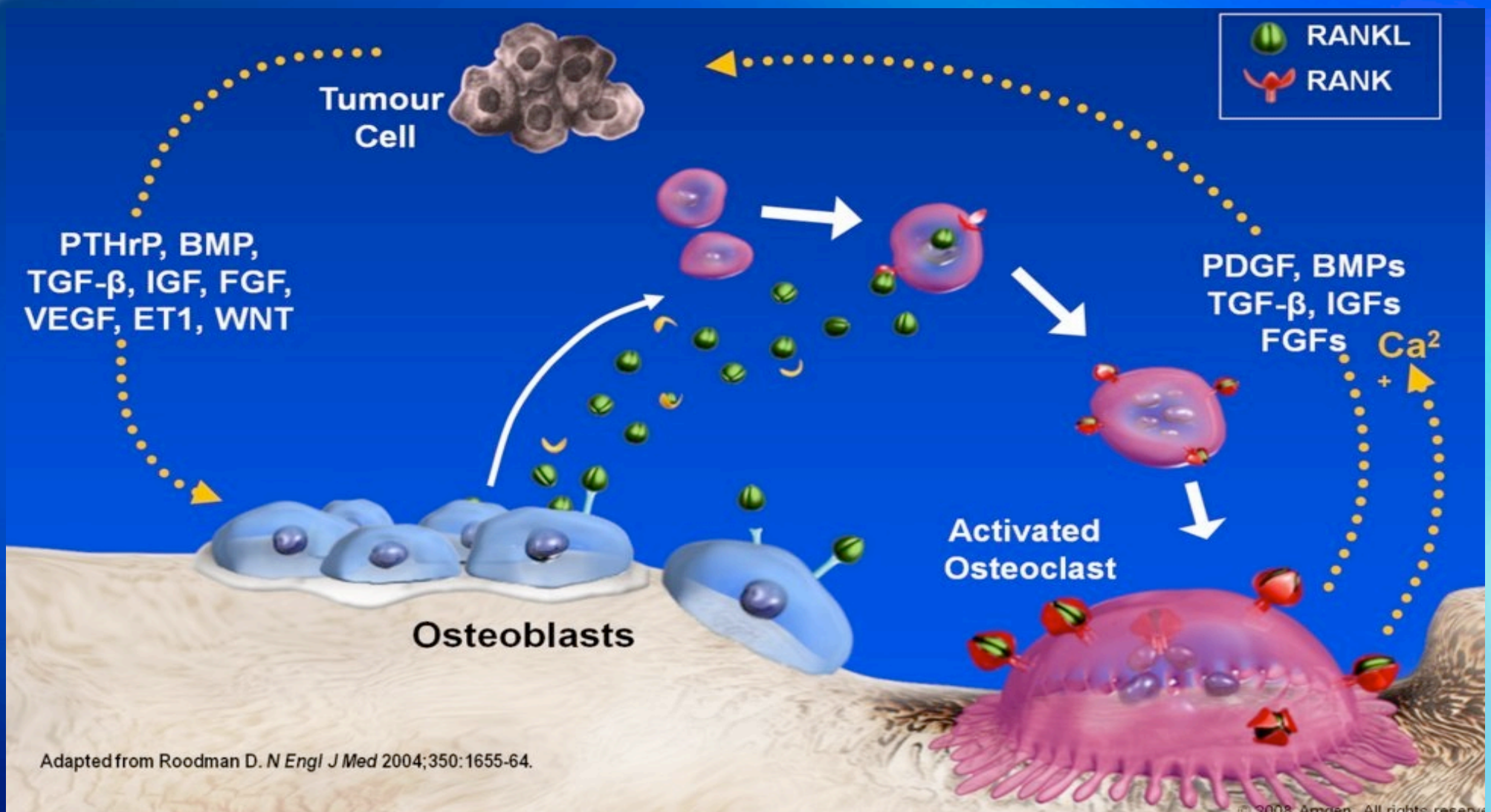
Adverse Events with Bisphosphonates

	Frequency[1] (% of patients)	Potential mechanisms[1]
Acute-phase reactions -Fever & myalgia IV administration	15-30%	Probably related to a systemic cytokine flare
Gastrointestinal symptoms Oral administration	Dose dependent	Probably result of local toxicity
Nephrotoxicity IV administration	Creatinine elevations: 2-8%[2]	Rapid IV infusion leads to high drug concentrations as bisphosphonates are rapidly cleared by the kidneys Risk factors: dehydration, pre-existing renal impairment, concomitant nephrotoxic drugs[3]
Osteonecrosis of the jaw (ONJ) IV administration (primarily)	IV: ~5% (range 0.83-7%)	ONJ associated with multiple factors Risk factors: dental disease, chemotherapy, corticosteroids, thalidomide

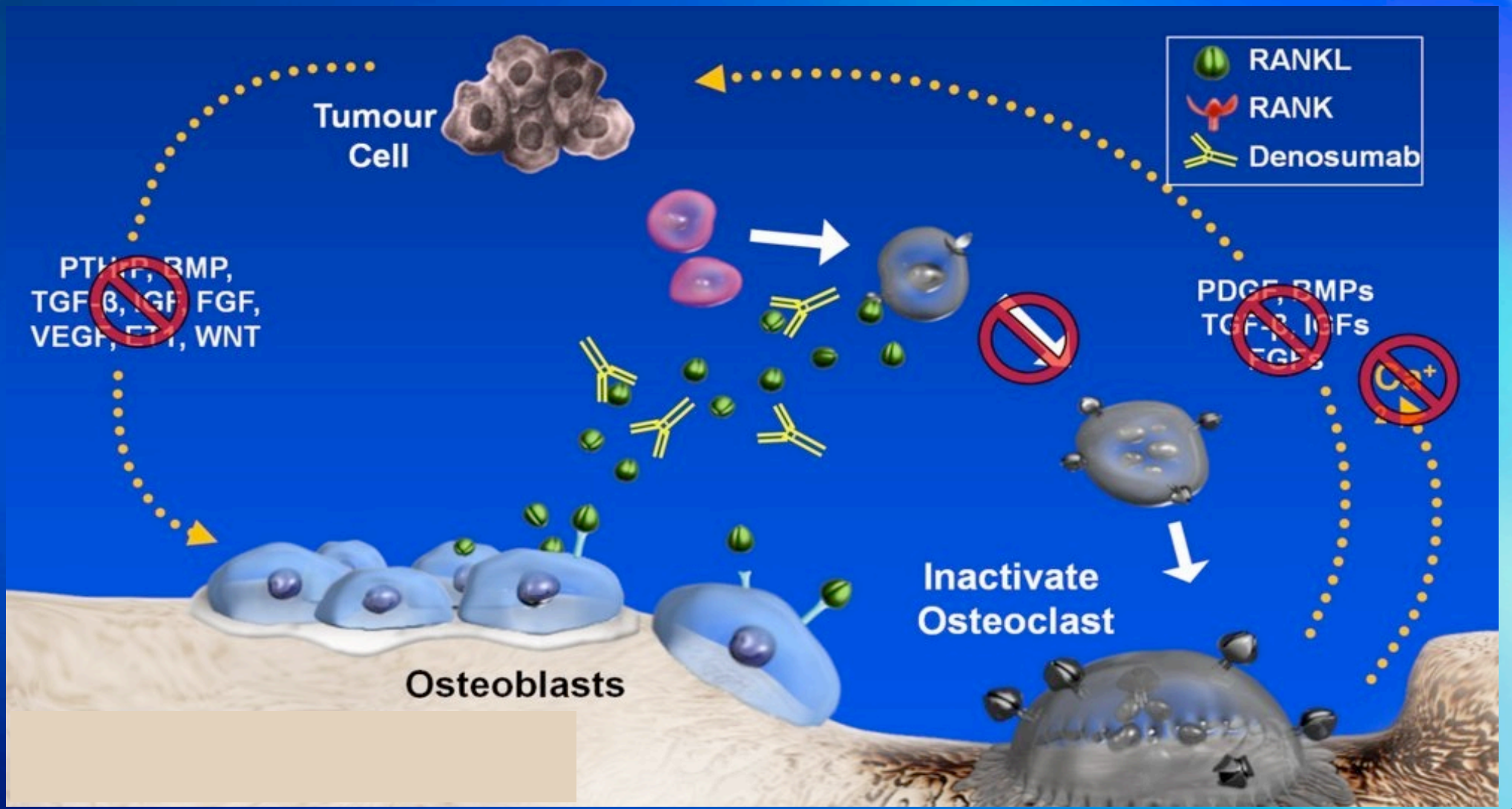
1. Dunstan et al. *Nat Clin Pract Oncol* 2007;4:42-55. 2. Aapro et al. *Ann Oncol* 2008;19:420-32. 3. Zometa product monograph. 2008.

Osteonecrosis of Jaw

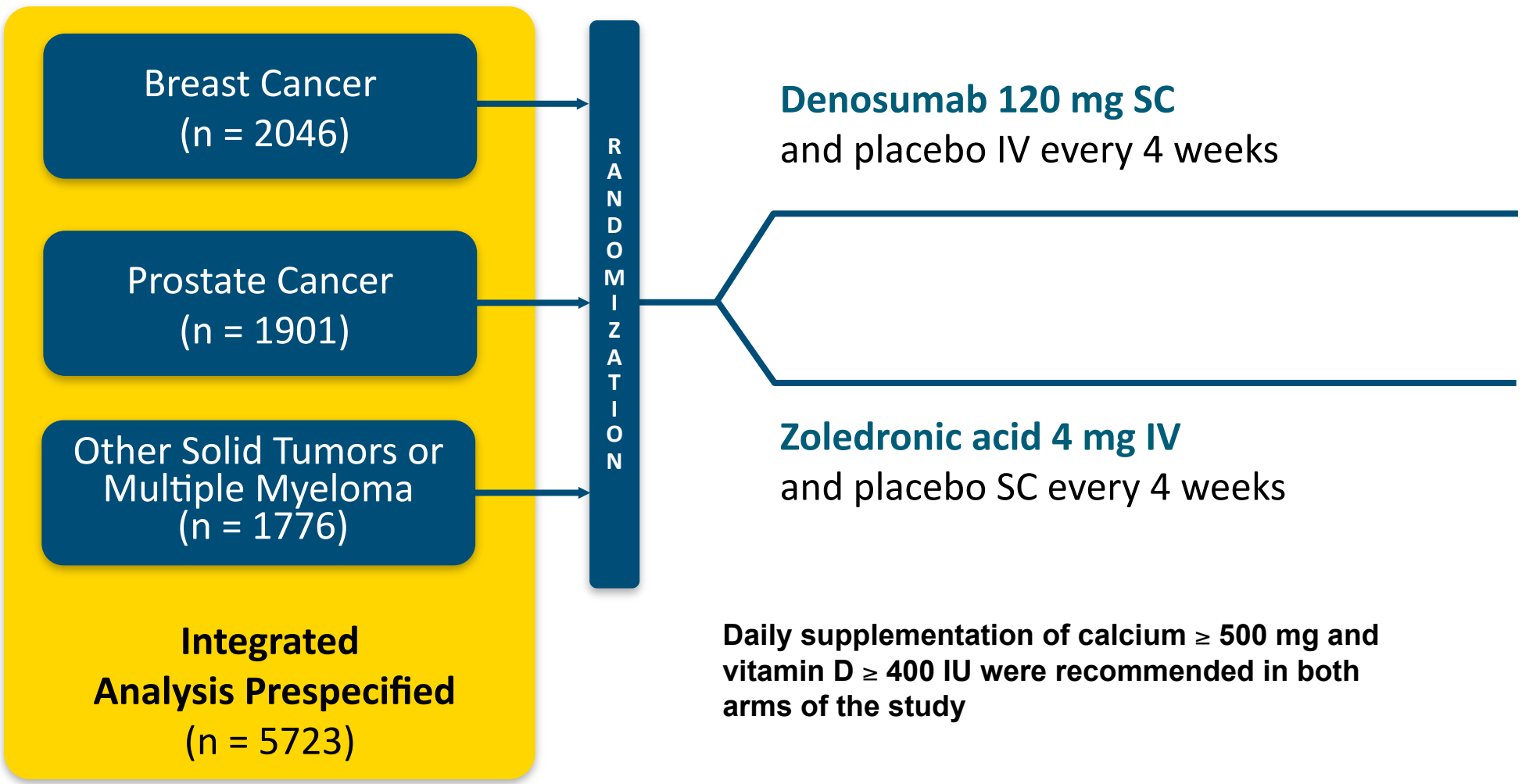
Viscious Cycle in Bone



Denosumab (Xgeva™)

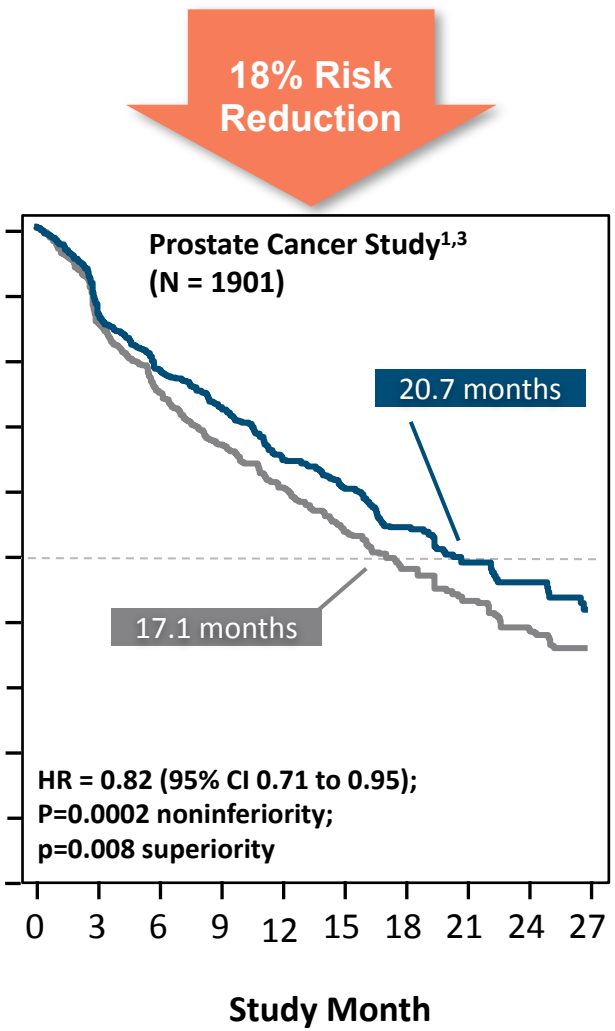


Three Identically Designed Head-to-Head StudiesComparing Denosumab vs Zoledronic Acid

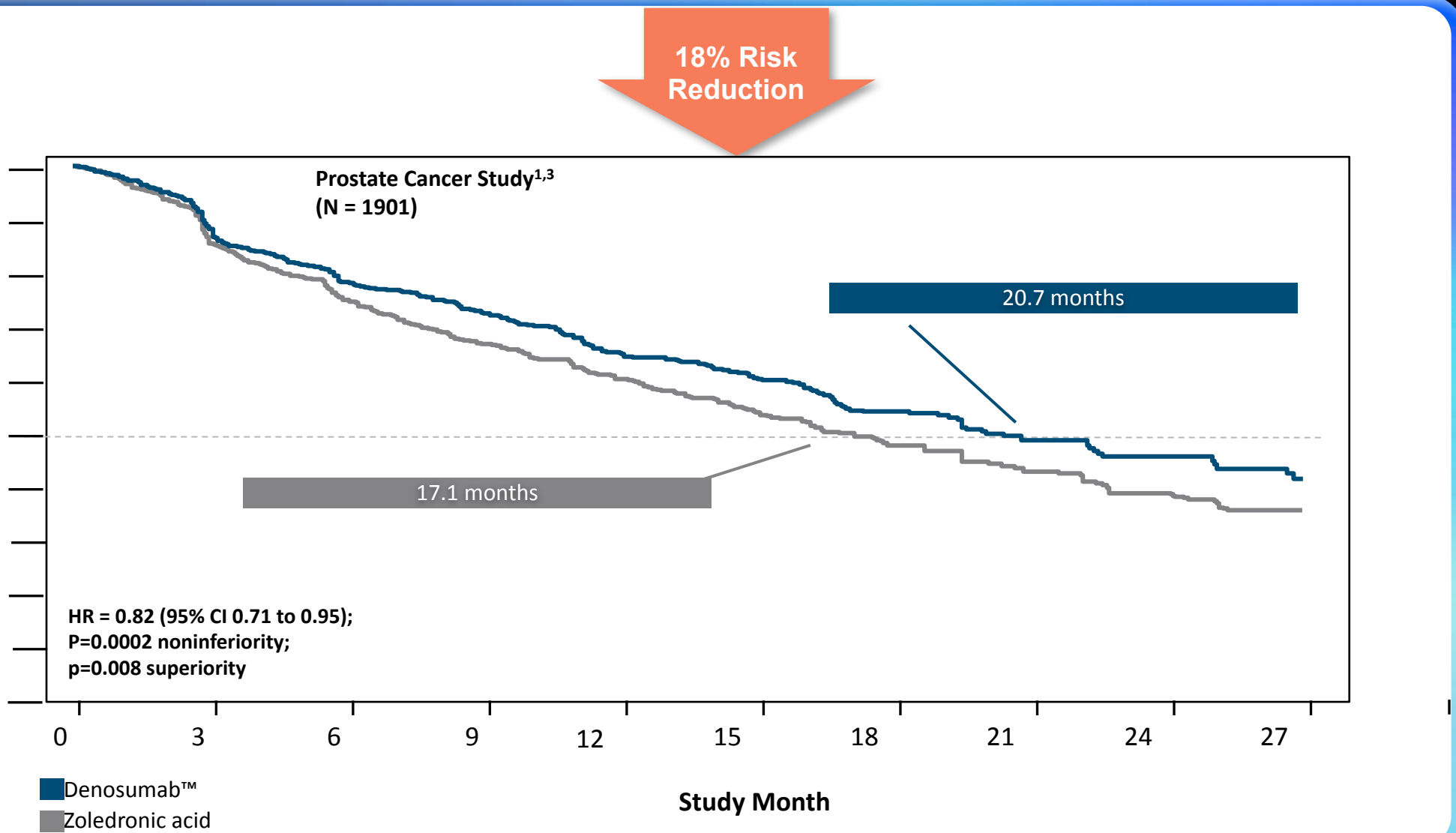


Daily supplementation of calcium ≥ 500 mg and vitamin D ≥ 400 IU were recommended in both arms of the study

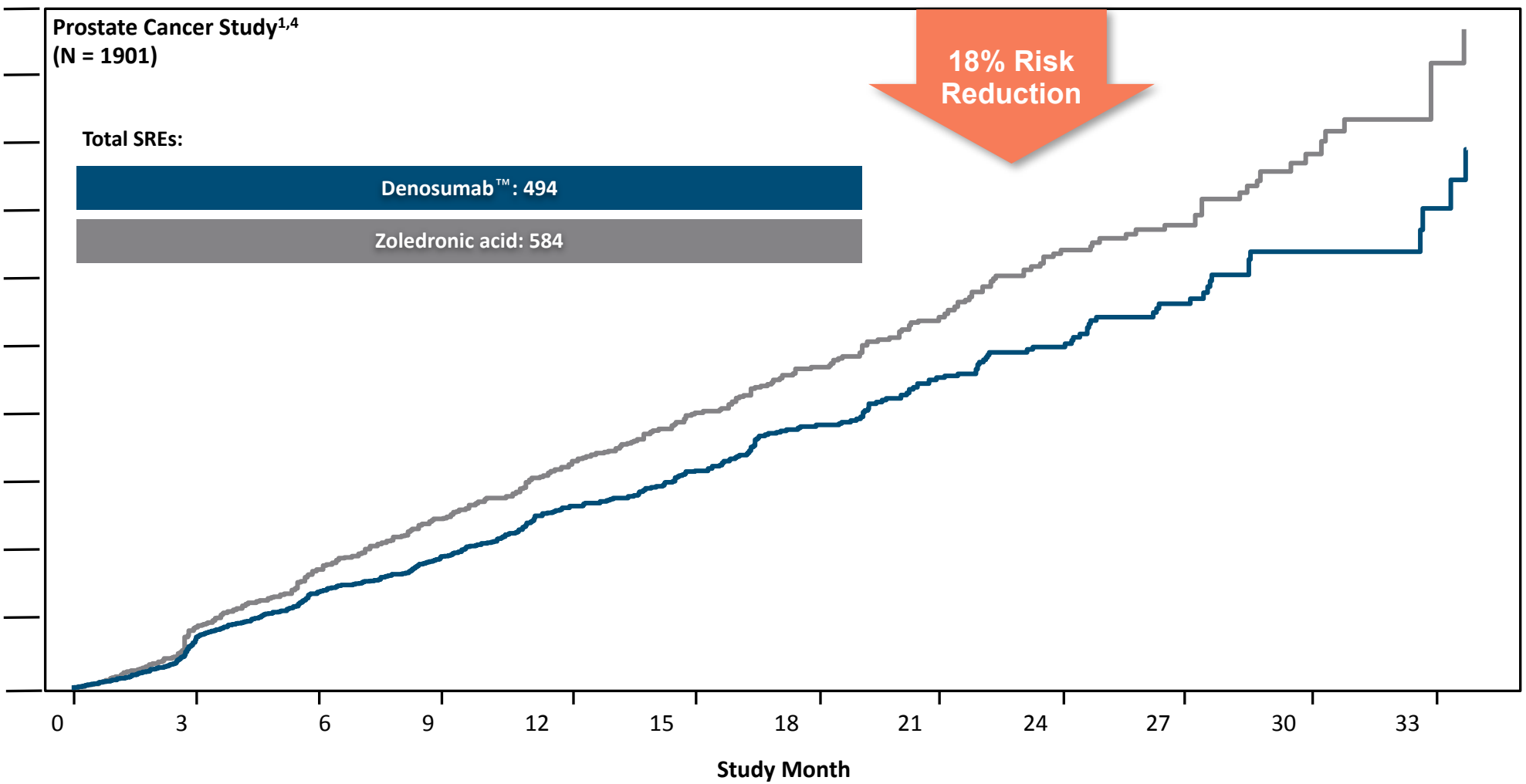
Risk of 1st SRE



Time to 1st SRE



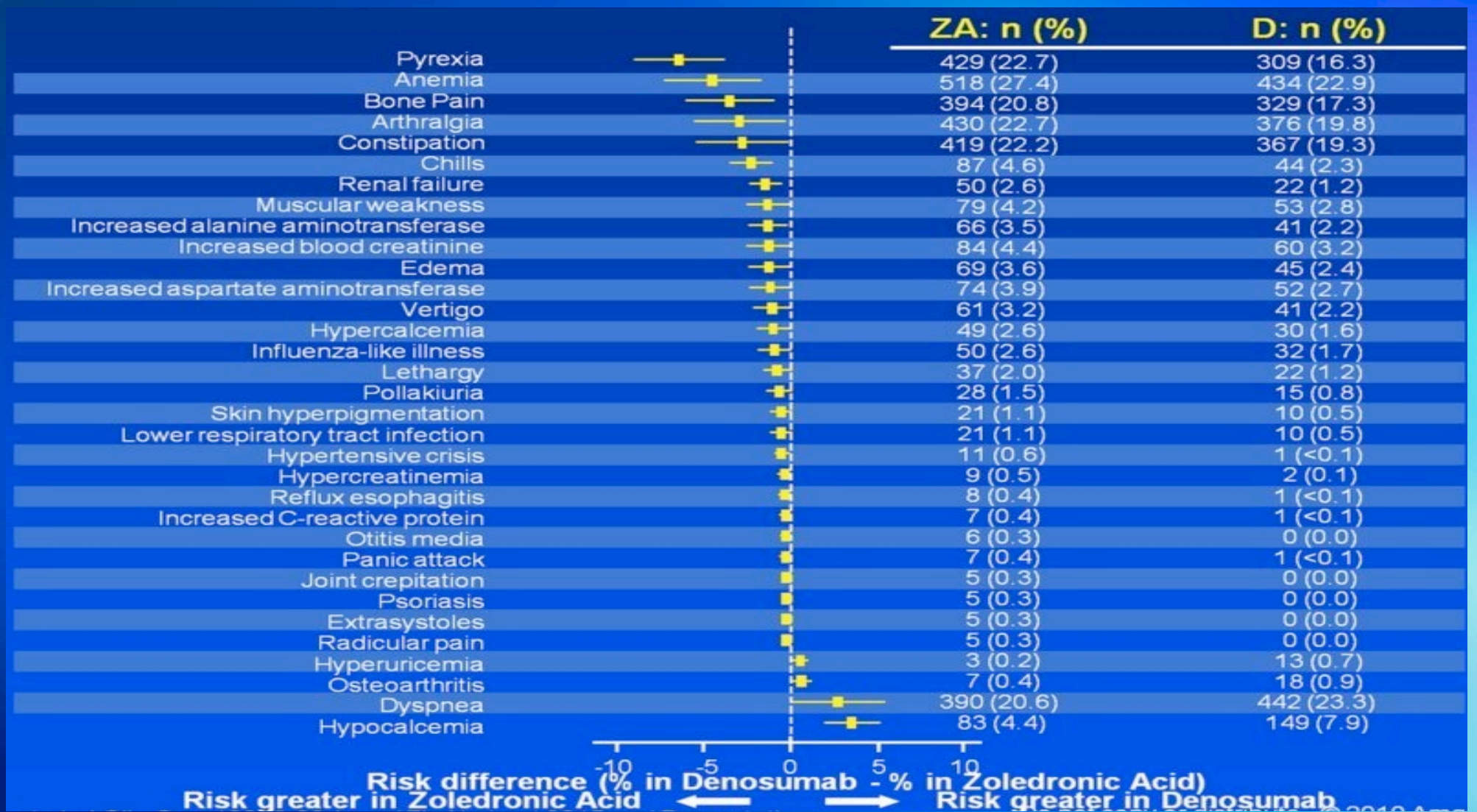
First and Subsequent SRE



Kidney Function

- Denosumab is not cleared by the kidneys
- Dose adjustment for renal impairment is not required

Side Effects



Jawbone Damage

Risk Factors for ONJ	Denosumab	Zoledronic Acid
Prior or concurrent tooth extraction	58%	65%
Use of a denture or other dental appliance	42%	27%
Poor oral Hygiene	31%	32%

- Oral exam pre Rx
- Dental examination with appropriate preventive dentistry pre Rx
- Good oral hygiene practices during Rx
- Avoid invasive dental procedures

Low Calcium Levels

- 9.6% with denosumab and 5.0% with zoledronic acid
- Severe in 3.1% with denosumab vs
  - 1.3% with zoledronate
- 33% experienced 2 or more episodes and 16% experienced 3 or more episodes

Prevention: Calcium

- Correct pre-existing hypocalcemia
- Rx: at least 500 mg calcium and 1000 IU vitamin D daily
- Monitor calcium levels
- Supplement orally or iv
- Tetany rare

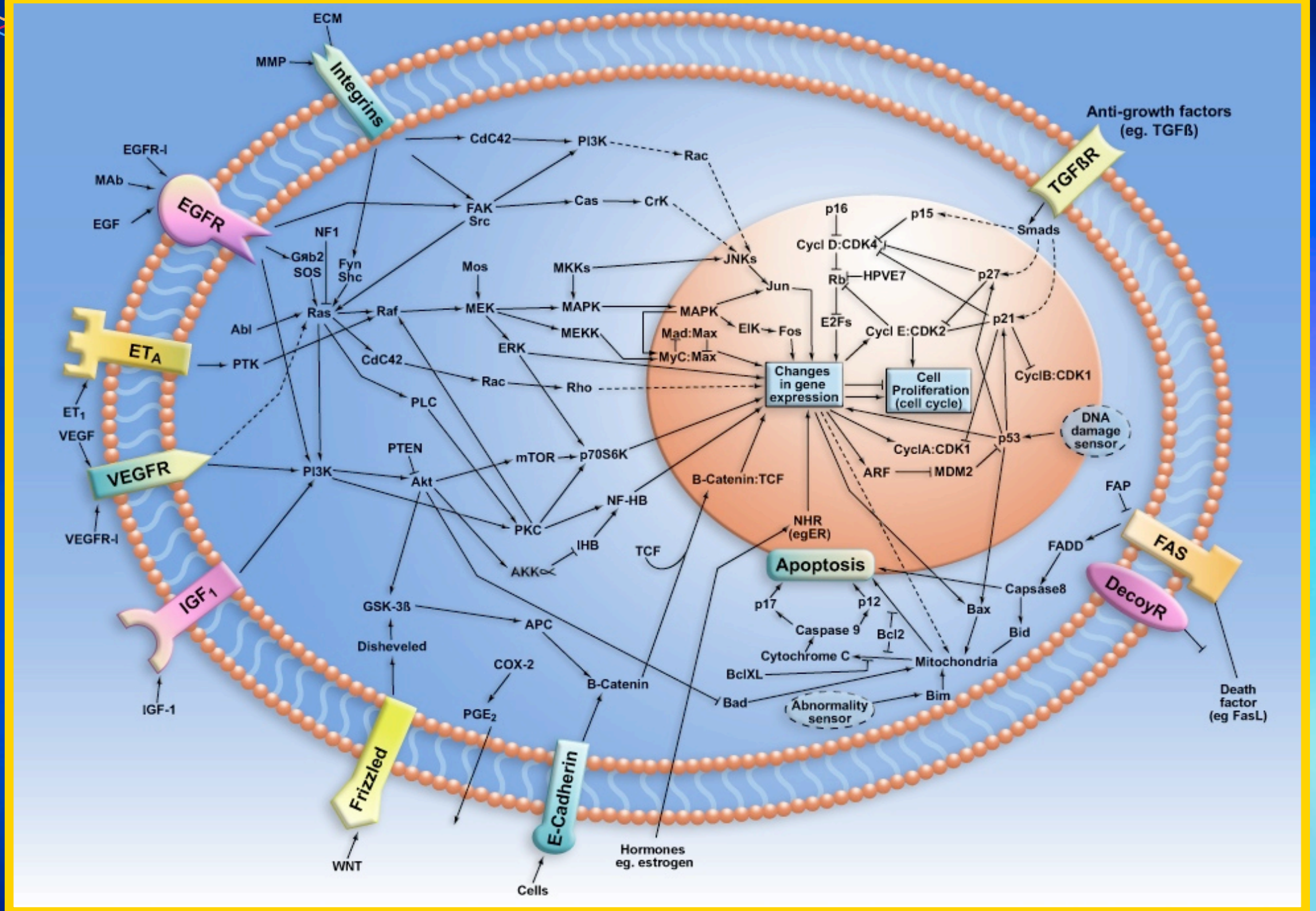
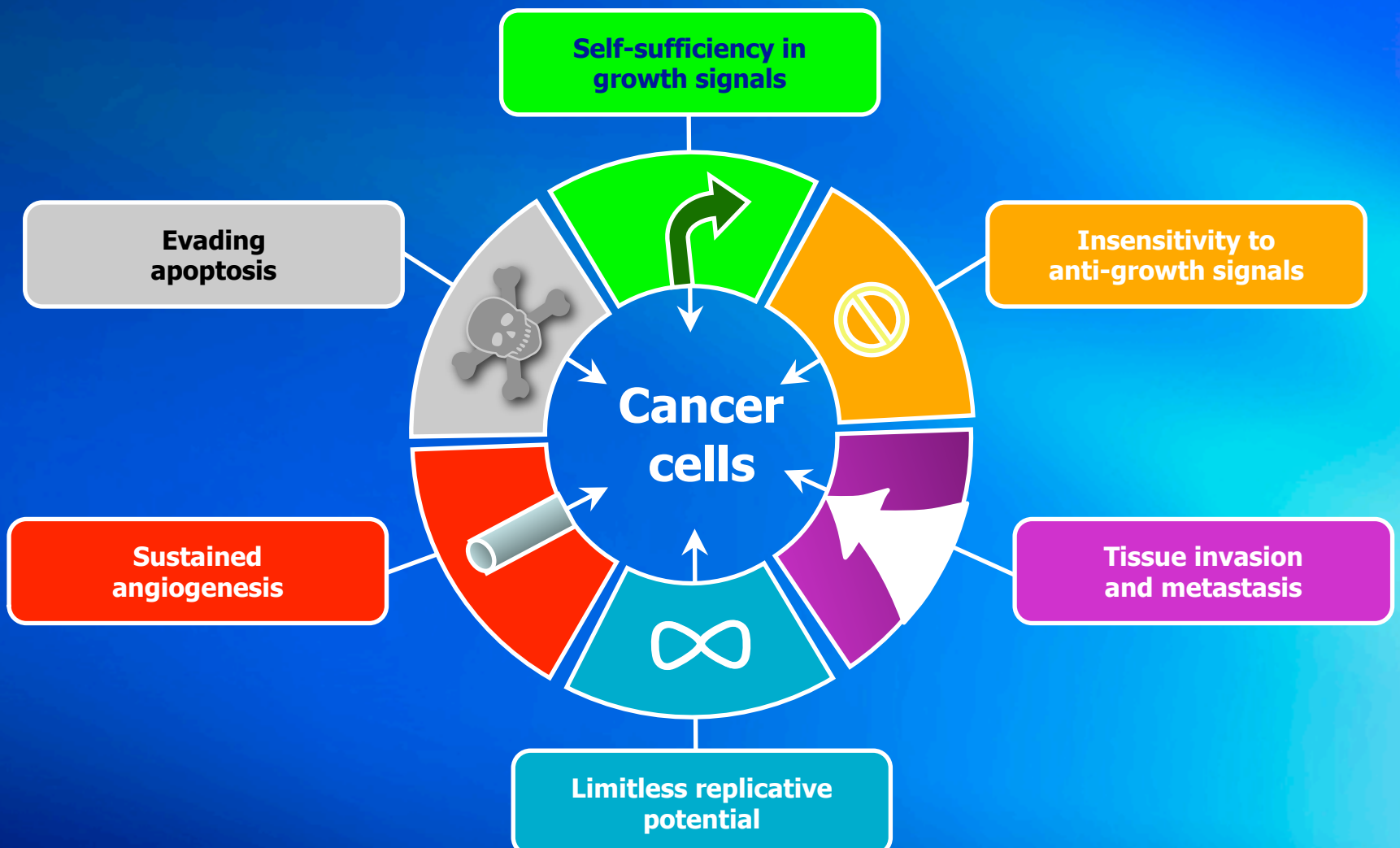


Diagram adapted from Hanahan and Weingberg, Cell 2000; 100; 57

Hallmarks of Cancer



Hanahan & Weinberg. Cell 2000;100:57-70

Thank you for your attention