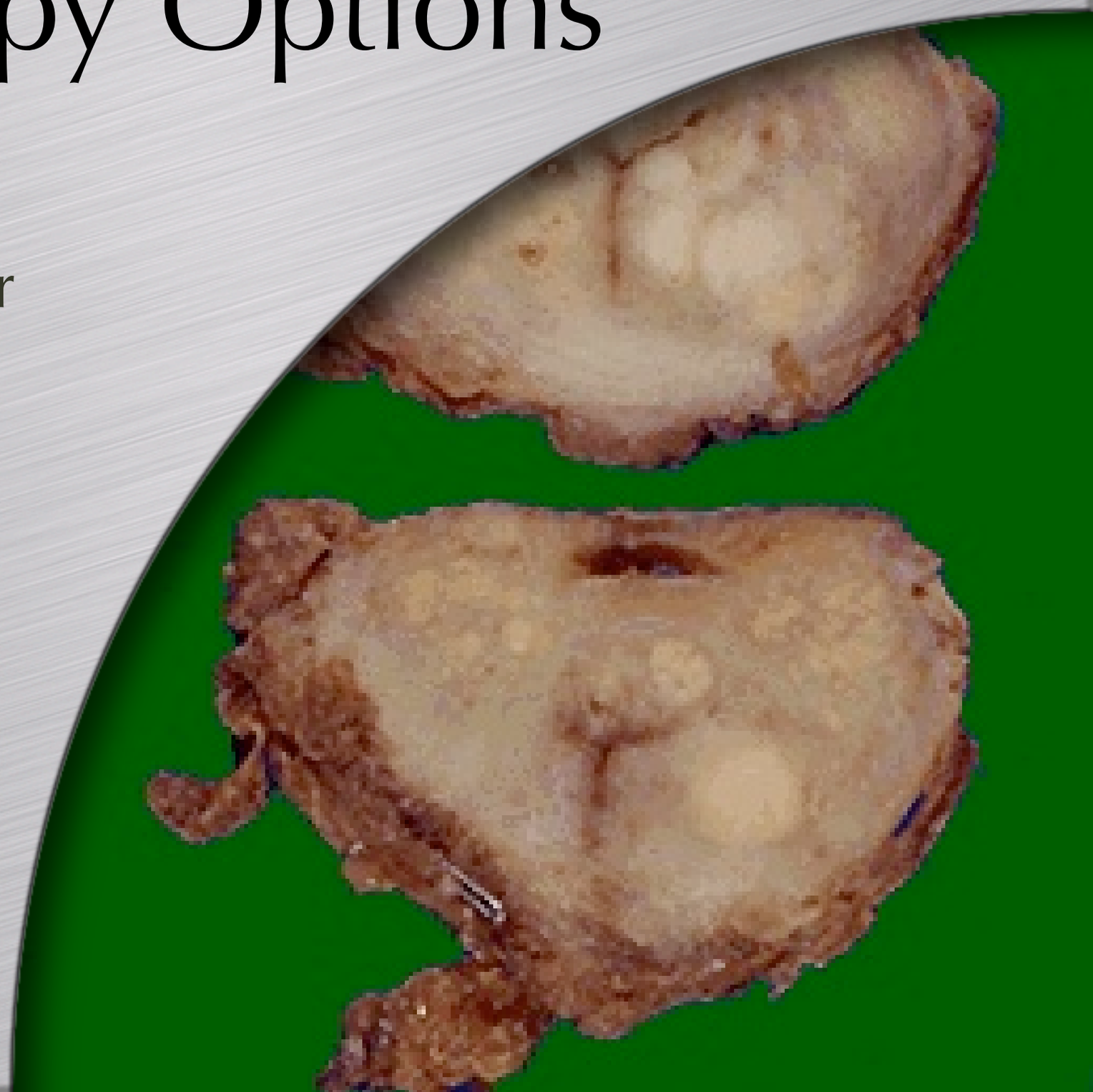
# Prostate Cancer: Chemotherapy Options

Dr. Sandy Sehdev
William Osler Health Ctr
Brampton

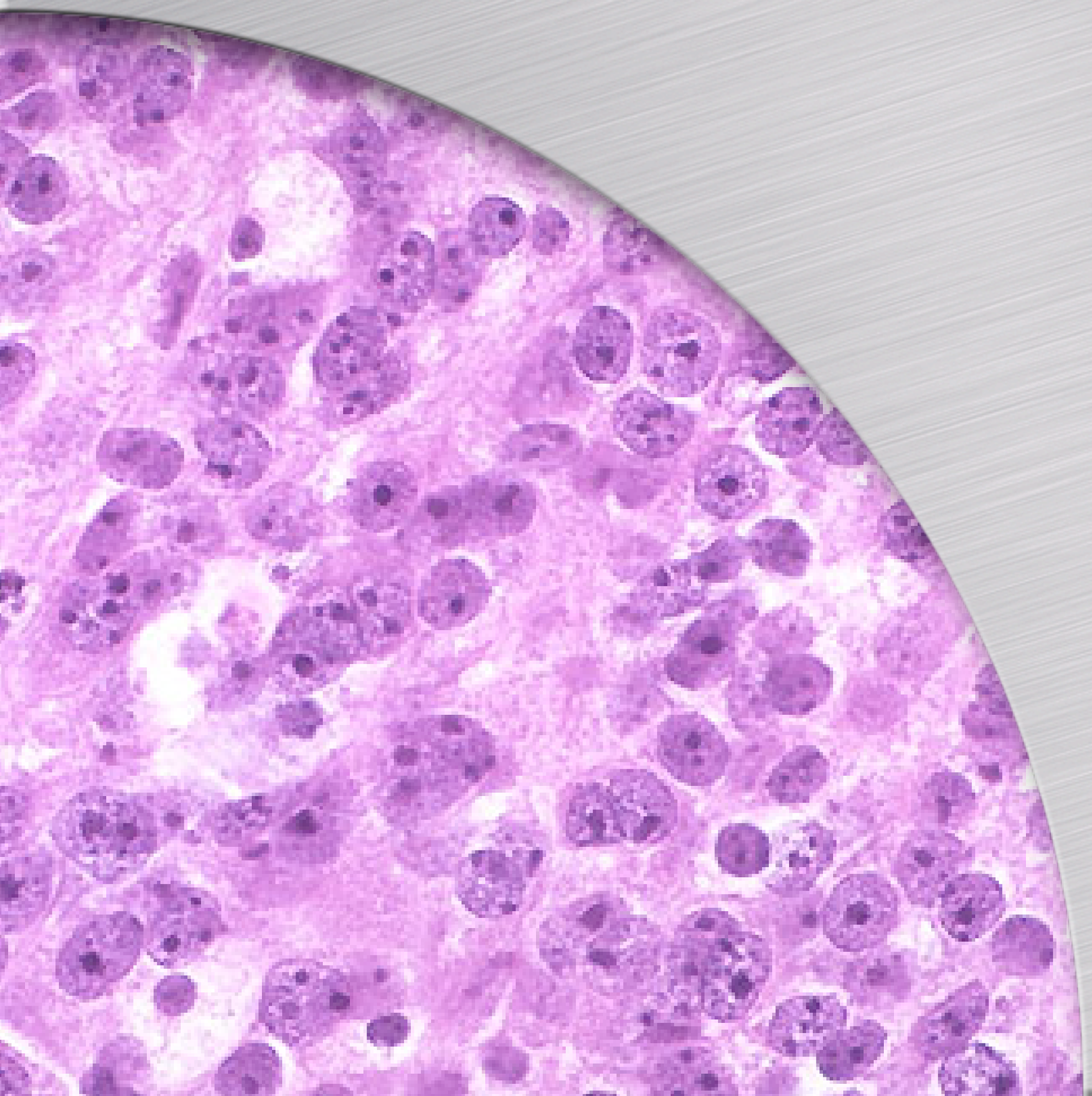
UsToo Group
Jan 11, 2005



WILLIAM OSLER HEALTH CENTRE

US TOO PROSTATE CANCER EDUCATION & SUPPORT

# Itinerary



Background

When Hormones no Longer Work

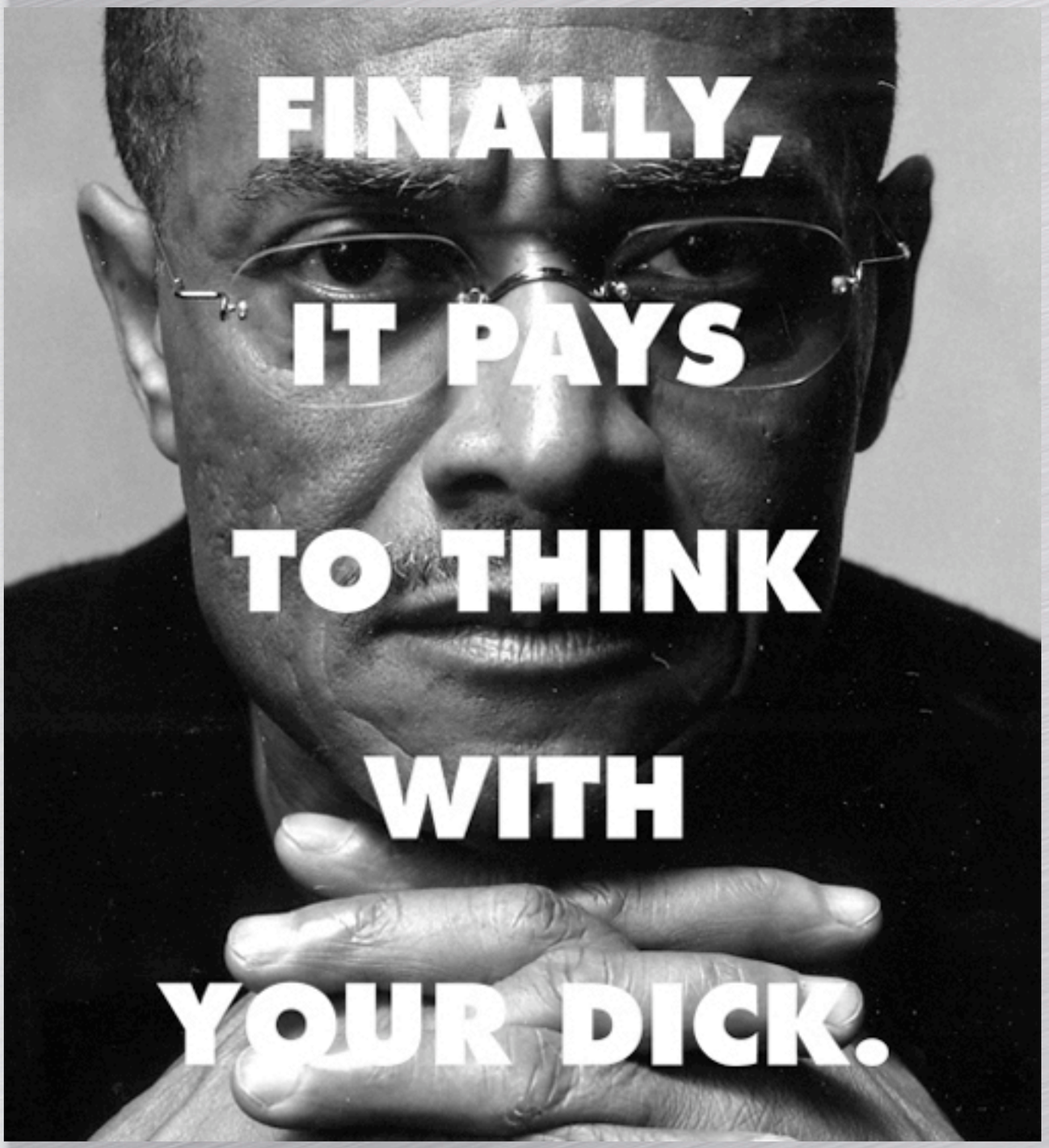
History of Chemo

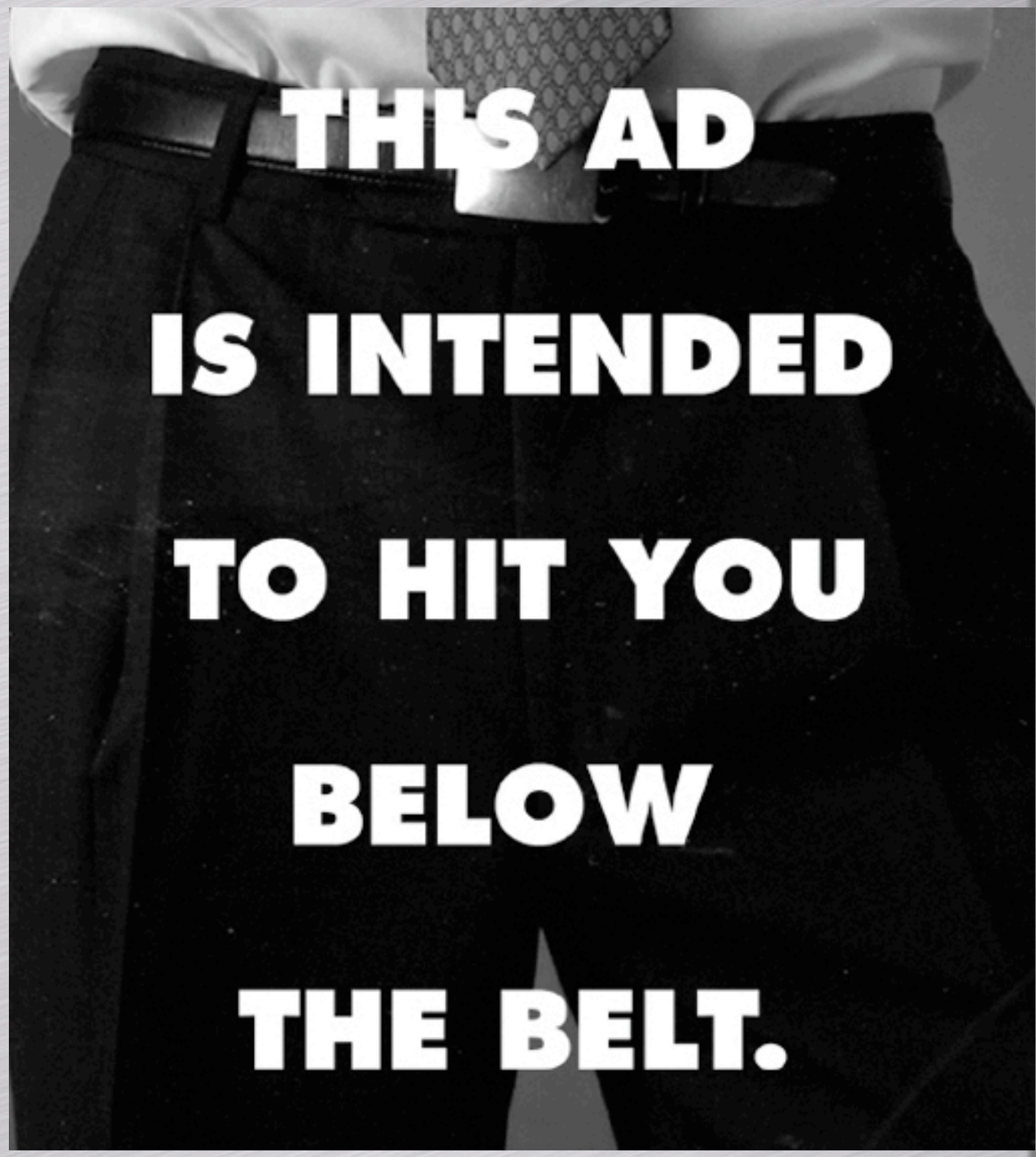
Newer chemo

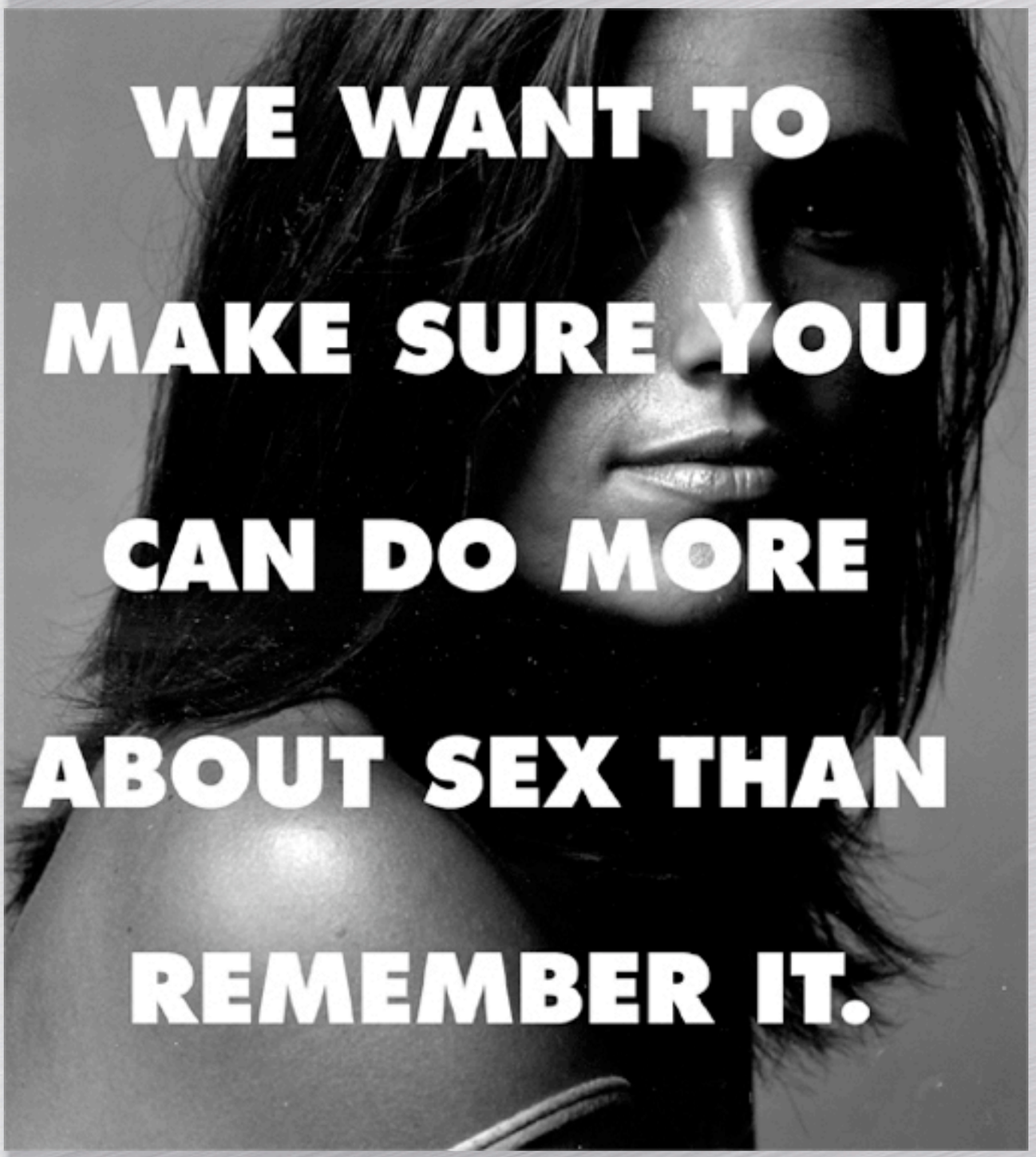
Future

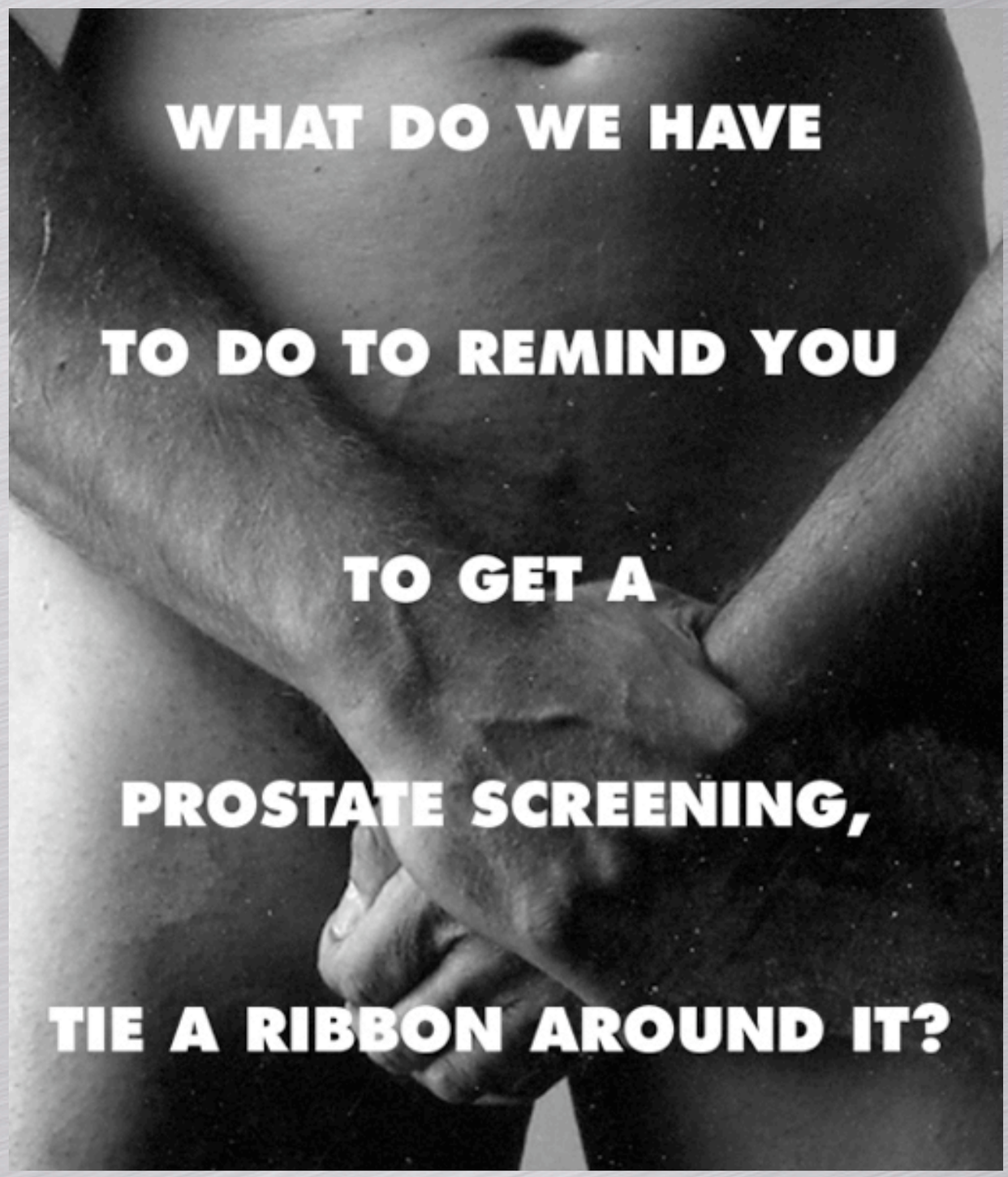
US TOO PROSTATE CANCER EDUCATION & SUPPORT

sanofi aventis
Because health matters


FINALLY,
IT PAYS
TO THINK
WITH
YOUR DICK.


THIS AD
IS INTENDED
TO HIT YOU
BELOW
THE BELT.


WE WANT TO
MAKE SURE YOU
CAN DO MORE
ABOUT SEX THAN
REMEMBER IT.


WHAT DO WE HAVE
TO DO TO REMIND YOU
TO GET A
PROSTATE SCREENING,
TIE A RIBBON AROUND IT?

# Prostate Cancer – Canadian Statistics

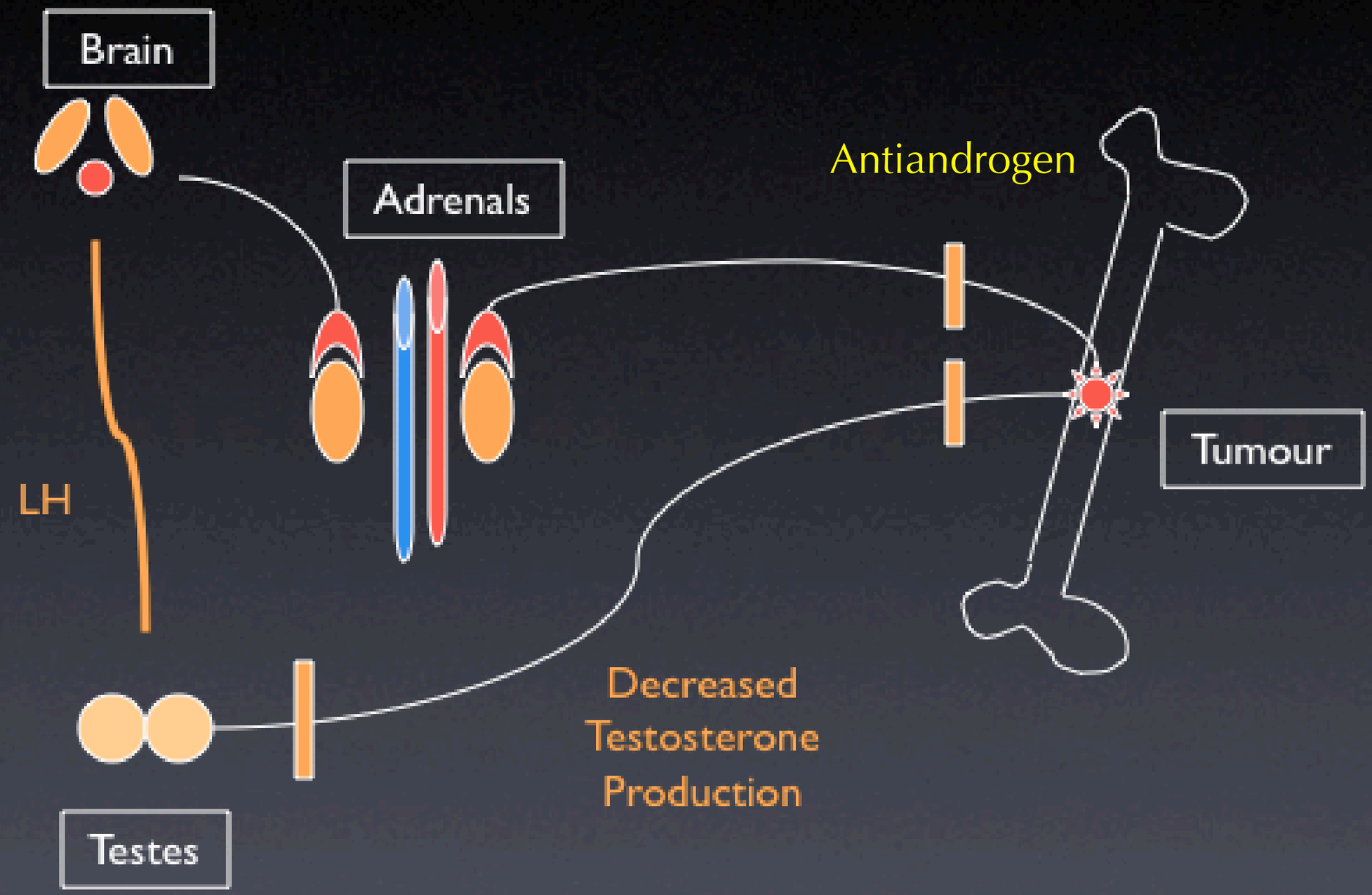
- Most frequently diagnosed cancer in men in 2003
- ~ 18,800 newly diagnosed cases in 2003
- ~ 4,200 estimated deaths in 2003
- 1 in 8 men will develop prostate cancer during their lifetime

National Cancer Institute of Canada: Canadian Cancer Statistics 2003

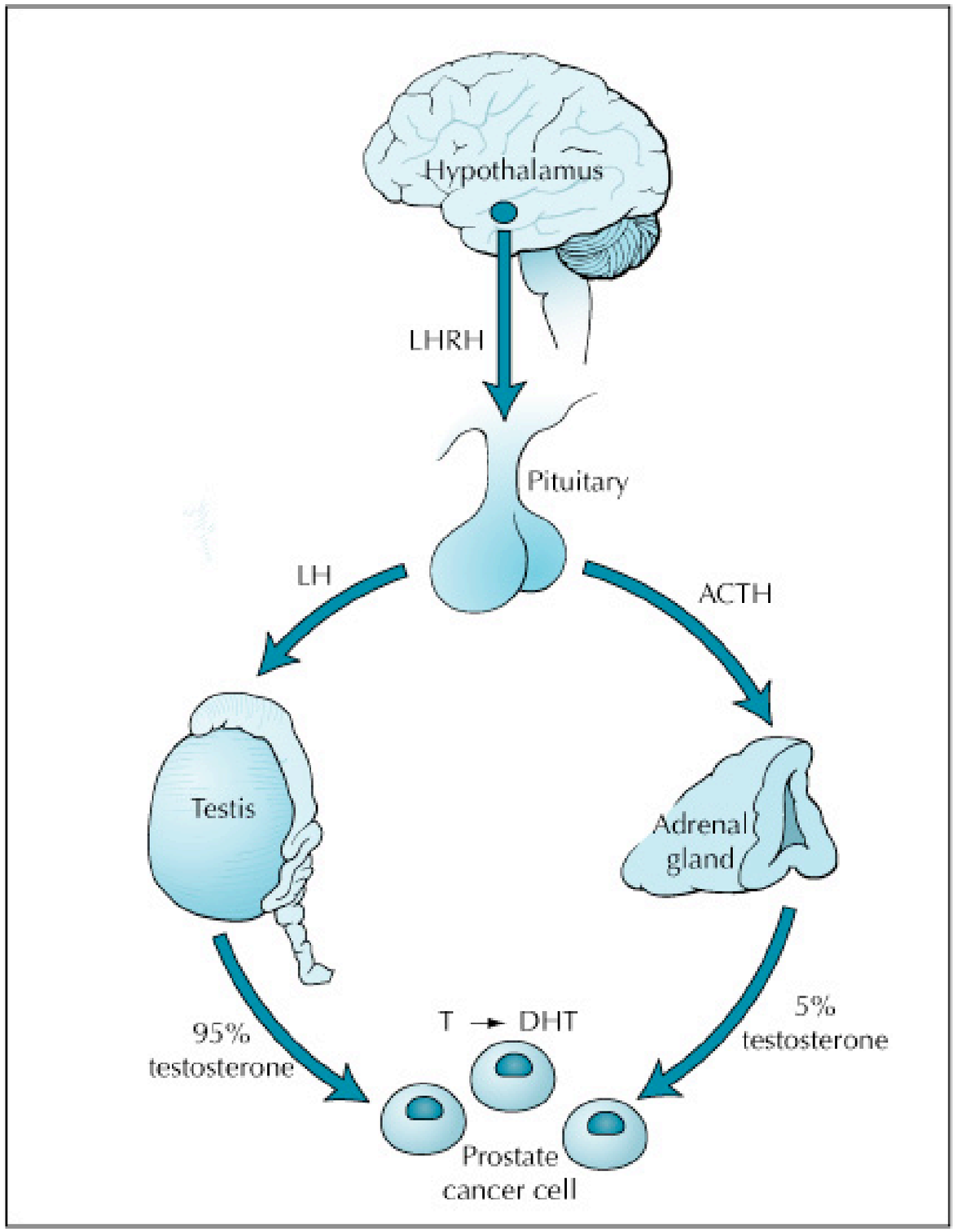
# The Changing Face of Prostate Cancer: The PSA Era

- Prostate cancer is being diagnosed earlier
  - younger and healthier at time of diagnosis
  - significant relapse in patients treated with curative intent
- Progressive disease is diagnosed earlier through PSA
- Increased demands for treatment options

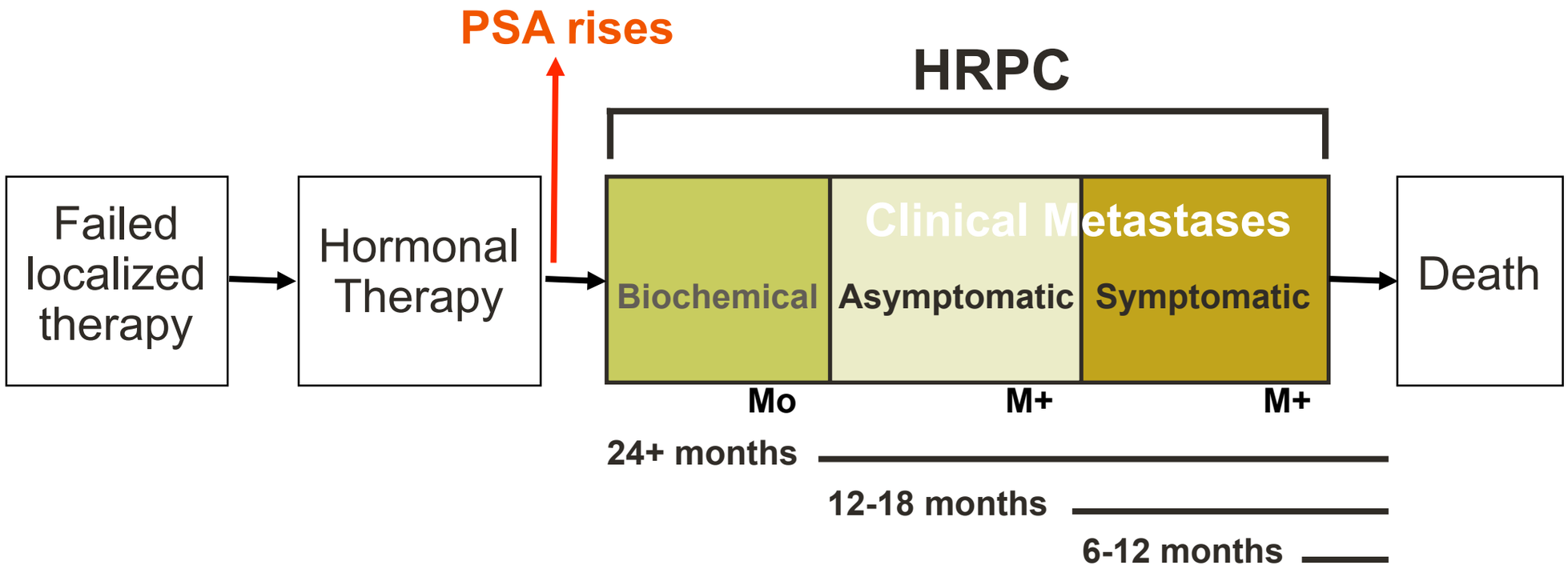
# Complete Androgen Blockade



# Sources of androgen production and control of androgen secretion



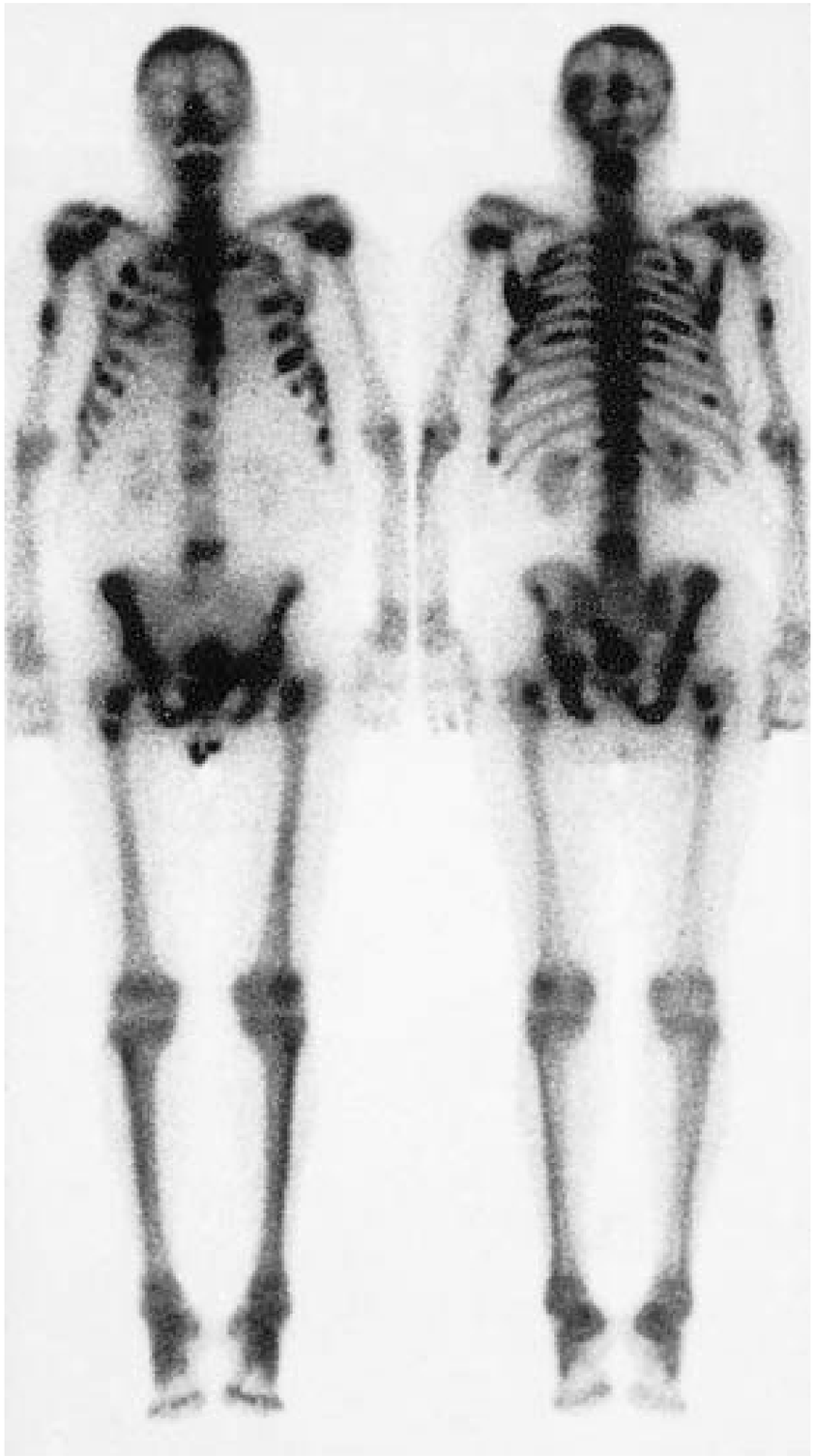
# Progression of Advanced Prostate Cancer



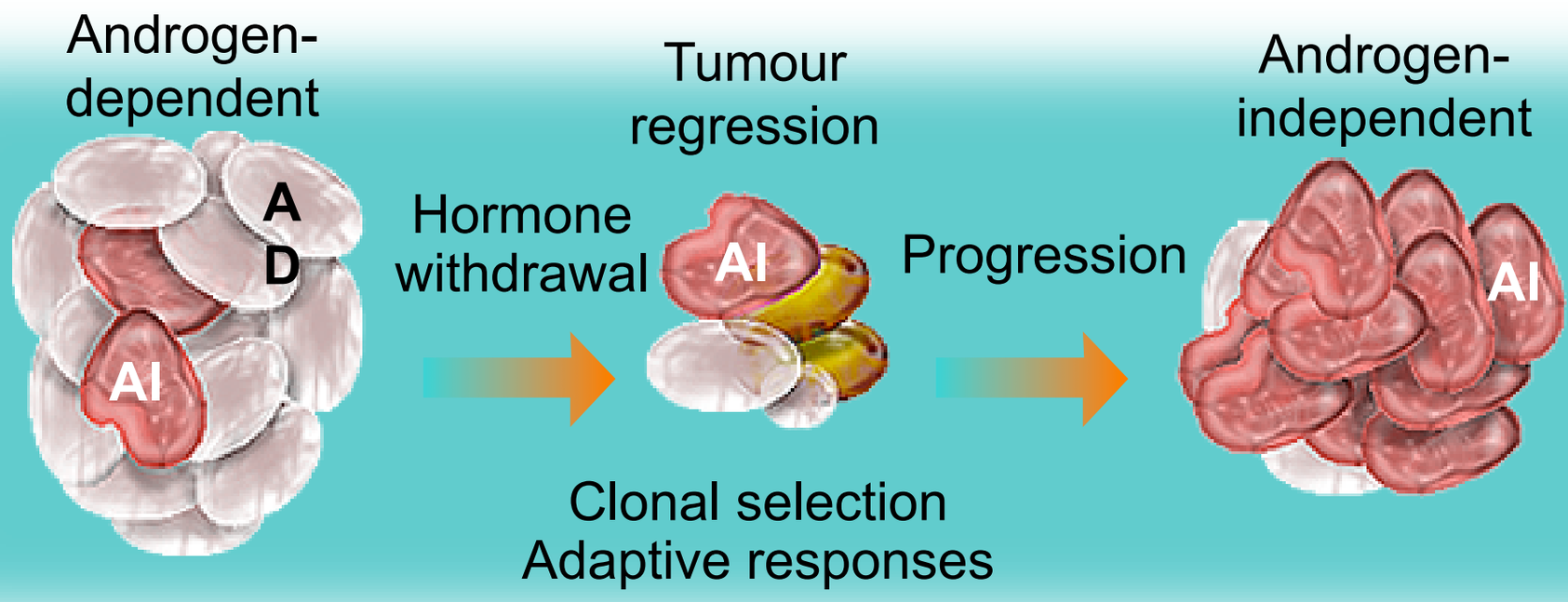

## Hormone-Refractory Prostate Cancer (HRPC)

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

# Radioscintigraphic bone scan: detecting metastases to bone



# Development of Hormone Resistance in Prostate Cancer



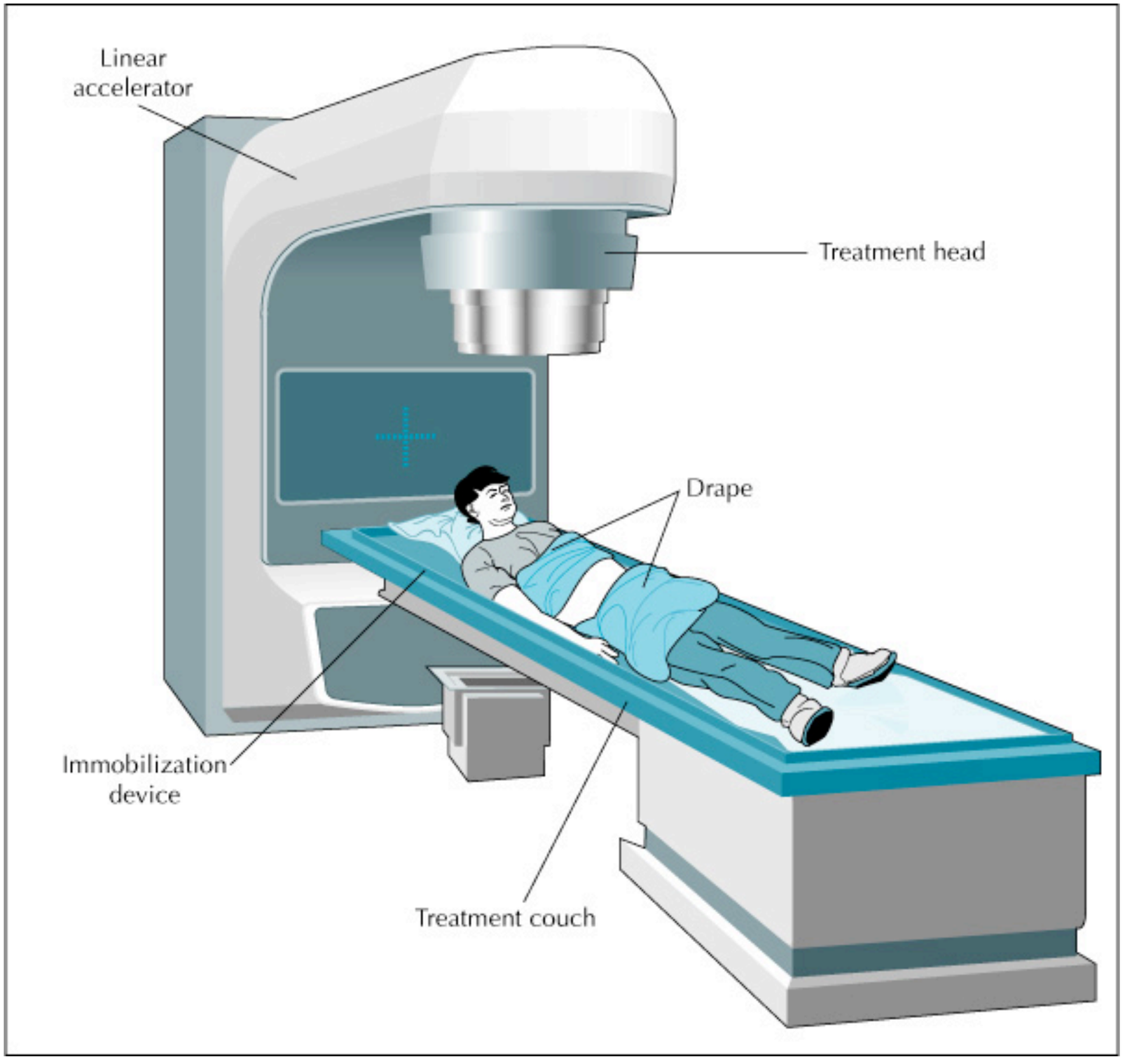
# HRPC – Goals of Therapy

- Improve survival
  - cancer therapy:  hormones, now chemo
- Improve symptoms and quality of life
  - symptom treatment, pain medication
  - radiation for painful lesions
  - supportive care
  - bisphosphonates:  Zometa™

# Treatment Options for HRPC

- Second-line hormonal manipulations
- 
- Radiation therapy
- Bisphosphonates
- Chemotherapy
- Novel agents

# External beam radiotherapy set-up on a linear accelerator



# 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

- Most trials require continuation of LHRH

Hussain M. J Clin Oncol 1994;12:1868  Taylor C. J Clin Oncol 1993;11:2167

# Second-line Hormonal Manipulations

Treatment options include:

- Antiandrogen withdrawal (AAW)
- Secondary use of antiandrogens (AA)
- Therapies targeted against adrenal steroid synthesis
  - ketoconazole, corticosteroids
- Estrogenic therapy
  - diethylstilbestrol

Sartor A. 38th ASCO Annual Meeting 2002 (Abstract 785) Kucuk O. Urology 2001;58:53 Desai A. Urology 2001;58:1016

# Antiandrogen Withdrawal Syndrome

- First described with flutamide
  - can occur with other hormones
  -
- Occurs 10% to 30% of time
-
- PSA decreases within weeks, depending on AA

- Median duration of response 3.5 months

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

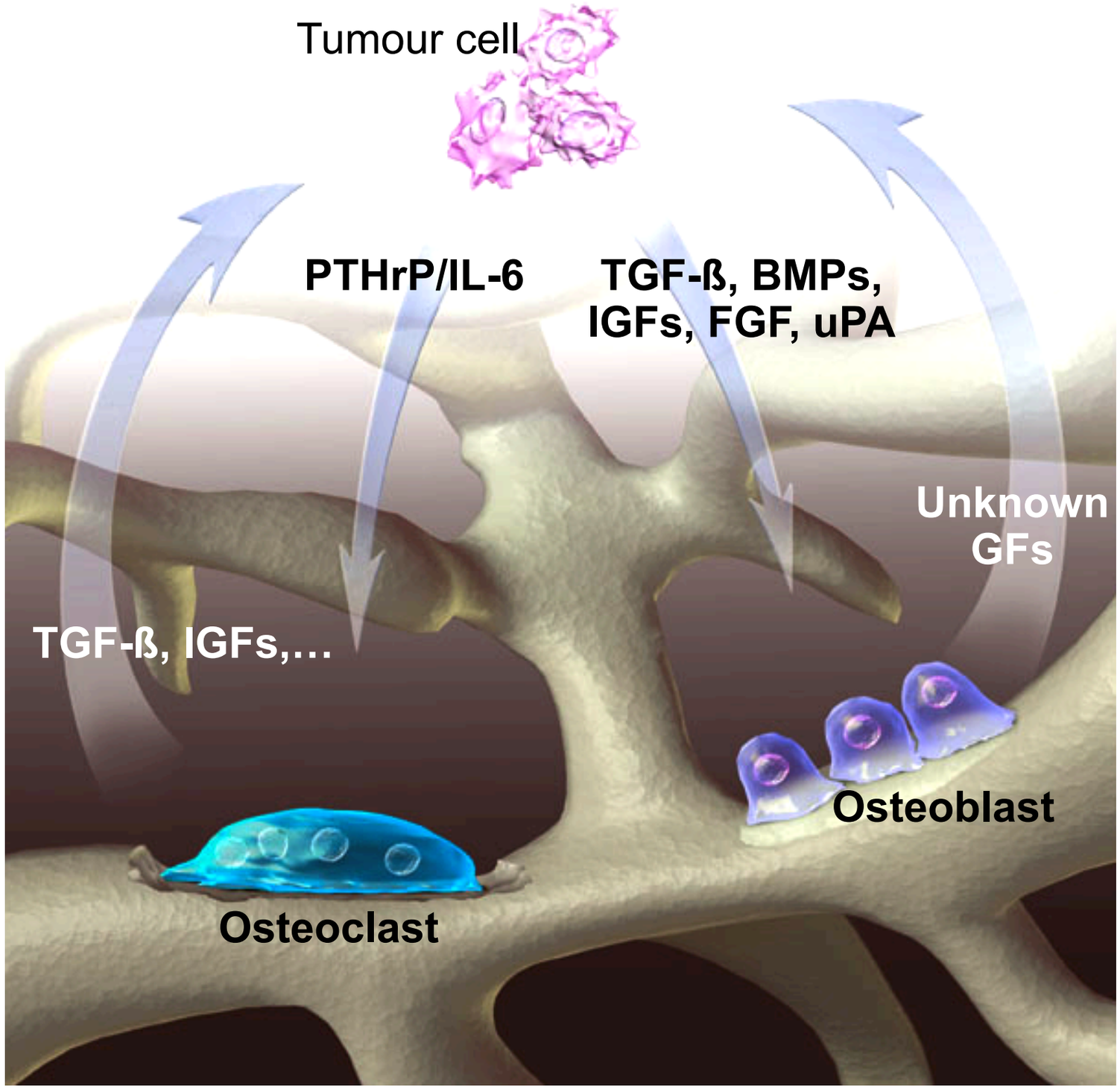
# Clinical Impact of Second-line Hormonal Manipulation Therapy

- Clinical and objective responses
  - PSA levels decline, patients may have symptomatic improvement
  -
- Survival benefit is unknown
- “Minimal side effects”

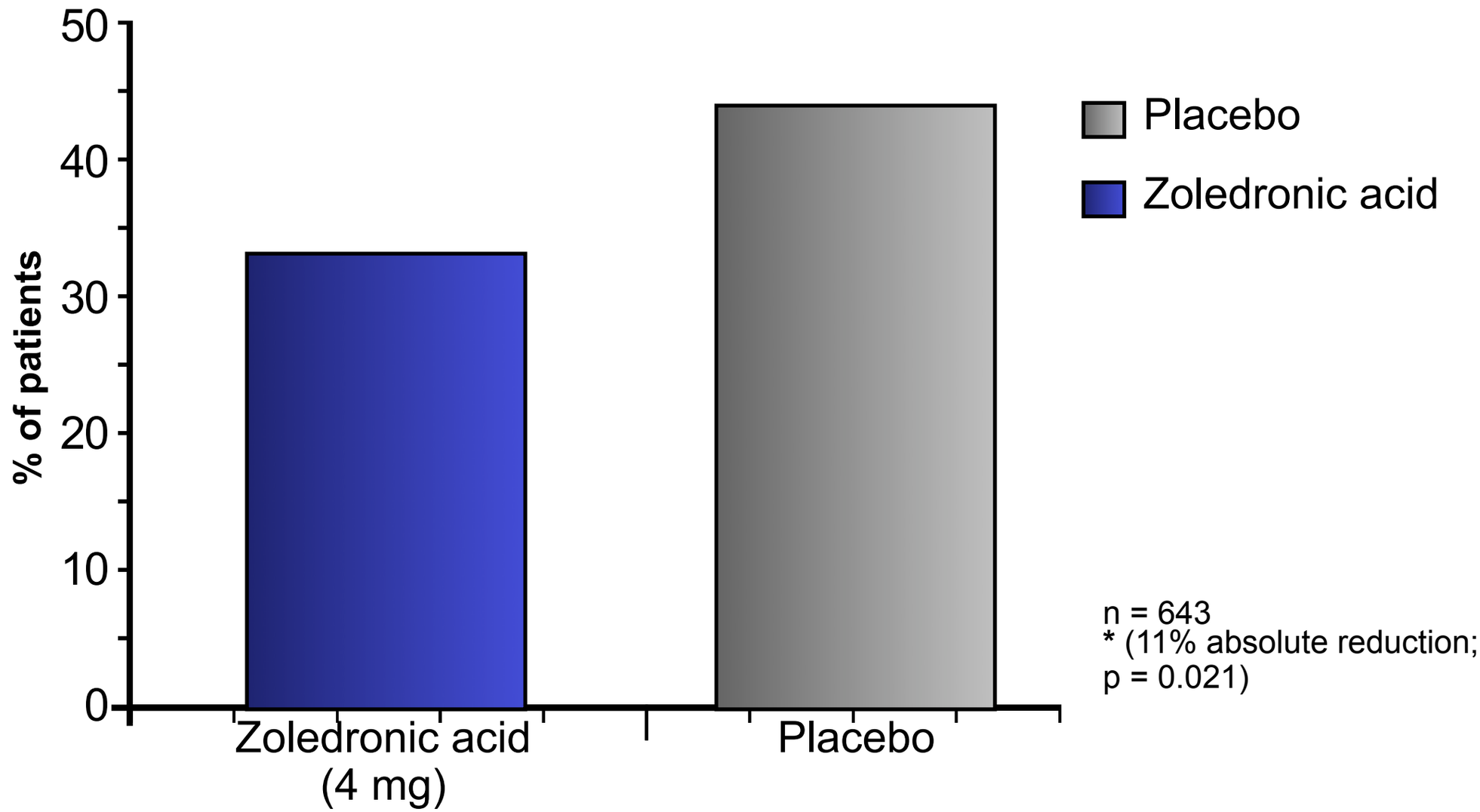
# Bisphosphonates

- Option in the management of bone metastasis
- 
- Zoledronic acid (Zometa™) – first bisphosphonate to show efficacy
- Powerful inhibitor of osteoclast–mediated bone resorption
- Nonmyelosuppressive
  - unlike chemo, does not effect blood counts

# Pathogenesis of Osteolytic/Osteoblastic Bone Metastases



# Zoledronic Acid Effect on Skeletal-related Events*




n = 643
* (11% absolute reduction; p = 0.021)

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

# Chemotherapy in Advanced Prostate Cancer

# Chemotherapy

- What is chemotherapy?
- Drugs given to fight cancer
  - often given i.v., some oral
  - newer agents more effective
  - newer agents less toxic
  - side effects now more manageable, preventable
  - now validated ways to prove benefits and QoL

WILLIAM
OSLER
HEALTH
CENTRE

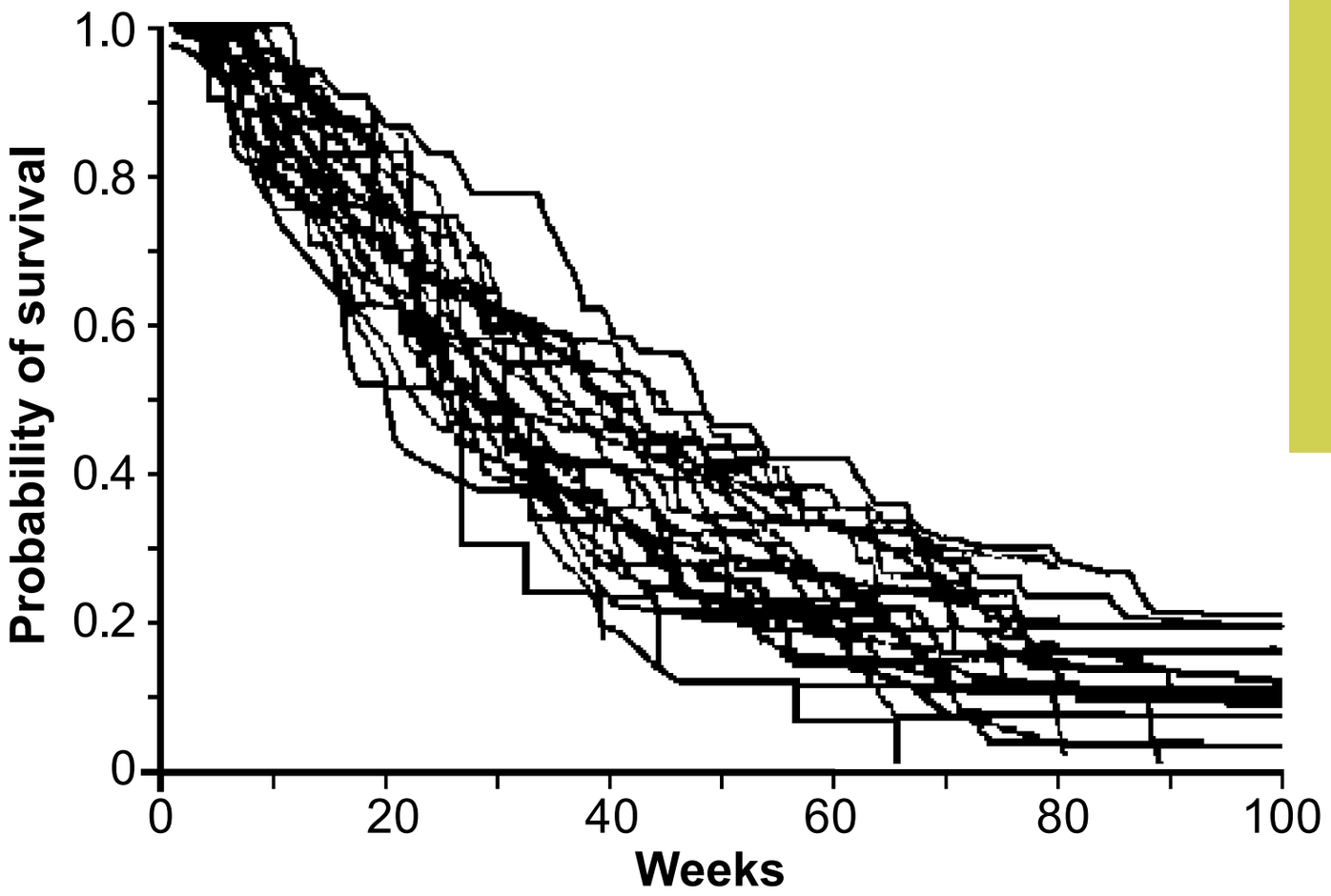
# Early Results With Chemotherapy

**Prior to 1985**

- Eisenberger et al
- 17 trials (n = 1,464)
  - overall 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

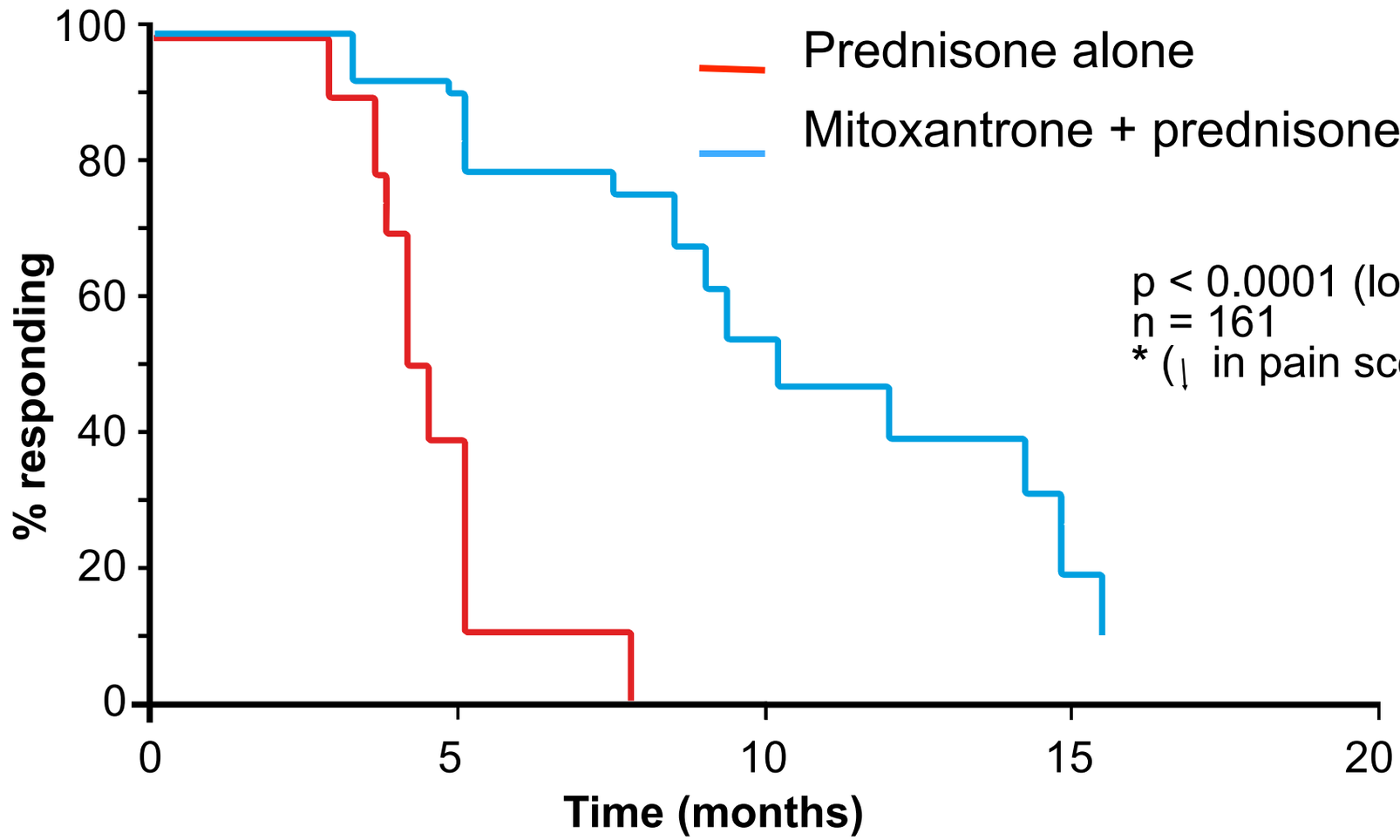
# Early Results With Chemotherapy (cont'd)

- Much sicker patient populations
- 
- No evidence that chemotherapy prolonged survival

- Concern for potential toxicity of chemotherapy

- Impact on quality of life was not assessed

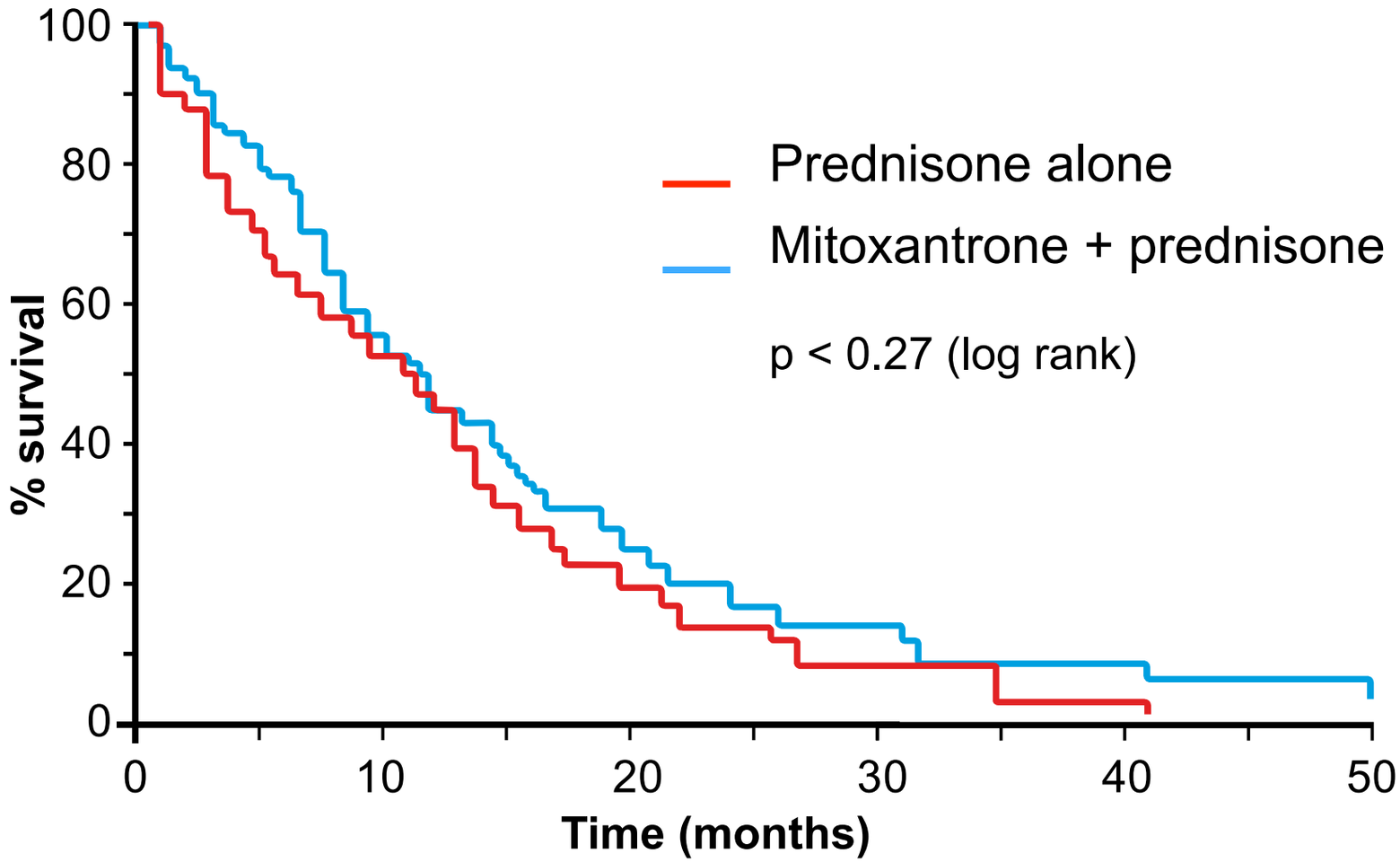
# Chemotherapy: Palliative Response*




- 29% vs. 12% palliative response for mitoxantrone + prednisone vs. prednisone alone
- Improved quality of life

Tannock I. J Clin Oncol 1996;14:1756

# Chemotherapy: Overall Survival




- No significant difference in overall survival and change in time to progression
- Similar results obtained with mitoxantrone + hydrocortisone

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

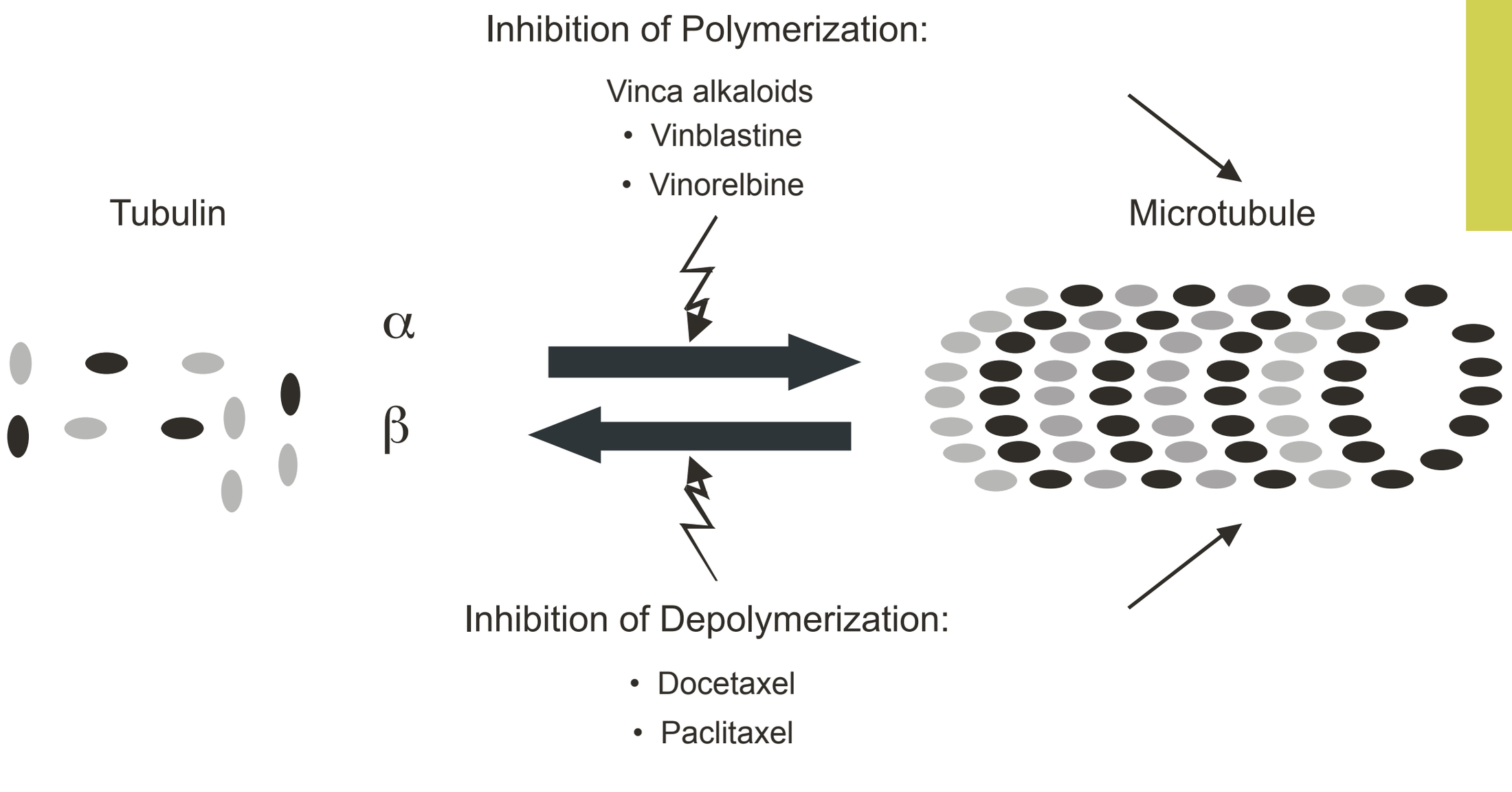
# Chemotherapy: Estramustine Phosphate

- Inhibits microtubule function and mitosis
-
- Significant estrogenic effects
  - risk of blood clots
  -
- When used alone, relatively low response rate with significant side effects
  - no phase III evidence as monotherapy
  - phase III evidence of PSA response and improved TTP in combination with vinblastine
  - approved in the U.S.
  - TOX:  nausea, vomiting, gynecomastia, clots

Perry C. Drugs Aging 1995;7:49  Hudes G. J Clin Oncol 1999;17:3160

# Estramustine-based Antimicrotubule Combinations: Rationale

- Combine estramustine with other agents that target microtubule proteins for synergistic effect



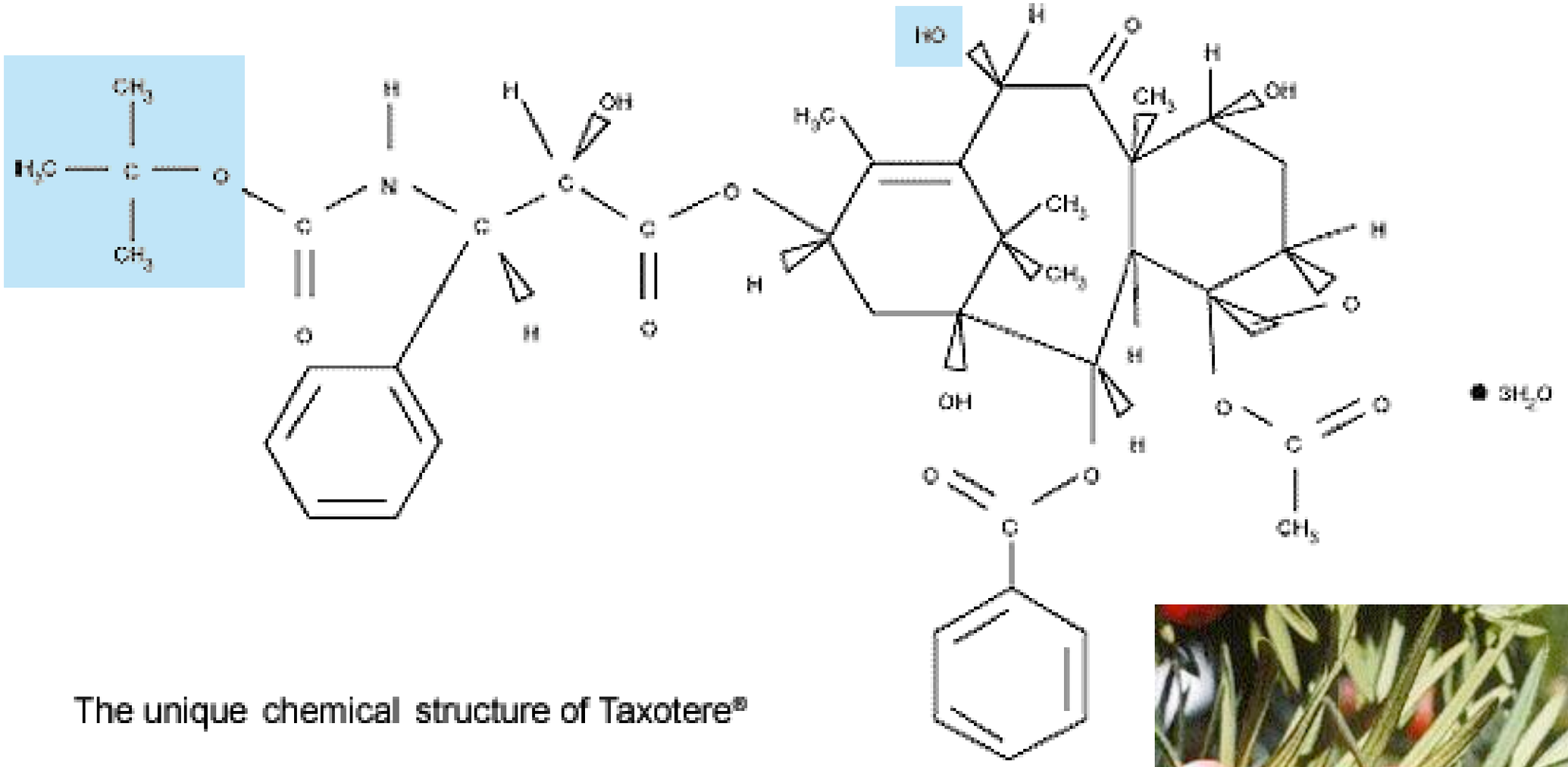
# Results of Phase II/III Trials With Estramustine Combinations

| Treatment | Trial | > 50% PSA decline (%) | Median survival (mo) |
|---|---|---|---|
| Vinblastine + estramustine | Phase III Hudes et al, 1999 | **25** | **12** |
| Vinorelbine + estramustine | Phase II Smith et al, 2000 | **24** | **14** |
| Paclitaxel + estramustine | Phase II Hudes et al, 1997 | **53** | **17** |
| Docetaxel + estramustine | Phase II Savarese et al, 2001 | **68** | **20** |

# Taxanes and HRPC: Phase II Studies

- Docetaxel as a single agent (every 3 weeks or weekly)
- Docetaxel + estramustine
- Docetaxel + estramustine + prednisone
- Docetaxel + thalidomide
- Docetaxel + calcitriol
- Paclitaxel as a single agent (every 3 weeks or weekly)
- Paclitaxel + estramustine

# Docetaxel (Taxotere™)

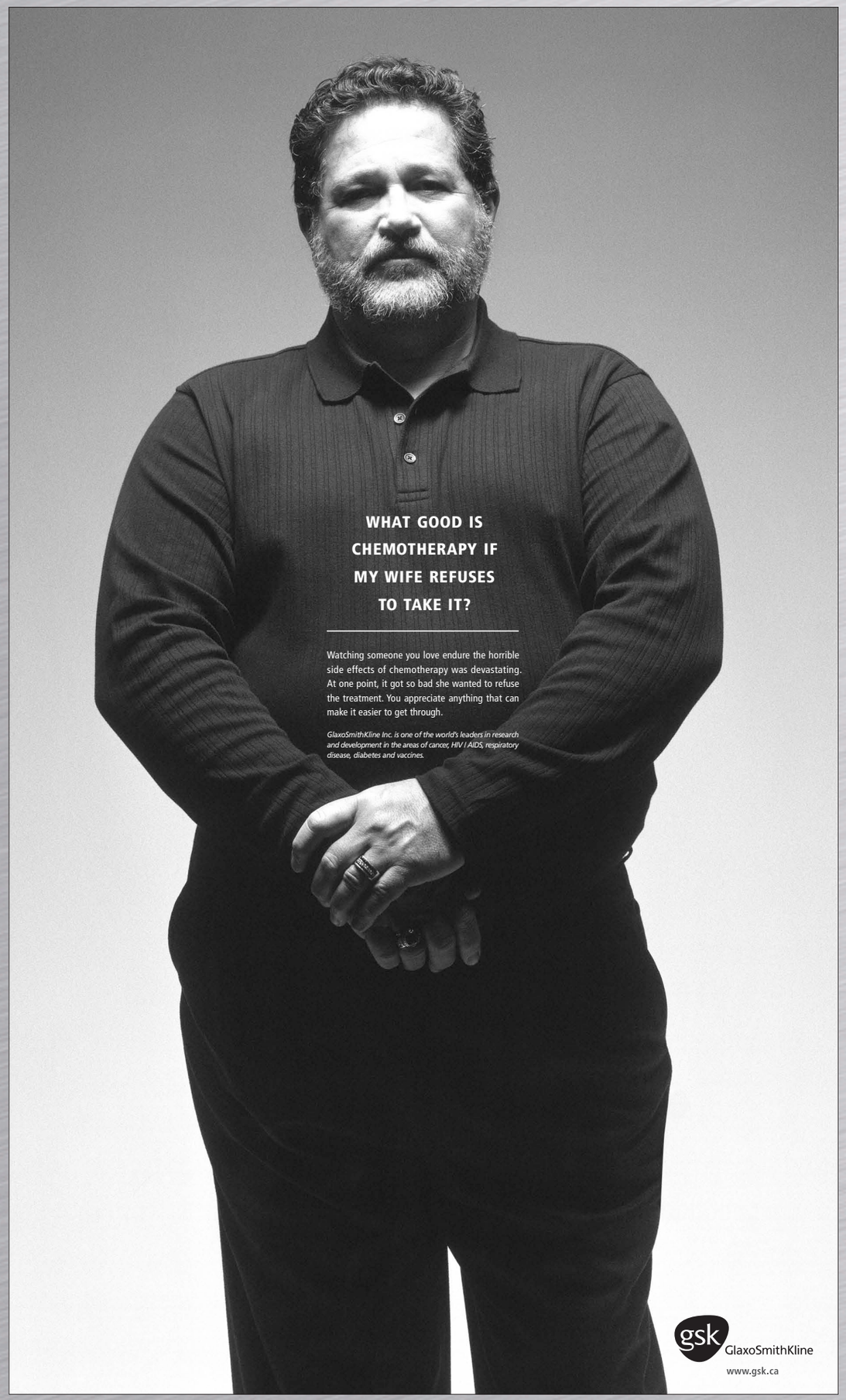


The unique chemical structure of Taxotere®

European Yew Tree Needles

# Docetaxel (Taxotere™)

- Premedications:
  - dexamethasone 8 mg bid x 5 doses, starting evening before each chemo, to prevent allergic reactions
  - ondansetron (Zofran™) 8 mg tabs to prevent vomiting
  - prochlorperazine 10 mg as needed for nausea




# Side effects

**Vomiting**: preventable with 5HT3 antagonists (Zofran™)

Allergies

Fingernails and hair

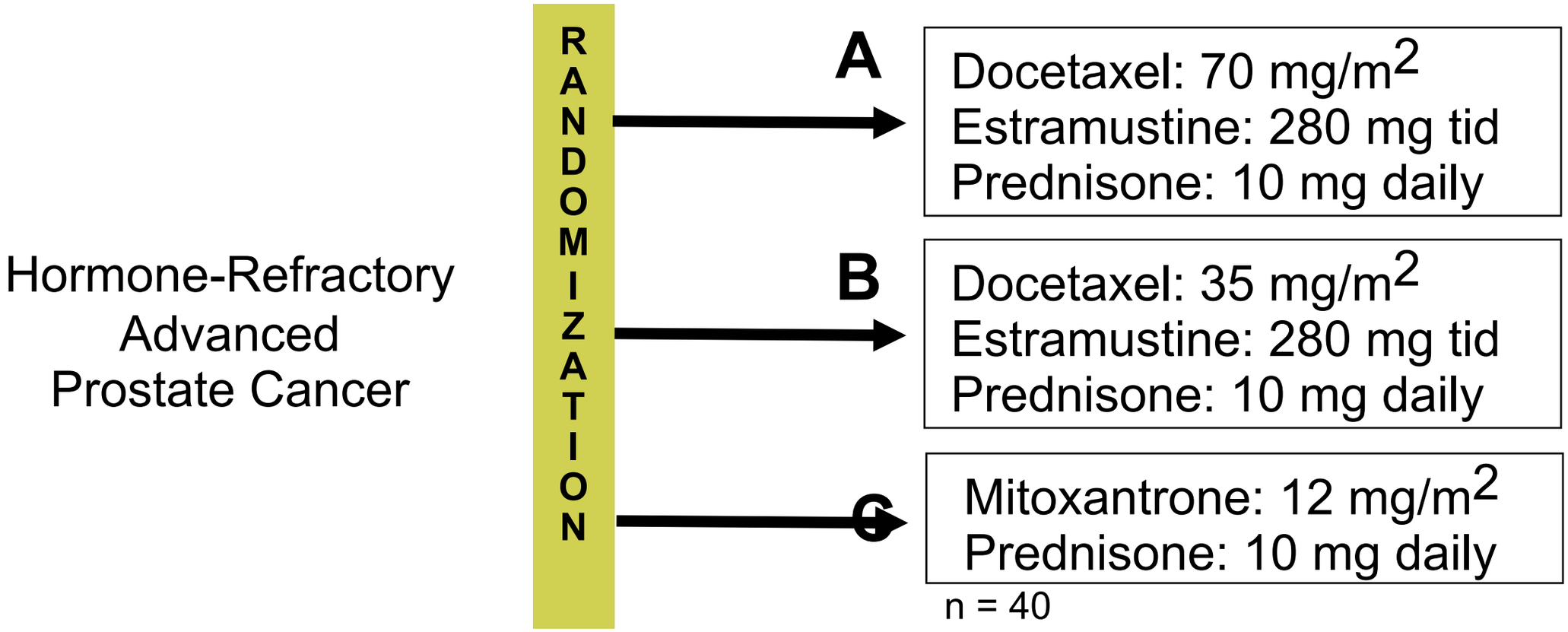
Tiredness

Anemia

White blood cell counts

Neuropathy

# Docetaxel + Estramustine + Prednisone: Phase II Study




- Primary endpoint: PSA decrease > 50%; objective tumour response

Oudard S. Ann Oncol 2002;13(Suppl 5):90

# Docetaxel + Estramustine + Prednisone: Efficacy

| Regimen | Patients | PSA > 50% | Disease response* | Median survival (mo) |
|---|---|---|---|---|
| Docetaxel: 70 mg/m$^2$<br>Estramustine: 280 mg tid<br>Prednisone: 10 mg daily | **44** | **67%** | **9/16** | 18.6 |
| Docetaxel: 35 mg/m$^2$<br>Estramustine: 280 mg tid<br>Prednisone: 10 mg daily | **44** | **62%** | **3/15** | 18 |
| Mitoxantrone: 12 mg/m$^2$<br>Prednisone: 10 mg daily | **42** | **17%** | **1/12** | *11.6** |

* Soft tissue response

Oudard S. Ann Oncol 2002;13(Suppl 5):90

# Summary of Docetaxel + Estramustine + Prednisone

- Better response rate compared with mitoxantrone/prednisone
- 
- Worthy of more study
- 
- Safety profile of docetaxel combinations predictable and manageable

# 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**

**RANDOMIZE**

**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**

# Key Eligibility Criteria

- Androgen independent prostate cancer (M +)
  - past  orchiectomy and/or LHRH agonist
  - Testosterone <50 ng/dL
- Progressive disease
- Stable pain scores and analgesia requirements
- Adequate organ function
- No prior chemotherapy
  - except estramustine

# Patient Characteristics (n=1006)

| | Docetaxel 3-wkly | Docetaxel wkly | Mitoxantrone |
|---|---|---|---|
| Randomized | 335 | 334 | 337 |
| Ineligible*(%) | 12 | 12 | 12 |
| Median age (range) | 68(42-92) | 69(36-92) | 68(43-86) |
| ≥ 80 Karnofsky PS (%) | 88 | 87 | 86 |
| Pain level ≥ PPI 2 or AS ≥ 10 (%) | 45 | 45 | 46 |
| Prior treatment (%) | | | |
| Prostatectomy | 19 | 24 | 21 |
| Radiotherapy | 52 | 44 | 51 |
| Estramustine | 19 | 18 | 21 |

# Patients Characteristics

| | Docetaxel 3-wkly | Docetaxel wkly | Mitoxantrone |
|---|---|---|---|
| **Hormonal Manipulations (%)** | | | |
| 1 | 9 | 8 | 6 |
| 2 | 68 | 72 | 69 |
| >2 | 23 | 21 | 25 |
| **Median PSA (ng/ml)** | 114 | 108 | 123 |
| **Gleason Score (%)** | | | |
| ≤7 | 42 | 40 | 42 |
| 8-10 | 31 | 31 | 28 |
| Not available | 26 | 29 | 30 |
| **Extent of Disease (%)** | | | |
| Bone metastases | 90 | 91 | 92 |
| Visceral disease | 22 | 24 | 22 |

# Patients Characteristics

| Criteria of progression at entry (%) | Docetaxel 3-wkly | Docetaxel wkly | Mitoxantrone |
|---|---|---|---|
| Bone scan | 71 | 70 | 69 |
| ↑Measurable lesions | 28 | 30 | 28 |
| ↑Non-measurable lesions | 13 | 16 | 15 |
| ↑PSA | 72 | 67 | 68 |

# Treatment

| | Docetaxel 3-wkly | Docetaxel wkly | Mitoxantrone |
|---|---|---|---|
| Randomized | 335 | 334 | 337 |
| Completed Rx (%) | 46% | 35% | 25% |
| Progression (%) | 38% | 35% | 56% |
| ADR (%) | 11% | 16% | 10% |
| Other | 5% | 13% | 9% |

# Grade 3-4 Hematologic Toxicity (%)

| | 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 |

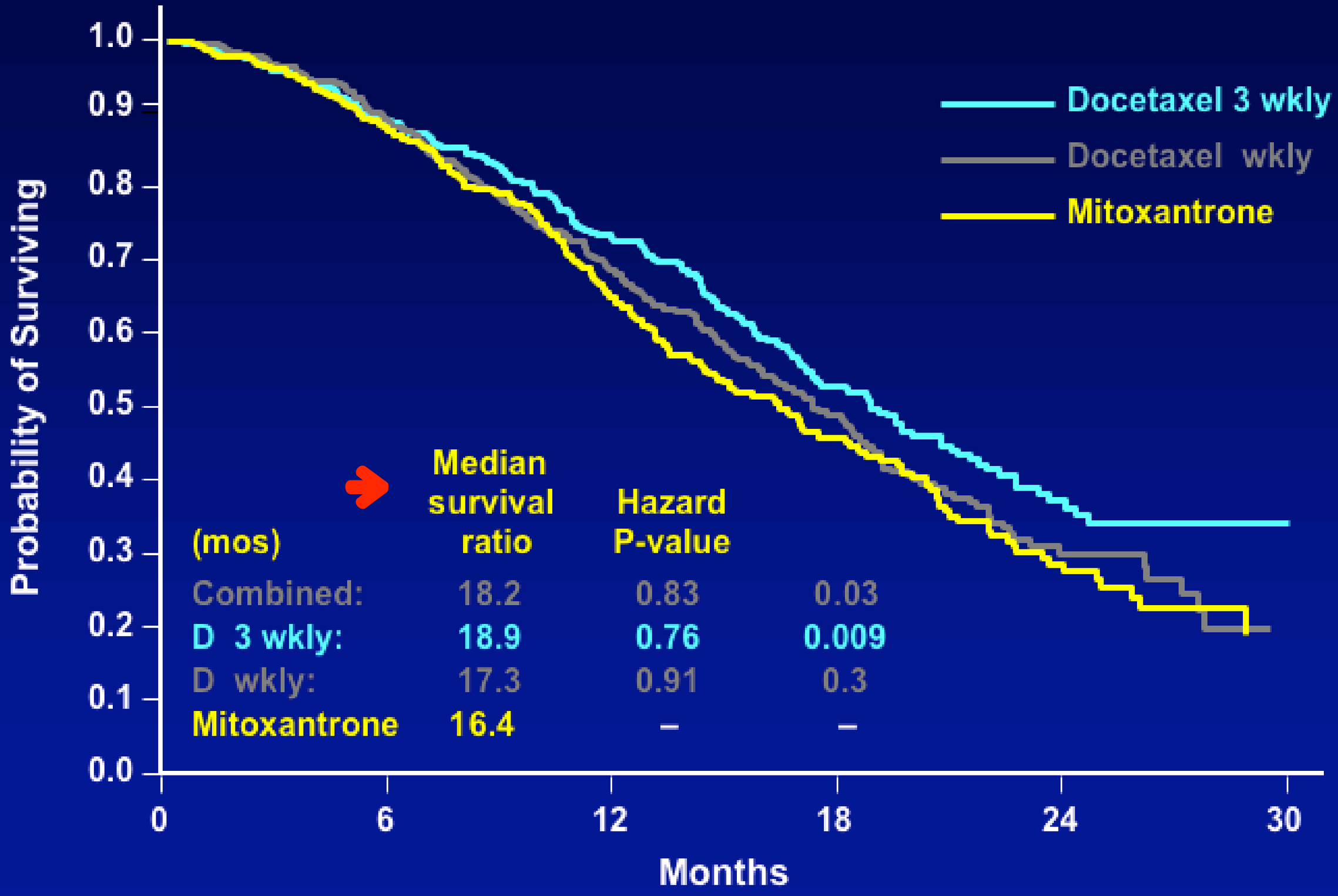
# Non-hematological Toxicity (%)

| | 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** |

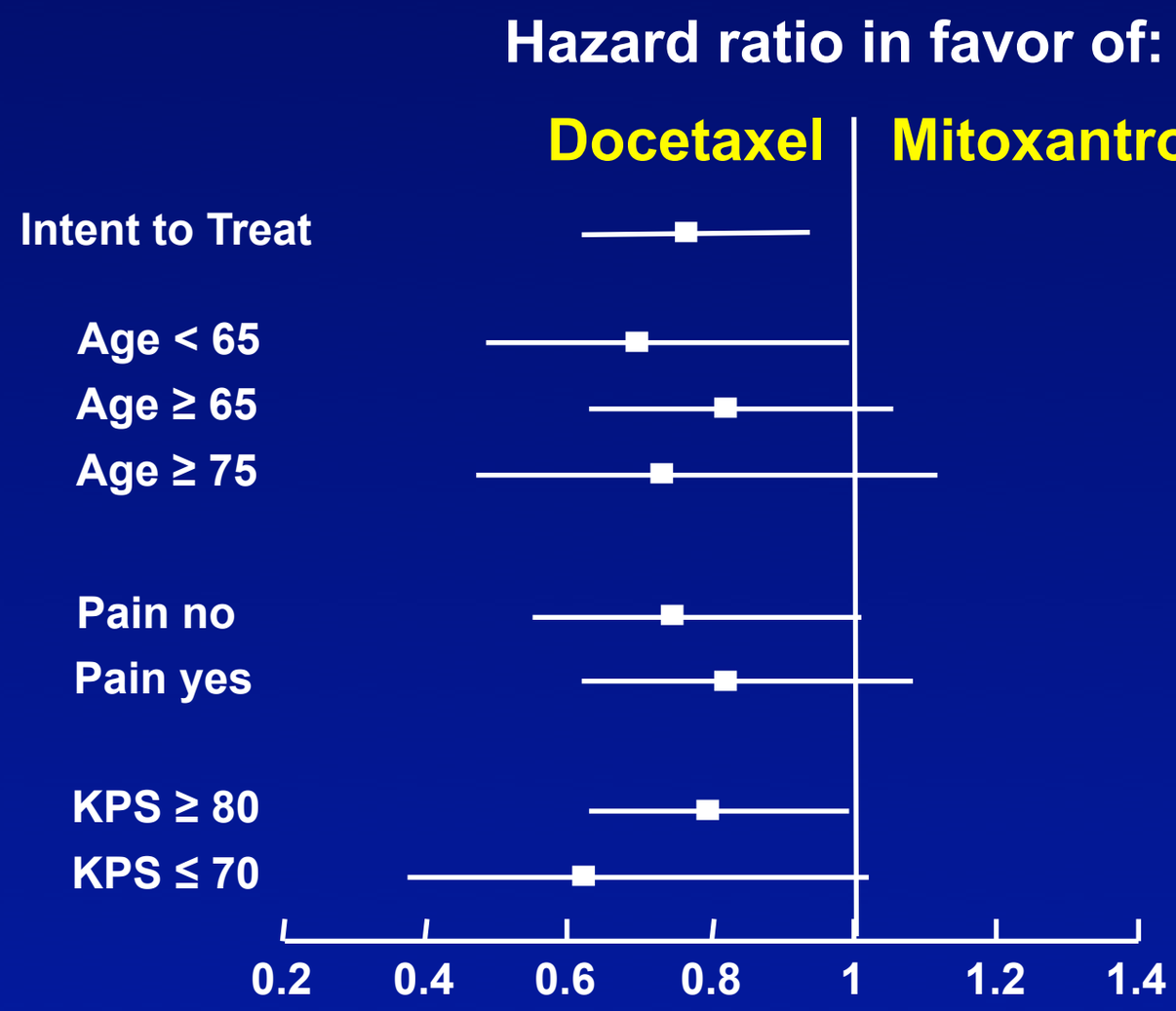
# Non-hematological Toxicity (%)

| | 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 |

# Overall Survival



# Survival in Subgroups
# Docetaxel 3 Weekly vs Mitoxantrone



# Secondary Objectives
# 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 | |

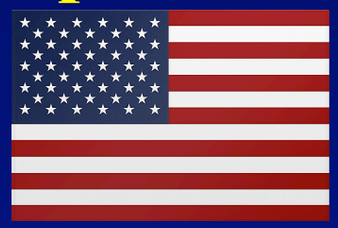
*Compared to mitoxantrone

# TAX 327
# Docetaxel 3 Weekly

- Safe

- Significantly improves:
  - Survival (18.9 vs 16.5 months)
    24% reduction in the risk of death
    ( 95% CI 0.62-0.94, p=.009)
  - PSA decline - 45% vs. 32%, p=.0005
  - Pain response - 35% vs. 22%, p=.01
  - Quality of life

# Docetaxel and Estramustine versus Mitoxantrone and Prednisone in Men with Androgen Independent Prostate Cancer: Results of Southwest Oncology Group Intergroup Protocol 99-16



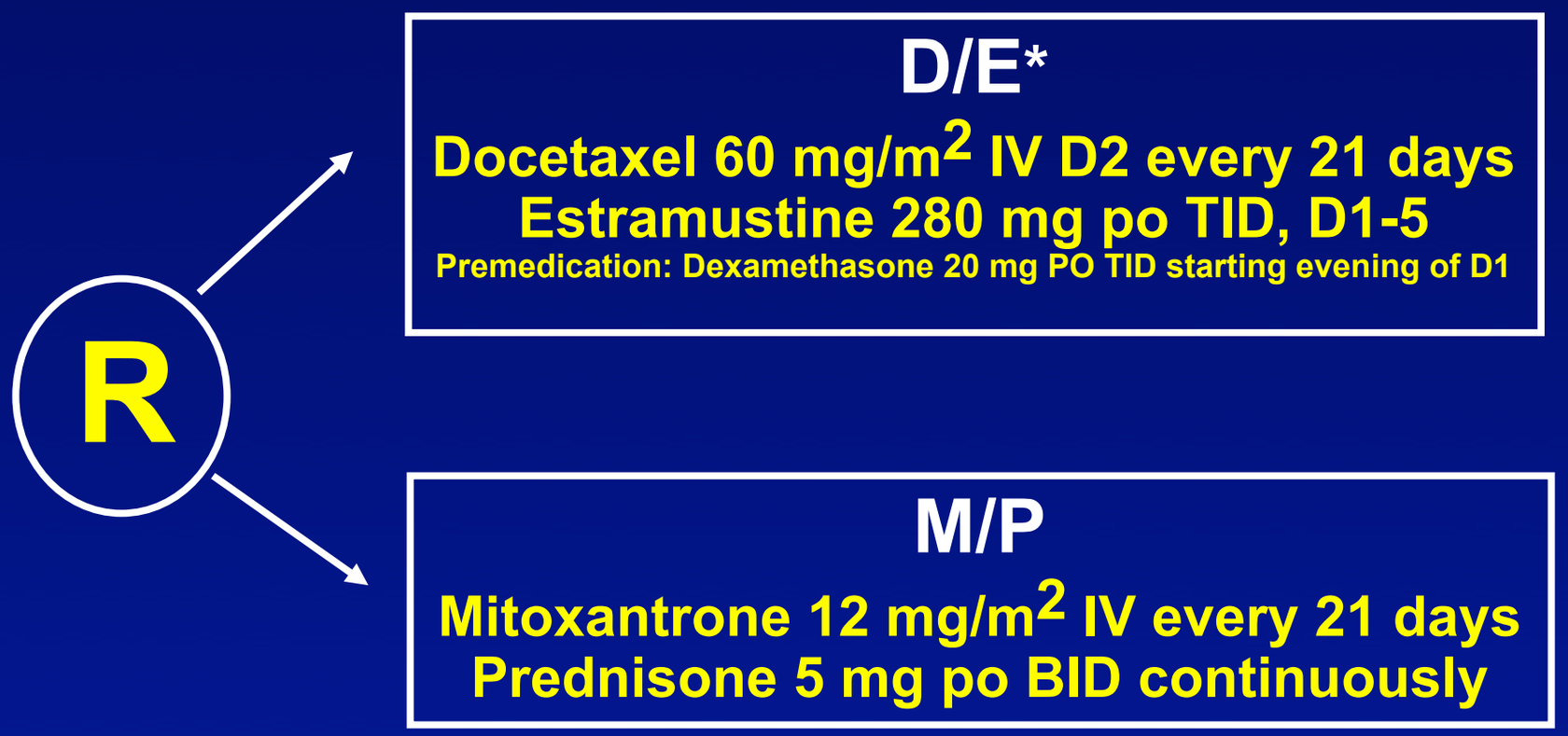

Daniel P. Petrylak, M.D.[1], Catherine M. Tangen, Dr.PH.[2], Maha A. Hussain, M.D.[3], Primo N. Lara Jr., M.D.[4], Jeffrey A. Jones, M.D.[5], Mary Ellen Taplin, M.D.[6], Patrick A. Burch, M.D.[7], Graham F. Greene, M.D.[8], Mitchell C. Benson, M.D.,[1] Eric J. Small, M.D.[9], Derek Raghavan, M.D., Ph.D,[10] E. David Crawford, M.D.[11]

[1]Columbia University, New York, NY [2]Southwest Oncology Group Statistical Center, Seattle, WA [3]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI [4]University of California, Davis, Sacramento, CA [5]Baylor College of Medicine, Houston, TX [6]University of Massachusetts Medical Center, Worcester, MA [7]Mayo Clinic, Rochester, MN [8]University of Arkansas for Medical Science, Little Rock, AR [9]University of California San Francisco Cancer Center, San Francisco, CA [10]Cleveland Clinic Foundation, Cleveland, OH [11]University of Colorado Health Science Center, Denver, CO

# Definition of Progression

- **Patients must have had at least one of the following:**
  - **Bi-dimensionally measurable lesion assessed within 28 days of study registration**
  - **Evaluable but not measurable disease (e.g., bone scan) assessed within 42 days of registration**
  - **Rising serum PSA, with at least 2 consecutive increasing measurements over baseline with each measurement obtained at least 7-days apart**

# Schema




*Per protocol amendment January 15, 2001: Coumadin 2 mg PO daily + ASA 325 mg PO daily was added

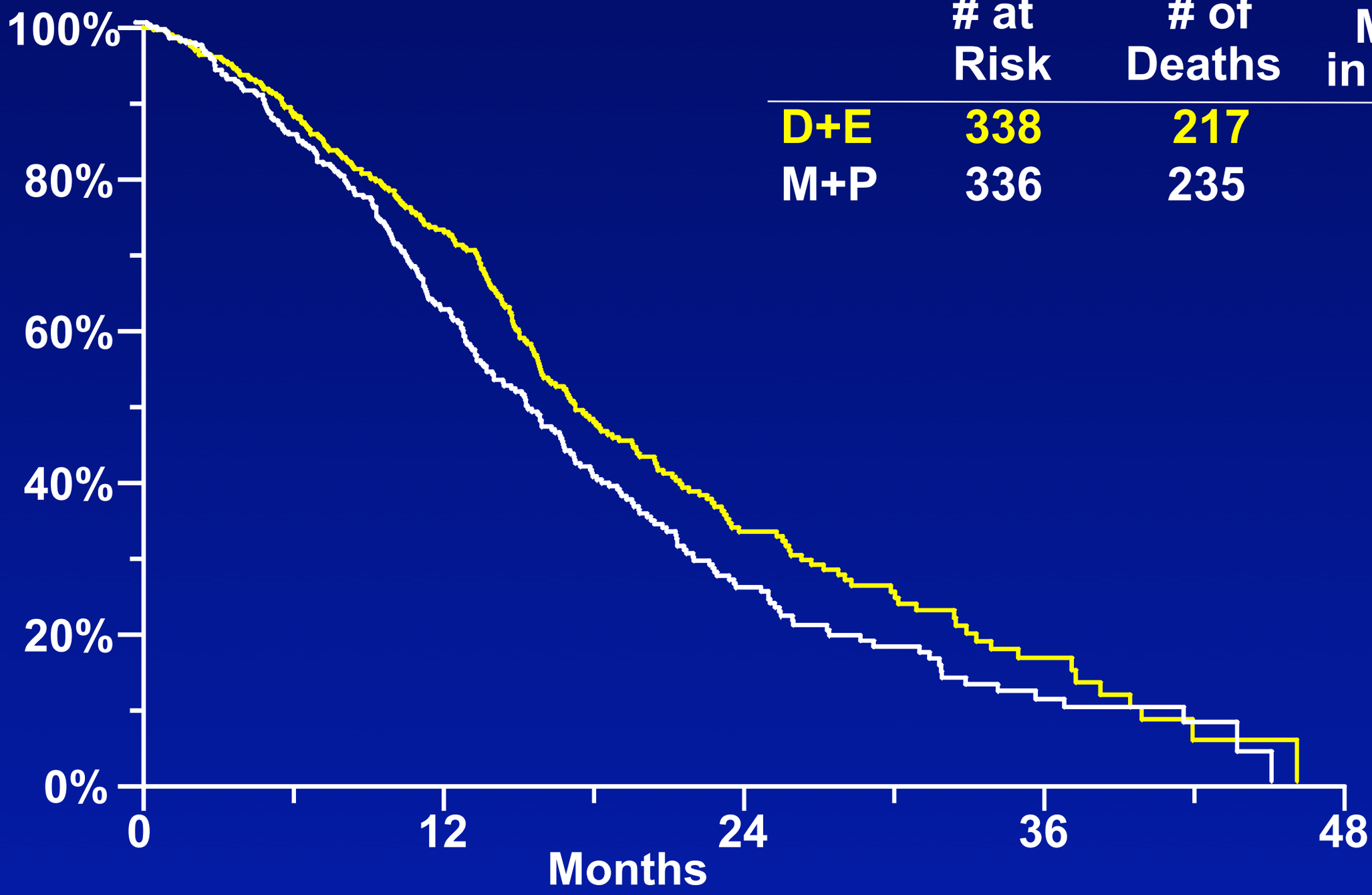
Docetaxel and mitoxantrone doses could be increased to 70 mg/m$^2$ and 14 mg/m$^2$, respectively, if no grade 3 or 4 toxicities were seen in cycle 1

# Patient Characteristics

| | D/E | M/P |
|---|---|---|
| Number randomized | 386 | 384 |
| Number eligible | 338 | 336 |
| Age median (range) | 70 (47-88) | 70 (43-87) |
| Race (%) | | |
| White | 86 | 82 |
| AA | 12 | 15 |
| Other | 9 | 8 |
| PSA ng/ml median (range) | 84 (0.1, 10,800) | 90 (0.1, 8378) |
| Performance Status 2-3 | 10% | 12% |
| PSA Only Progression | 19% | 18% |
| Bone Pain ≥ Grade 2 | 36% | 36% |
| Site of Disease | | |
| Bone | 84% | 88% |
| Lymph node | 24% | 26% |
| Liver/lung | 18% | 19% |

# Overall Survival

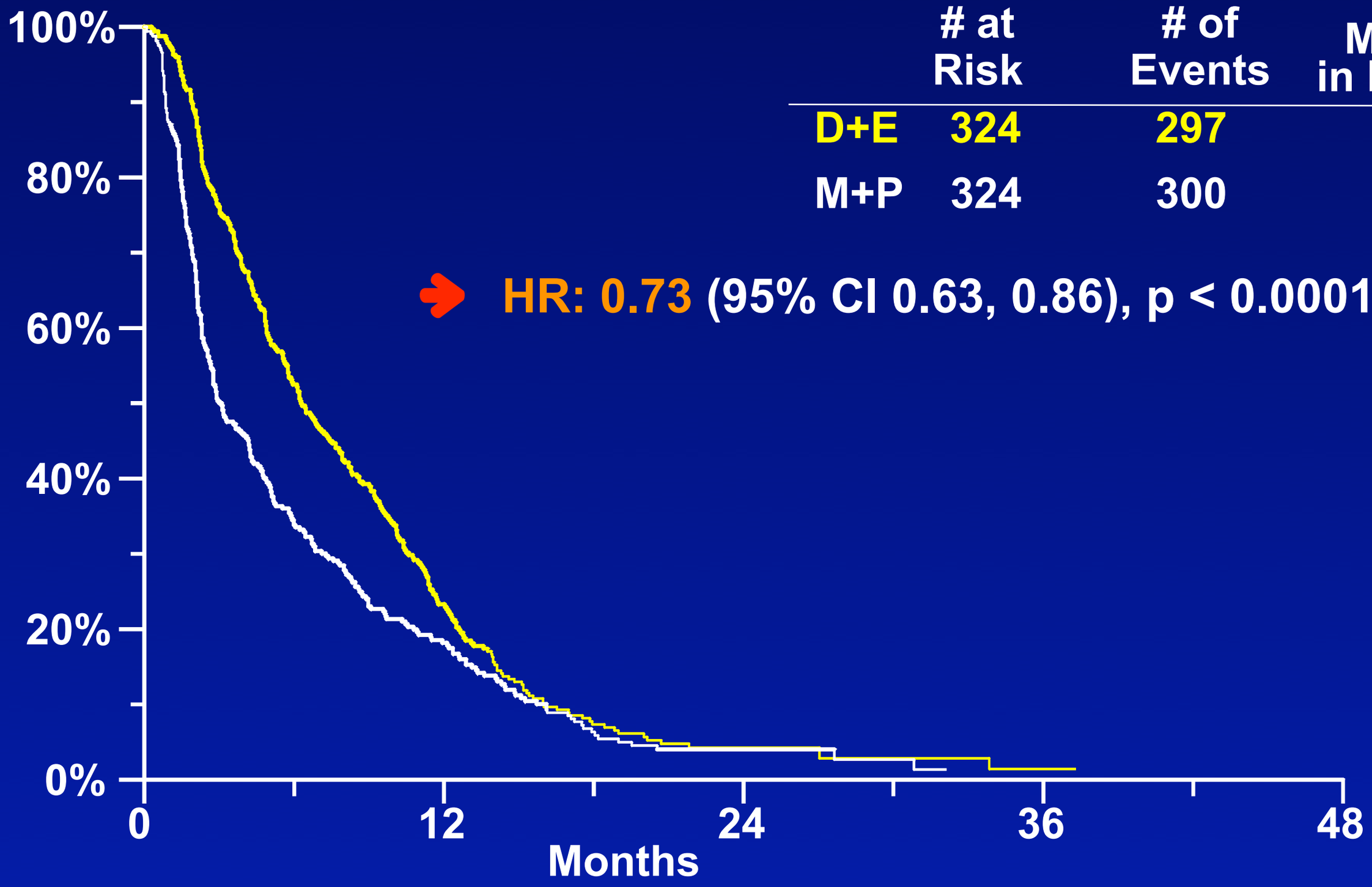
➔ **HR: 0.80 (95% CI 0.67, 0.97), p = 0.01**




| | # at Risk | # of Deaths | Median in Months |
|---|---|---|---|
| D+E | 338 | 217 | 18 |
| M+P | 336 | 235 | 16 |

# Progression Free Survival

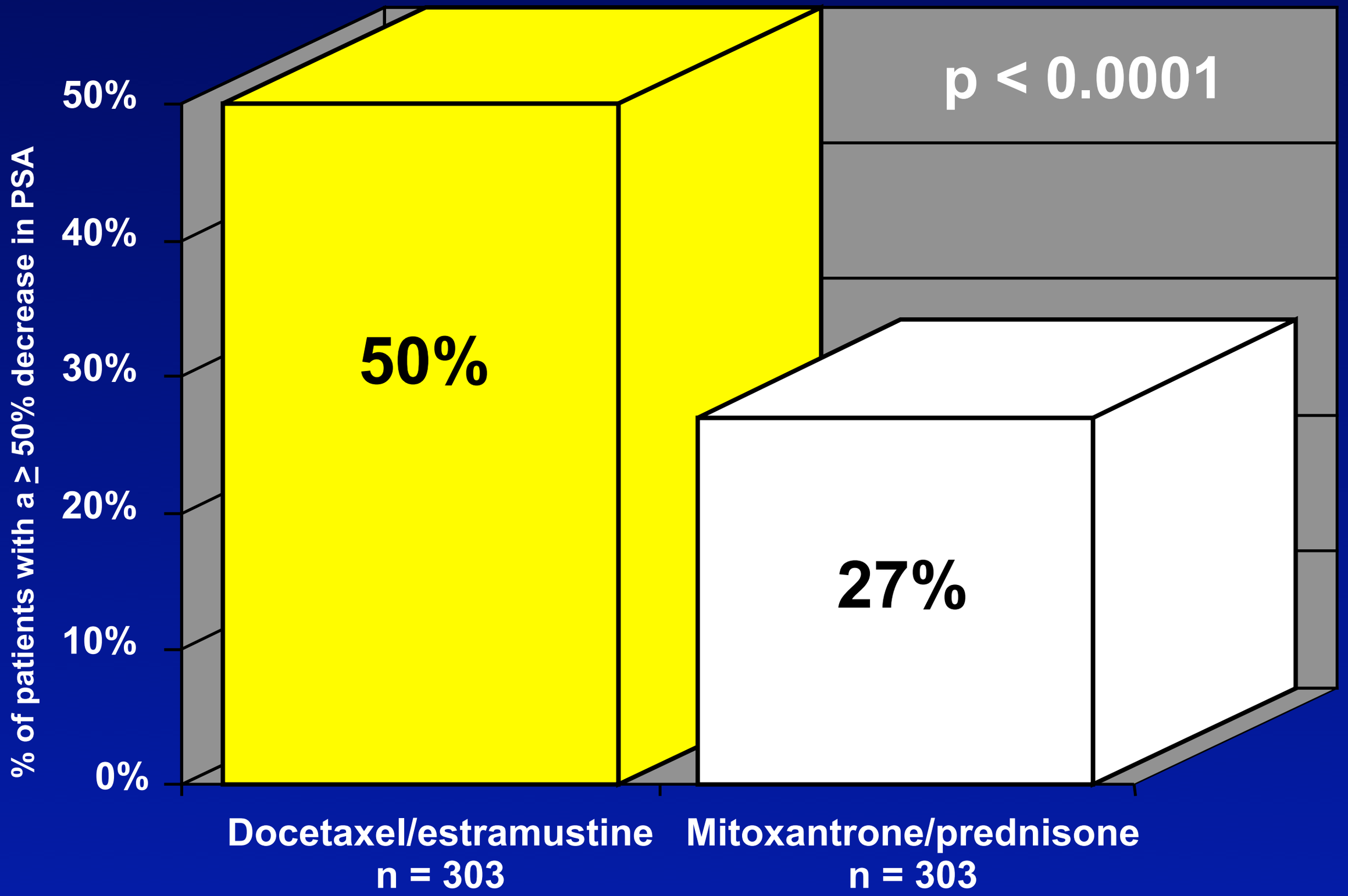
## Stratified by Treatment Arm



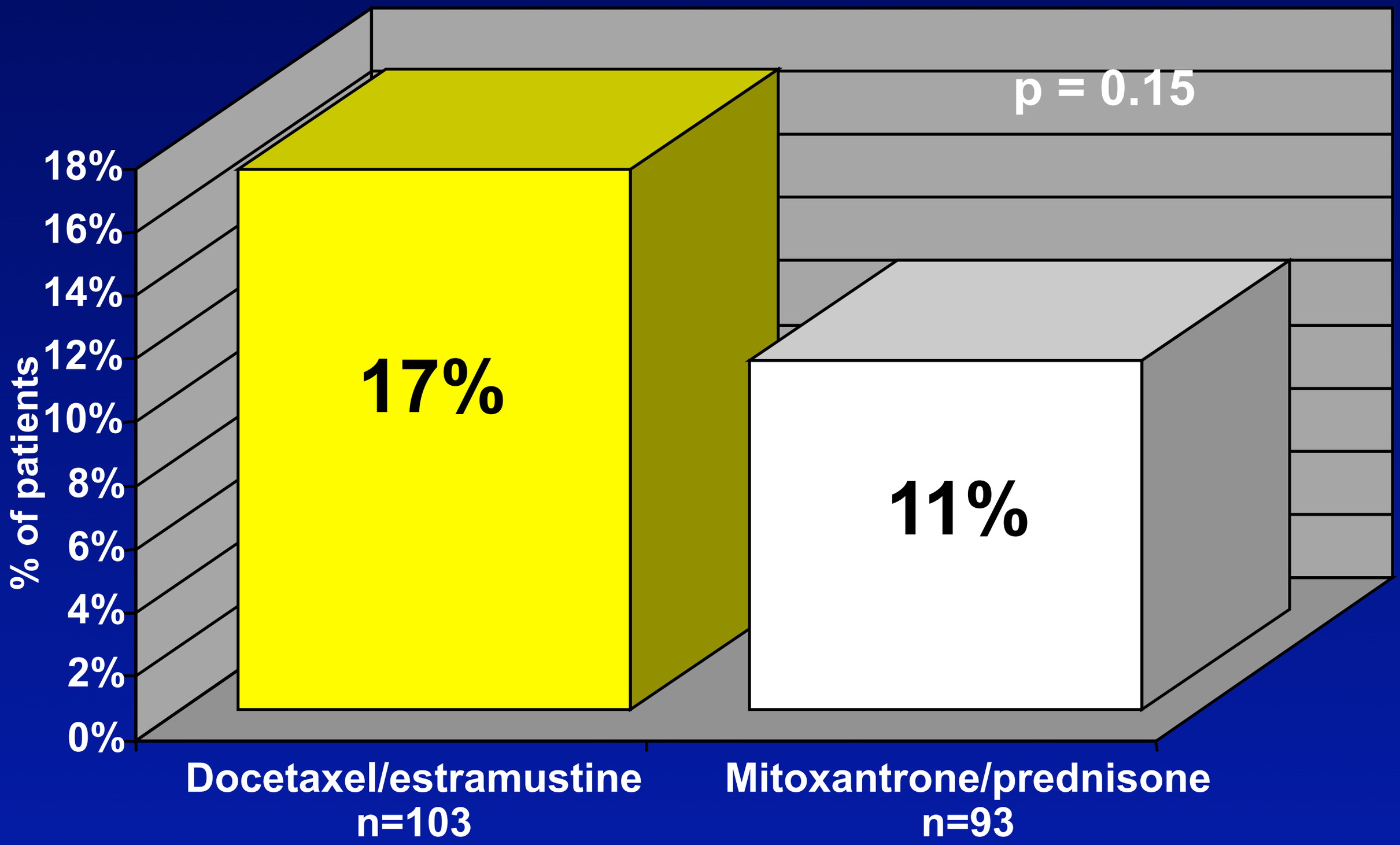

| | # at Risk | # of Events | Median in Months |
|---|---|---|---|
| D+E | 324 | 297 | 6 |
| M+P | 324 | 300 | 3 |

HR: 0.73 (95% CI 0.63, 0.86), p < 0.0001

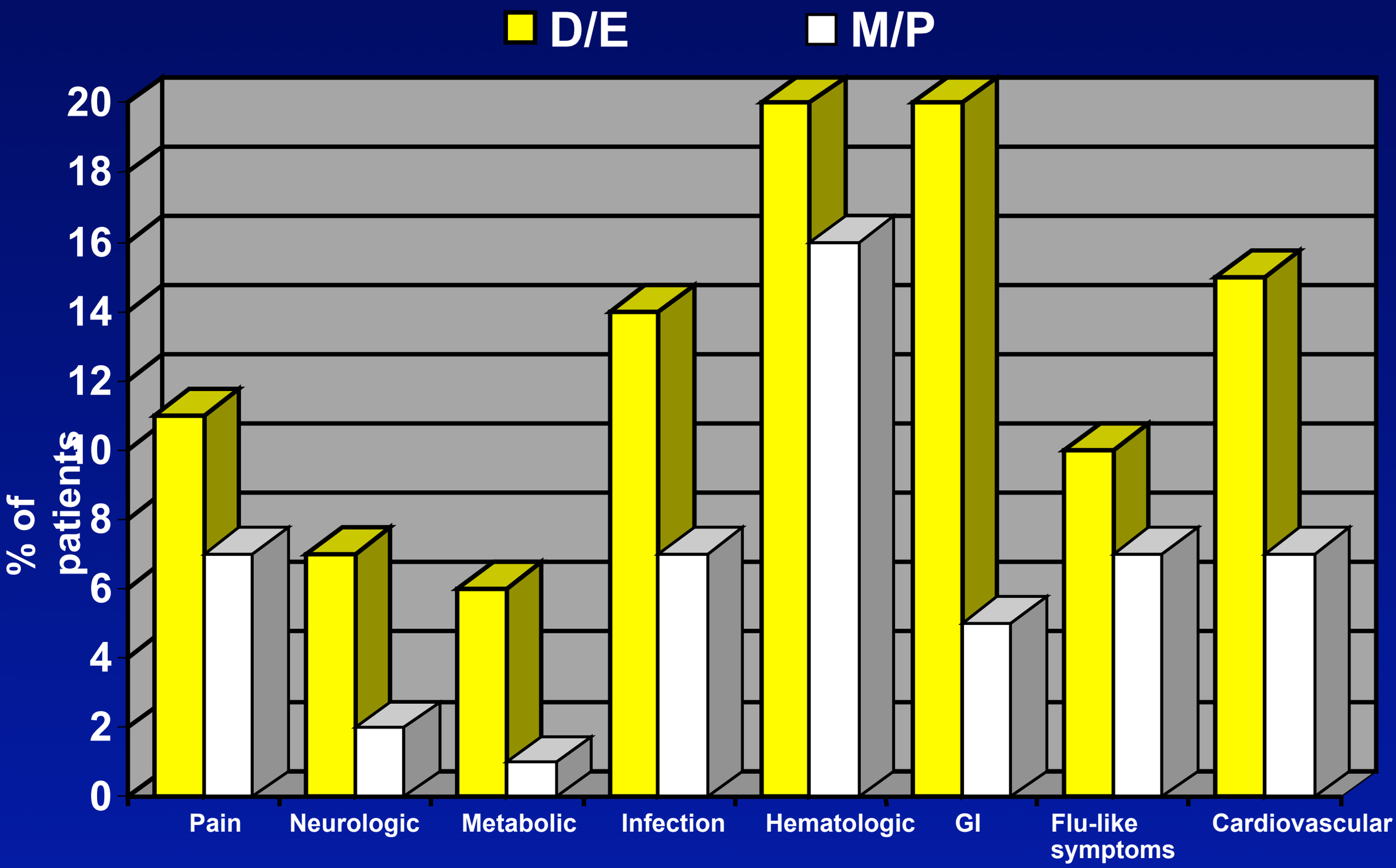
# PSA Response Rate



# Objective Response Rate



# Grade ≥ 3 toxicity




- there was no difference in toxic deaths between treatment arms

# SUMMARY

| |  |  |
|---|---|---|
| PSA response (%) | 50 | 45.4 |
| Objective RR (%) | 17 | 12.1 |
| Median survival - mos (vs M+P) | 18 (16) | 18.9 (16.49) |
| Hazard ratio vs M+P | 0.8 | 0.76 |
| p value (vs M+P) | 0.01 | 0.0094 |

# TAXANES WEEKLY vs q 3 WEEKS

- **<u>Perception</u>**: widespread belief that weekly taxanes more efficacious and less toxic than q 3 weeks across disease types

# TAX 327

- Study not powered to compare the two docetaxel arms but observations:
-
- Q 3-week therapy resulted in:
-
  - 11% higher rate of completion of therapy with 5% fewer adverse events
  - 30% higher rate of grade 3 and 4 neutropenia but only 2.7% incidence of febrile neutropenia
  - Less epistaxis, hyperlacrimation, nail changes, and vomiting
  - Survival advantage vs. M + P

# ESTRAMUSTINE?

- Phase II trials of docetaxel + EMP demonstrate higher PSA response rates than those with docetaxel alone (ASCO 2004, Abst. #4603)

# ESTRAMUSTINE?

- In SWOG 9916, EMP-containing arm resulted in significantly more toxicities: nausea/vomiting, metabolic disturbances, and thromboembolic complications

- No apparent decrease in thromboembolic events with prophylactic anticoagulation

- In the 2 current studies, no observed survival advantage for q 3-week docetaxel + EMP vs q 3-week docetaxel + prednisone

- Difficult to support continued use of EMP

# Summary

- Two large randomized trials that demonstrate that docetaxel is superior to mitoxantrone:
-
  - Median survival improvement of 2 – 2.5 months
  - Overall survival improvement of 20 – 24%
  - Statistically and clinically important improvement in Pain Response and QOL

# Summary

- The preferred method of administration of Docetaxel is q 3 weeks, NOT WEEKLY
- 
- Estramustine is dead
- 
- ? Role in asymptomatic men

# Where do we go from here?

- Phase III “Docetaxel + Trials”
- 
  - COMPLETED:
    - Docetaxel + Calcitriol vs Docetaxel
    - 
  - PLANNED
    - Docetaxel + Bevacizumab vs Docetaxel (CALGB)
    - Docetaxel + Oblimersen vs Docetaxel (NCIC)

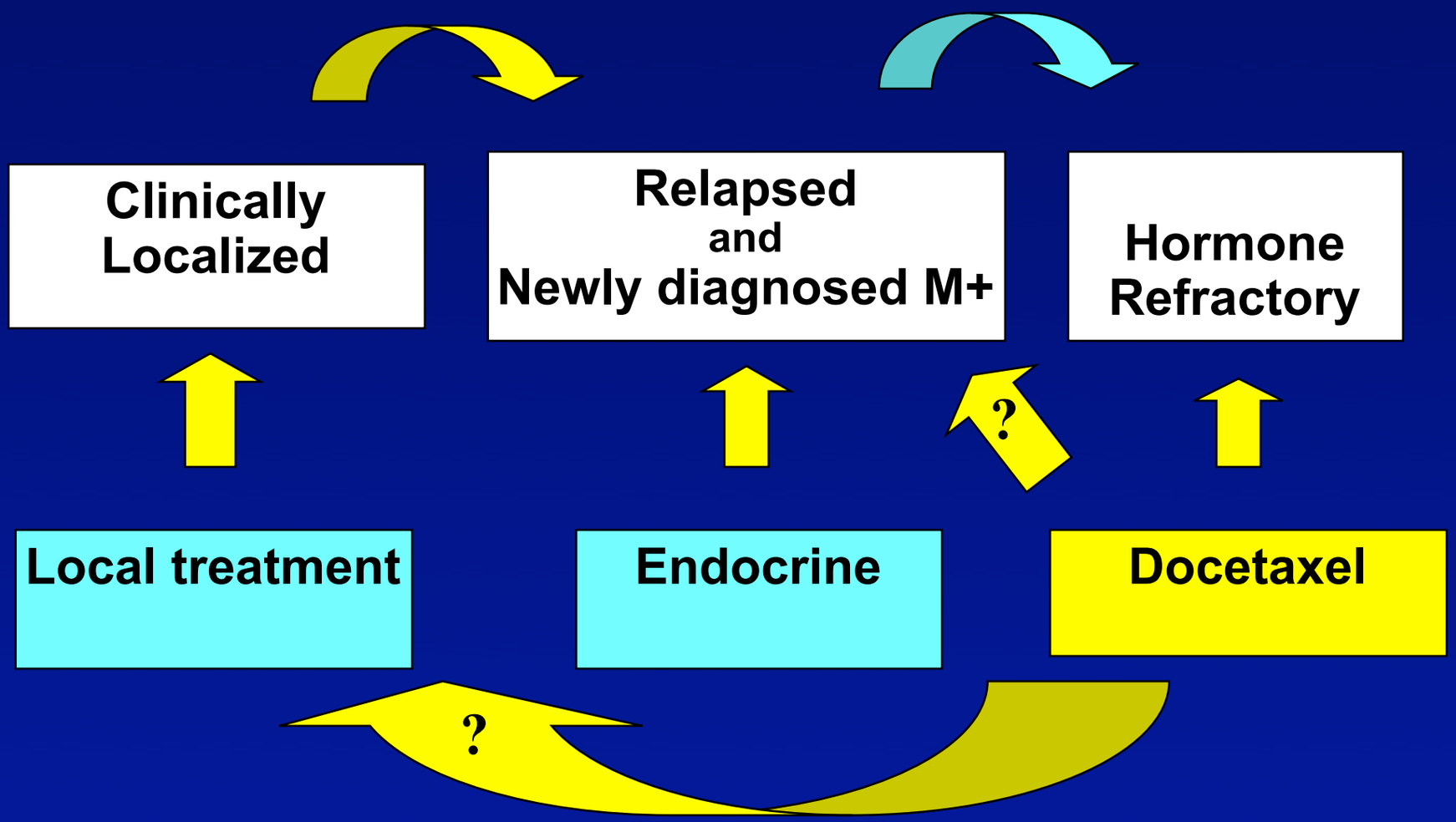
# Docetaxel Doublets Under Investigation

Docetaxel + ...

Exisulind
Calcitriol
Thalidomide
Tarceva
Gleevec
Bevacizumab
Iressa

Celecoxib
Imanitib
Capecitabine
Bortezomib

# Prostate Cancer
## Treatment Paradigms



# Overall Summary

- Approach must be individualized
- Hormonal therapy is an early option in the therapeutic armamentarium
- Radiation therapy a primary option for pain control
- Zoledronic acid promising for reducing HRPC-related bone complications
- Modern chemotherapy regimens have lower toxicity
- Current role for chemotherapy remains palliative
- Survival benefit with docetaxel-based regimens emerging

WILLIAM OSLER HEALTH CENTRE

Etobicoke Hospital Campus
Brampton Memorial Hospital Campus
Georgetown Hospital Campus

www.williamoslerhc.on.ca

New WOHC Hospital - South View


NCC-1701-E