



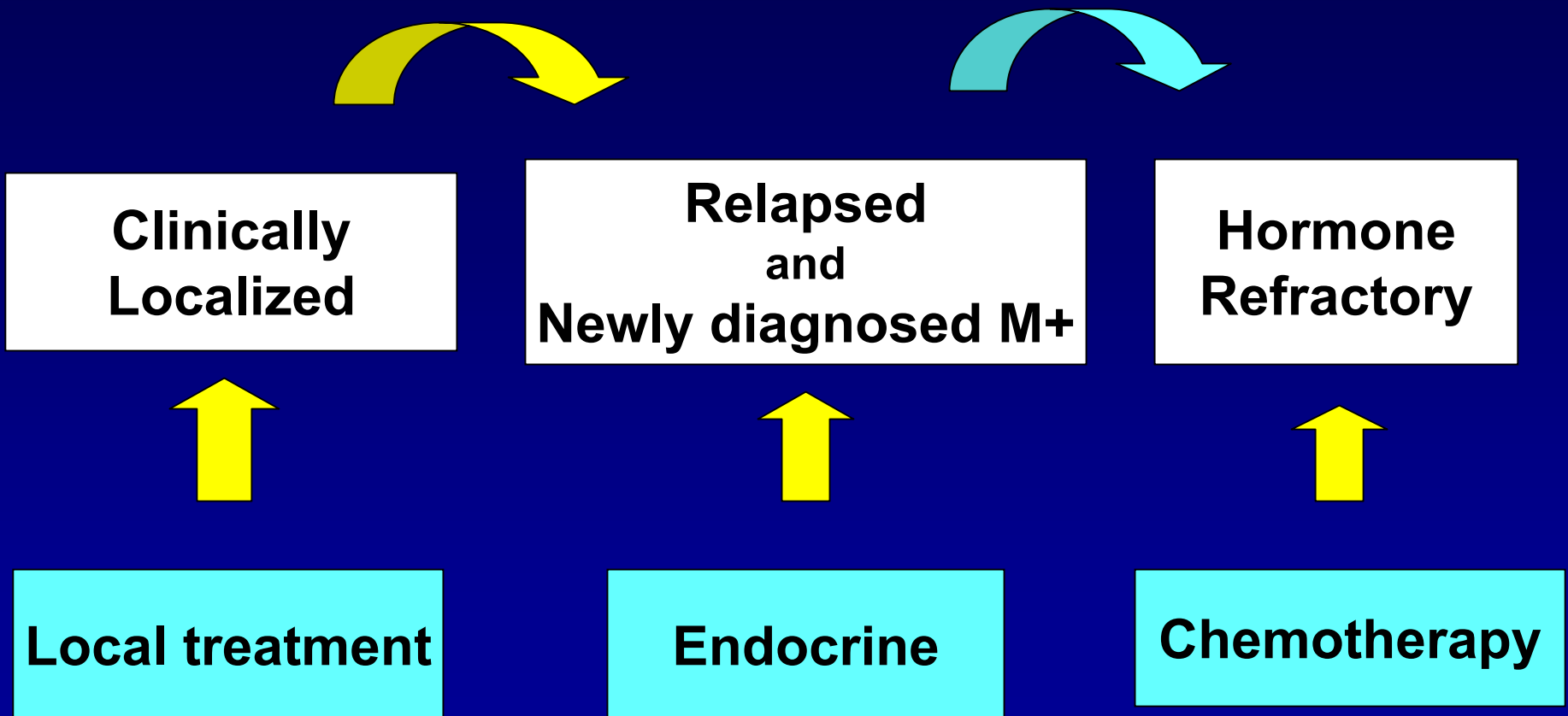
# Advances In Chemotherapy For Hormone Refractory Prostate Cancer

TAX 327 study results  
&  
SWOG 99-16 study results  
presented at ASCO 2004

# Prostate Cancer Epidemiology

- Prostate cancer is the leading cancer diagnosis in men and the second leading cancer killer, with 35.000 deaths from this disease in the US alone, each year

# Prostate Cancer Treatment Paradigms



# Advanced Prostate Cancer: *Treatment 1*

- Androgen ablation has been the standard treatment for advanced prostate cancer for 40 years
- Despite rapid and dramatic responses, almost all patients progress
- Median duration of response is 18 months
- No agent or combination treatment has proven to prolong survival once patients are refractory to androgen ablation (HRPC)

# Advanced Prostate Cancer: *Treatment 2*

- Median survival in HRPC is 6-15 months, depending on symptoms and performance status
- Mitoxantrone with low-dose prednisone relieves pain due to metastatic disease in 30% of patients, but does not improve survival\*

\* Tannock et al, J Clin Onc 1996;14:1756-64.

\* Kantoff et al, J Clin Onc 1999;17:2506-13.

# Docetaxel\* in HRPC

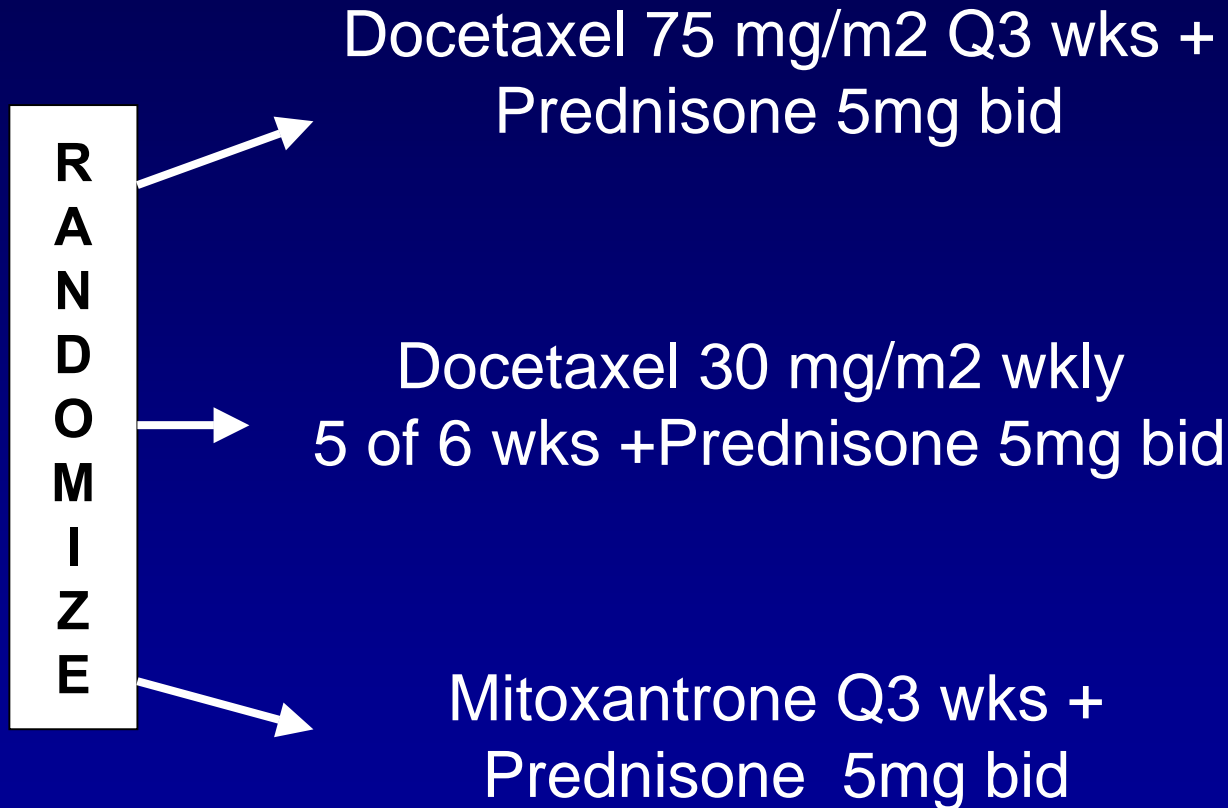
- Docetaxel is effective chemotherapeutic agent in variety of solid cancers
  - Efficacy of Docetaxel in HRPC in phase I/II trials
    - Docetaxel q 3 weeks
    - Docetaxel weekly schedules
    - Docetaxel / estramustine
- pain response ranges from 35-70%
- median survival ranges from 12-23 months

# A Multicenter Comparison of Docetaxel Given Weekly or Every Three Weeks + Prednisone with Mitoxantrone + Prednisone in HRPC

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

# TAX327

## Study Design



# Study Objectives

- Primary objective  
Survival
- Secondary objectives
  - Pain response
  - PSA response
  - Quality of life
  - Objective tumor response



# Patient Characteristics (n=1006)

	Docetaxel 3-wkly	Docetaxel wkly	Mitoxantrone
Randomized	335	334	337
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

# Patient Characteristics

	Docetaxel 3-wkly	Docetaxel wkly	Mitoxantrone
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## Hormonal Manipulations (%)

1-2	77	80	75
>2	23	21	25

## Median PSA (ng/ml)

114	108	123
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## Gleason Grade (%)

≤7	42	40	42
8-10	31	31	28
Not available	26	29	30

## Bone metastases (%)

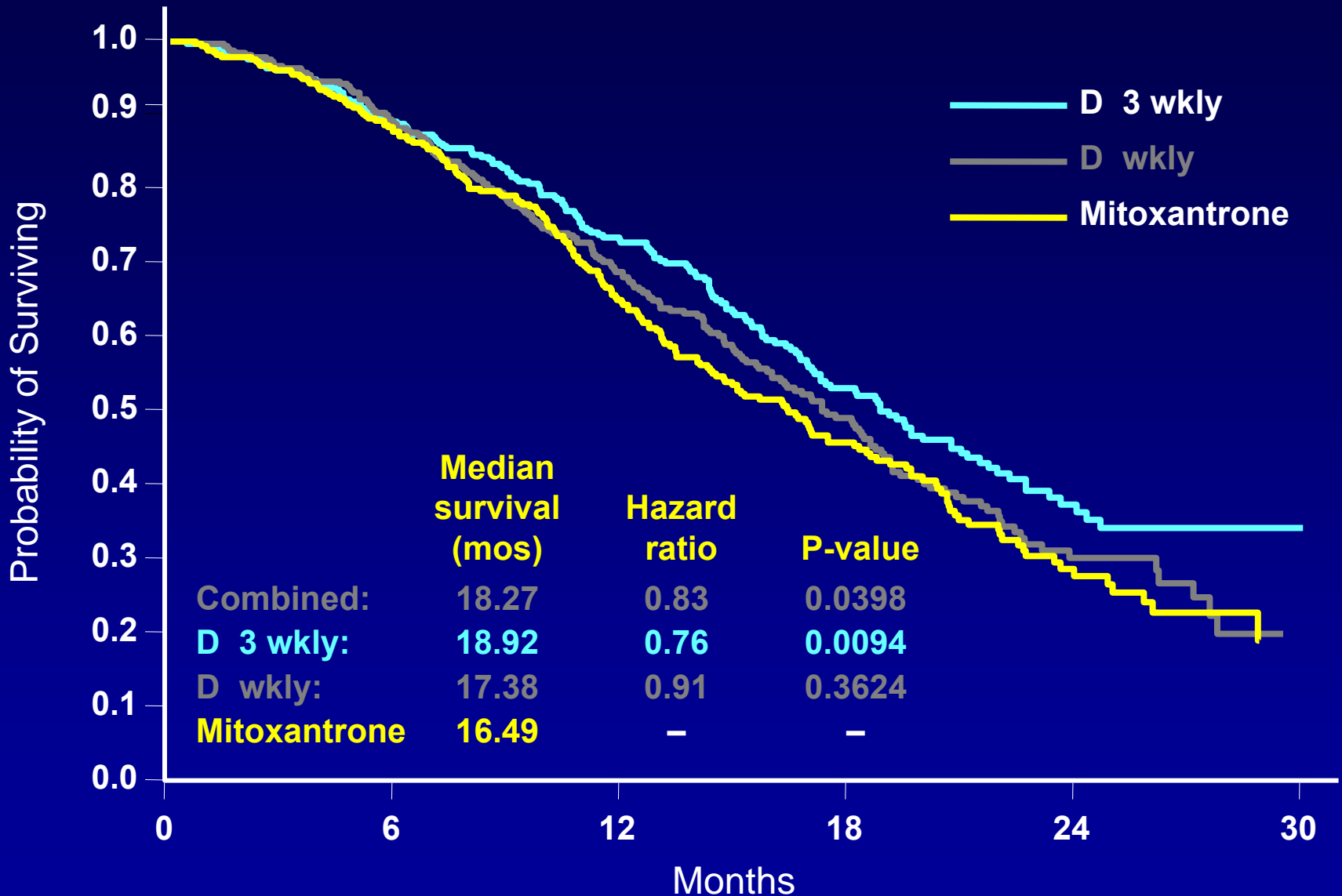
90	91	92
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## Visceral disease (%)

22	24	22
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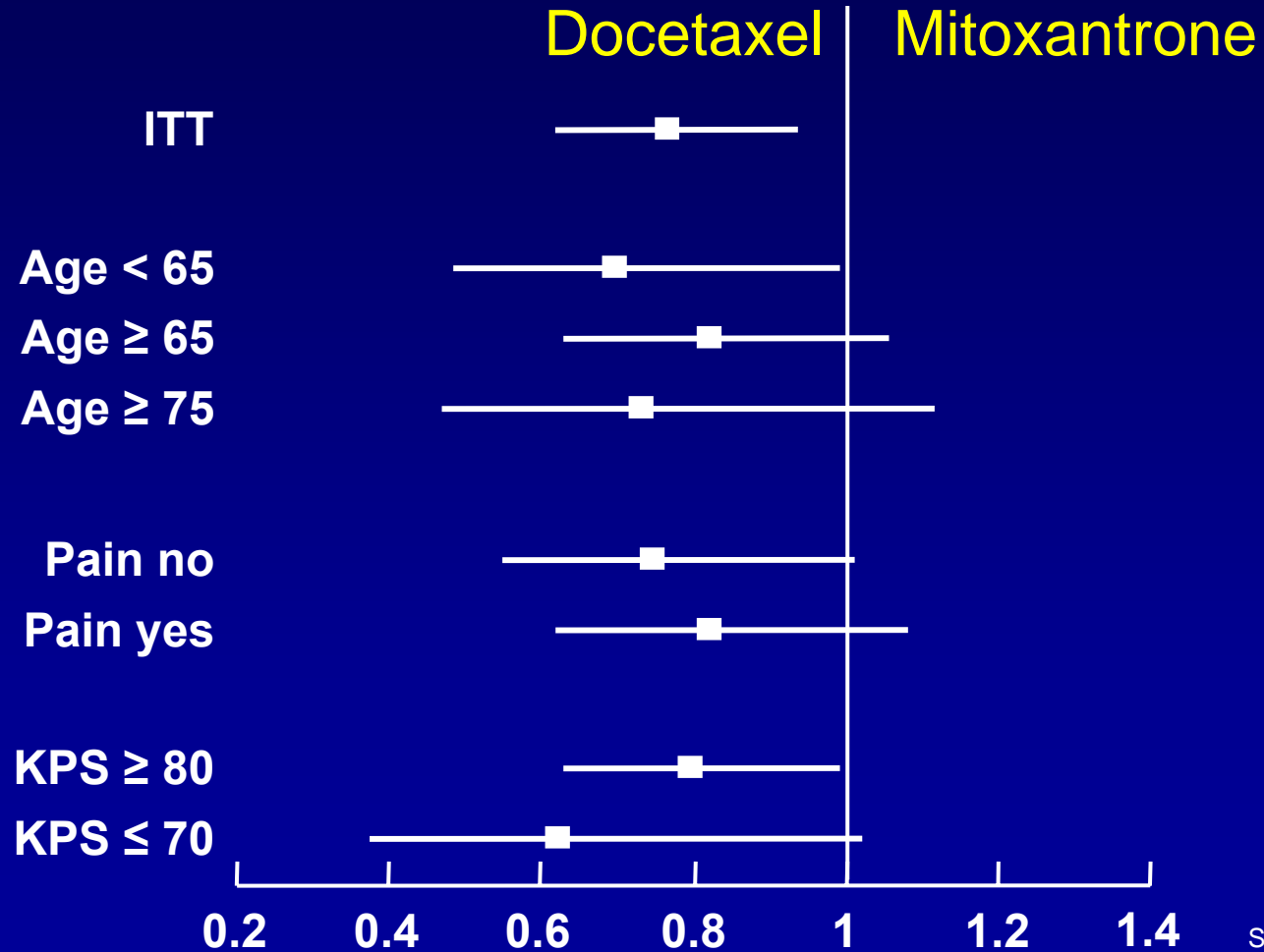
# Overall Survival



# Survival in Subgroups

## Docetaxel 3 wkly vs Mitoxantrone

Hazard ratio in favor of





# Secondary Objectives Response Rates

	Docetaxel 3 wkly	Docetaxel wkly	Mitoxantrone
<b>Pain Response Rate*</b>			
Pain response rate (%)	34.6	31.2	21.7
P-value (vs. Mitoxantrone)	0.01	0.08	-
<b>PSA Response Rate*</b>			
PSA response rate (%)	45.4	47.9	31.7
P-value (vs. Mitoxantrone)	0.0005	<0.0001	-
<b>Tumor Response Rate*</b>			
PSA response rate (%)	12.1	8.2	6.6
P-value (vs. Mitoxantrone)	0.11	0.59	-

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

# Grade 3-4 Hematologic Toxicity (%)

	Docetaxel 3 wkly	Docetaxel wkly	Mitoxantrone
Treated	332	330	335
Anemia	5	5	2
Neutropenia	32.0	1.5	21.7
Neutropenic infection %	3.0	0	0.9
Febrile neutropenia %	2.7	0	1.8
Septic death (%)	0	0.3	0.3



# Non-hematological Toxicity (%)

Toxicity	Docetaxel 3 wkly		Docetaxel wkly		Mitoxantrone	
	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

\* NA = not applicable



# Non-hematological Toxicity (%)

Toxicity	Docetaxel 3 wkly		Docetaxel wkly		Mitoxantrone	
	All grades	3/4	All grades	3/4	All grades	3/4
Stomatitis	20	0.9	17	0.3	8	0
Peripheral edema	19	0.6	12	0.6	1	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
Tearing	10	0.6	21	0.3	1	0
Epistaxis	6	0.3	17	0.6	2	0

# 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% C.I )	22 (17-27)	23 (18-28)	13 (9-18)
P-value*	0.009	0.005	

\*Compared to mitoxantrone

# TAX 327

## Docetaxel

- 3 weeks schedule improves median survival by 2.5 months (HR 0.76, 95% C.I. 0.62-0.94,  $p=0.0094$ )
- Safe
- Improves Pain (34% vs. 21%,  $p=0.01$ )
- Reduces PSA ( $p < 0.0005$ )
- Improves Quality of Life
- Measurable Responses

# Randomized phase III trial of Docetaxel + Estramustine vs Mitoxantrone + Prednisone In HRPC

Daniel Petrylak, M.D.

David Crawford, M.D.

and

SWOG 99-16 investigators

# SWOG 99-16

## Study Design

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Docetaxel 60 (70) mg/m<sup>2</sup> Q 3 weeks +  
Estramustine 280 mg PO days 1-5



Mitoxantrone 12 (14) mg/m<sup>2</sup> Q 3 weeks +  
Prednisone 5 mg PO bid

# SWOG 99-16

## Overall Survival

	Med. Surv.	Med. TTP	HR (surv.)	P-value
Docetaxel + Estramustine (n = 334)	18	(6)	0.77	0.008
Mitoxantrone + Prednisone (n = 332)	15	(3)	-	-



# Grade 3-4 Non-Hematological Toxicity

Docetaxel +  
Estramustine

Mitoxantrone +  
prednisone

	N (%)	N (%)
All grade 3-4 toxicity	175 (54)	109 (34)
Gastrointestinal	63 (19)	21 (6)
Cardiovascular	44 (13)	20 (6)
Toxic deaths	7 (2)	4 (1)

# SWOG 99-16

## Docetaxel + Estramustine

- Improves survival by 3 months  
(HR 0.77, 95% CI 0.64 - 0.94,  $p = 0.008$ )
- Increases gastrointestinal + cardiovascular toxicity

# Treatment of hormone refractory prostate cancer

Effective chemotherapy at last:

Docetaxel 3-weekly plus prednisone

New directions for clinical studies:

- combining Docetaxel with other new drugs in HRPC
- investigating Docetaxel in earlier stage prostate cancer