New Developments in Chemotherapy for Prostate Cancer

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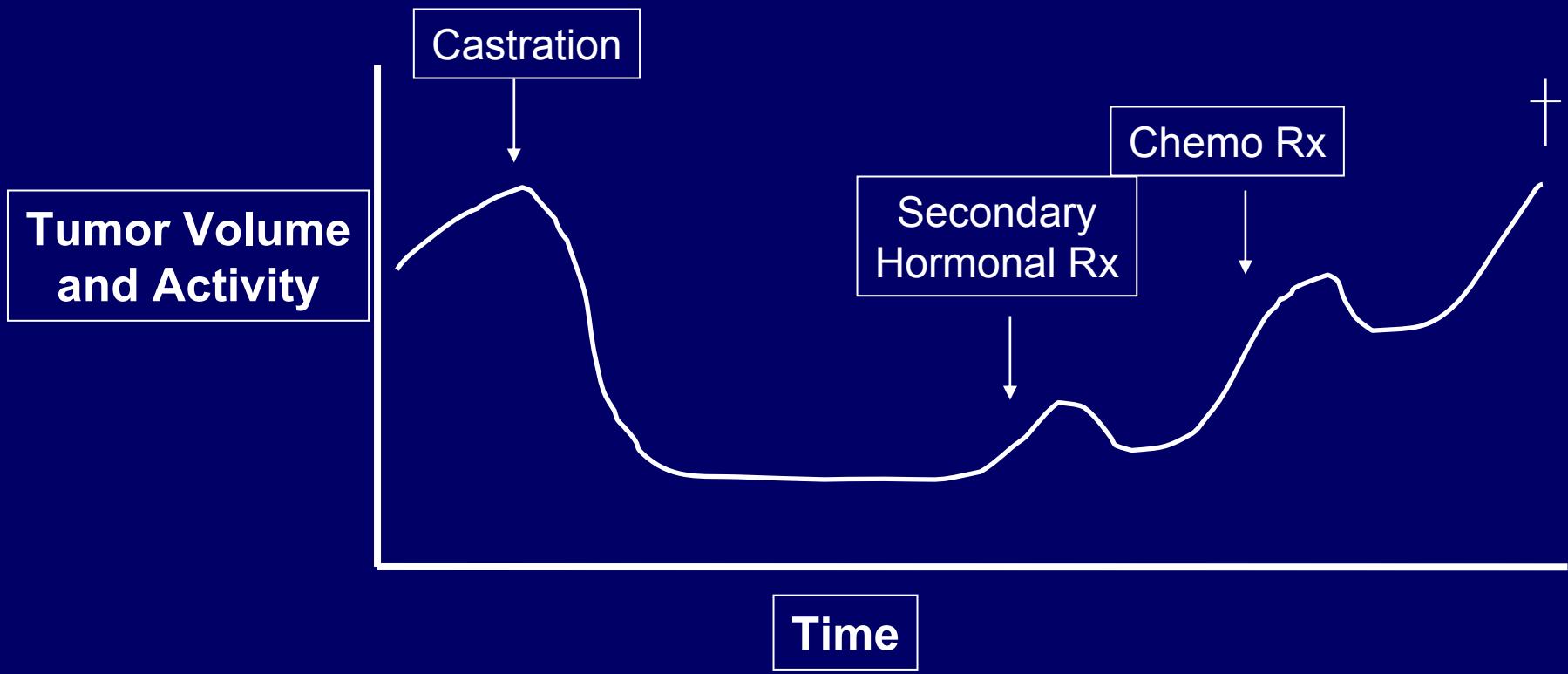
Natural History of Metastatic Prostate Cancer



Types of Progression in AIPC

- PSA progression only
  - Rising PSA often precedes + scan by 6 mo
- Symptomatic progression
- Bone metastases (80%)
  - Positive bone scan with or without rising PSA
- Soft tissue only (≈20%)
  - Lymph nodes, lung, liver, adrenal, dura sites
- Soft tissue plus bone metastases

Treatment Options

- Secondary hormonal therapy
- Chemotherapy
- Investigational treatments
  - Targeted therapy
  - Immune therapy

Second-Line Antiandrogen Addition

Study	Agent/Dose	Number (%) Patients with ≥50% PSA Drop	Median Response (Months)
Fowler	Flutamide 250 tid	27/50 (54)	4
Scher	Bicalutamide 200/day	2/13 (15)	4
Joyce	Bicalutamide 150/day	7/31 (22)	4
Desai	Nilutamide 150 or 300/day	7/14 (50)	11

Fowler JE, Jr, et al. *J Urol*. 1995;154:448-453.
Scher HI, et al. *J Clin Oncol*. 1997;15:2928-2938.
Joyce R, et al. *J Urol*. 1998;159:149-153.
Desai A, et al. *Urology*. 2001;58:1016-1020.

Ketoconazole

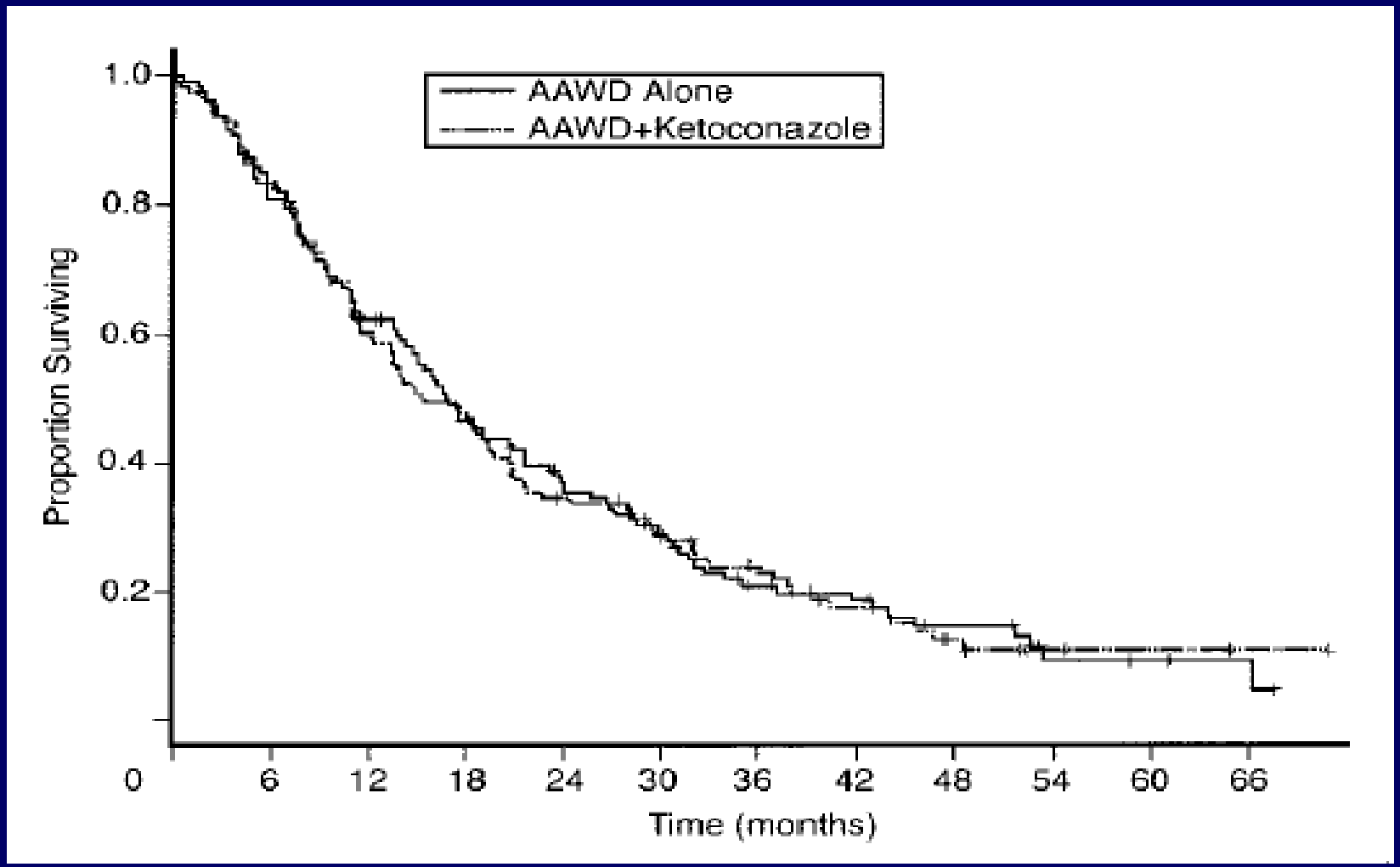
- Inhibits cytochrome P-450 enzymes
  - Blocks testicular and adrenal androgenesis
  - Alters some drug metabolism (eg, warfarin)
- 50%–70% have ≥50% reduction in PSA
- Start with 200 mg tid
  - This dose may be effective
  - If not effective, titrate up to 400 mg tid and add hydrocortisone replacement 20 mg in the am, 10 mg at 4 pm

Ketoconazole (cont'd)

- Take on empty stomach
- Acid environment required for absorption
  - If on acid-lowering drugs, take with 1 g vitamin C or 6 oz cola
- Now generic
- Nausea, LFT abnormalities, "sticky skin," increase in creatinine

LFT=liver function test

Small. CALGB. ASCO, 2001.


AAWD Alone
AAWD+Ketoconazole
Proportion Surviving
1.0
0.8
0.6
0.4
0.2
0
6
12
18
24
30
36
42
48
54
60
66
Time (months)

Prostate Cancer Chemotherapy Trials

- 22 single-agent trials between 1988 and 1991
- CR + PR=8.8%, 95% CI=6.4–9.0%

Mitoxantrone + Corticosteroids

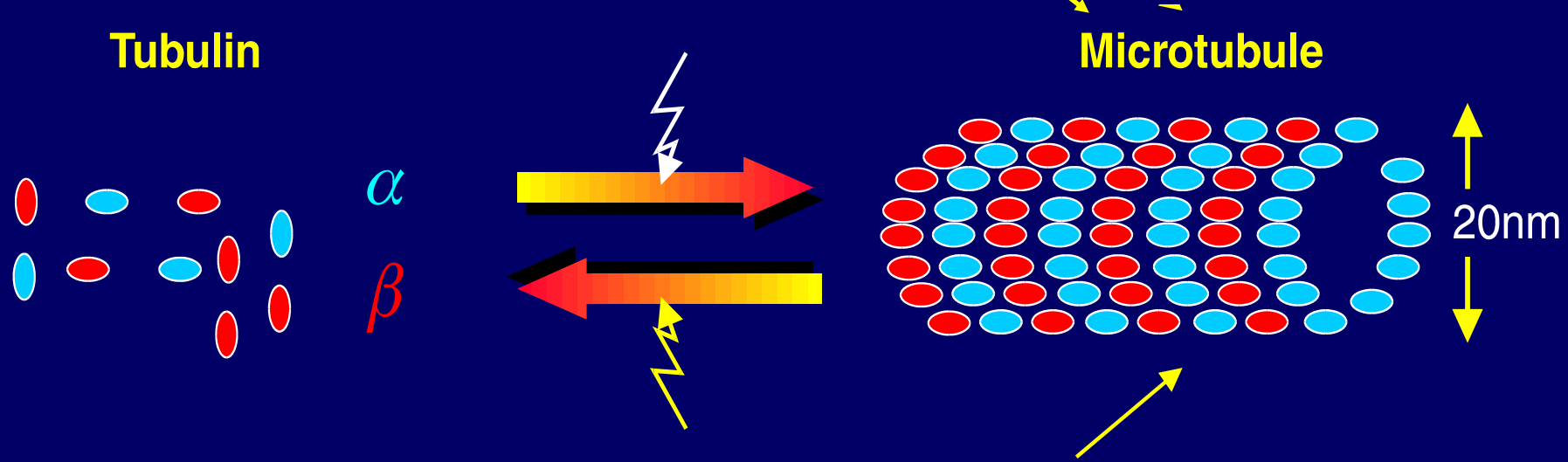
	Canadian	CALGB
Mitoxantrone	12 mg/m2 Q3 weeks	14 mg/m2 Q3 weeks
Steroid	Prednisone 10 mg/day	Hydrocortisone 40 mg/day
N	161	243
Objective	Palliation	Survival
Symptomatic disease?	Required	Not required
Crossover?	Allowed	Not allowed
Median age	68 years	72 years

Tannock et al. *J Clin Oncol* 1996;14:1756-1764; Kantoff et al. *J Clin Oncol* 1999;17:2506-2513.

Mechanism of action

Inhibition of Polymerization:

- colchicine
- vinca alkaloids



Inhibition of Depolymerization:

- taxoids

Docetaxel HRPC Trials

TAX 327[1]

N=1006

Randomize

- **Mitoxantrone 12 mg/m²**
  Prednisone 10 mg q day
  Q 21 days up to 10 cycles
- **Docetaxel 30 mg/m²/wk**
  Prednisone 10 mg q day
  5 on; 1 off x 6 cycles
- **Docetaxel 75 mg/m²**
  Prednisone 10 mg q day
  Q 21 days up to 10 cycles

SWOG 9916[2]

N=770

Randomize

- **Mitoxantrone** 12 mg/m²
  Prednisone 5 mg bid
  Q 21 days
- **Docetaxel** 60 mg/m² d 2
  Estramustine 280 mg d1-5*
  Dexamethasone 20 mg, tid d 1 & 2

*Warfarin and aspirin

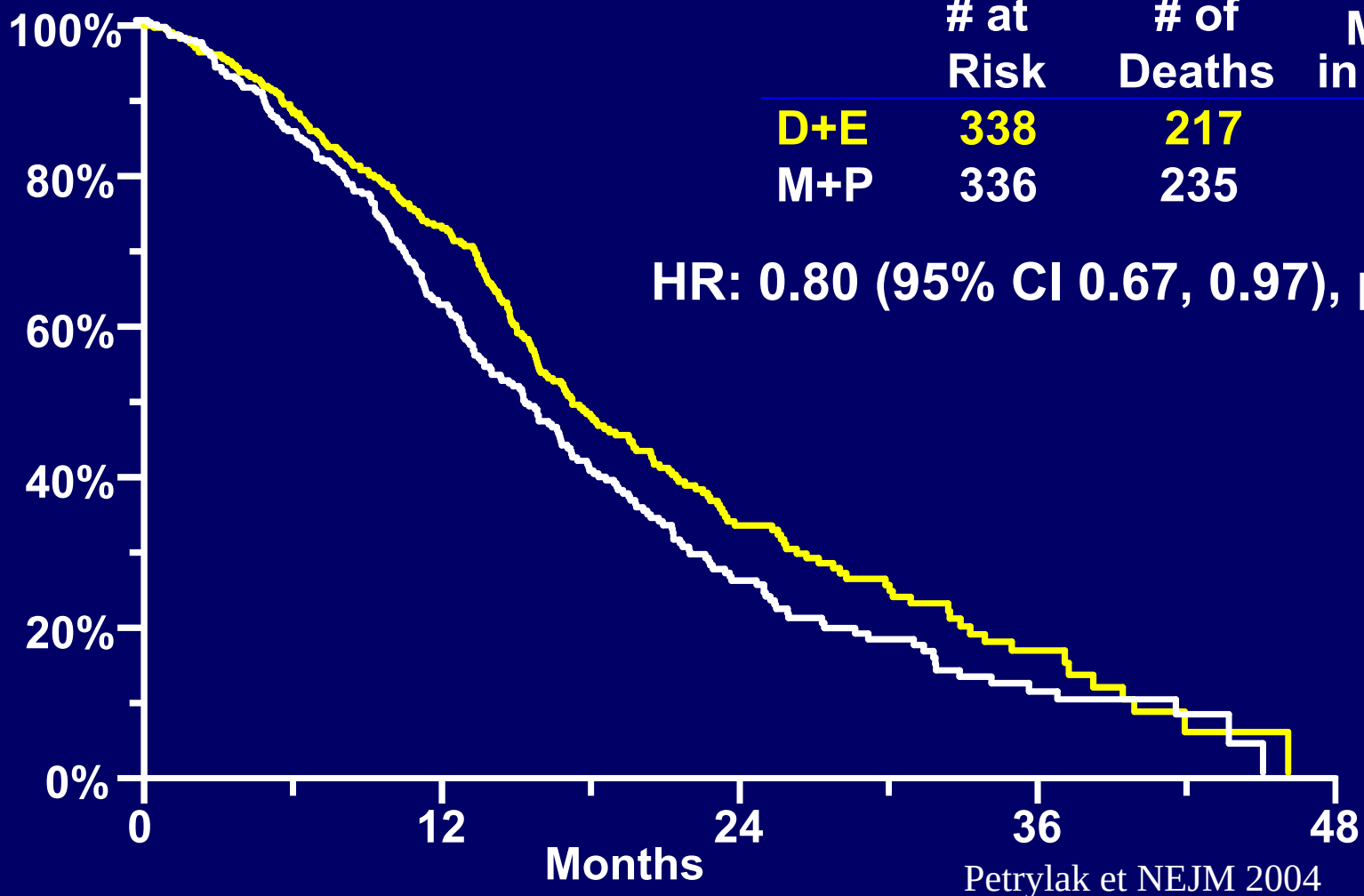
1. Tannock et al. *N Engl J Med* 2004:351;1502-1512. 2. Petrylak et al. *N Engl J Med* 2004;351:1513-1520.

Docetaxel HRPC Trials
Patient Characteristics

	TAX 327[1]			SWOG 9916[2]	
	Docetaxel 3-weekly	Docetaxel weekly	M+P	DE Q 3 wk	M+P
N	335	334	337	386	384
Pain ≥ 2	45%	46%	46%	36%	36%
PS	≤70 12%	≤70 13%	≤70 14%	2/3 10%	2/3 12%
Median Age	68	69	68	70	70
Bone mets	90%	91%	92%	84%	88%

1. Tannock et al. *N Engl J Med* 2004:351;1502-1512. 2. Petrylak et al. *N Engl J Med* 2004;351:1513-1520.

Overall Survival

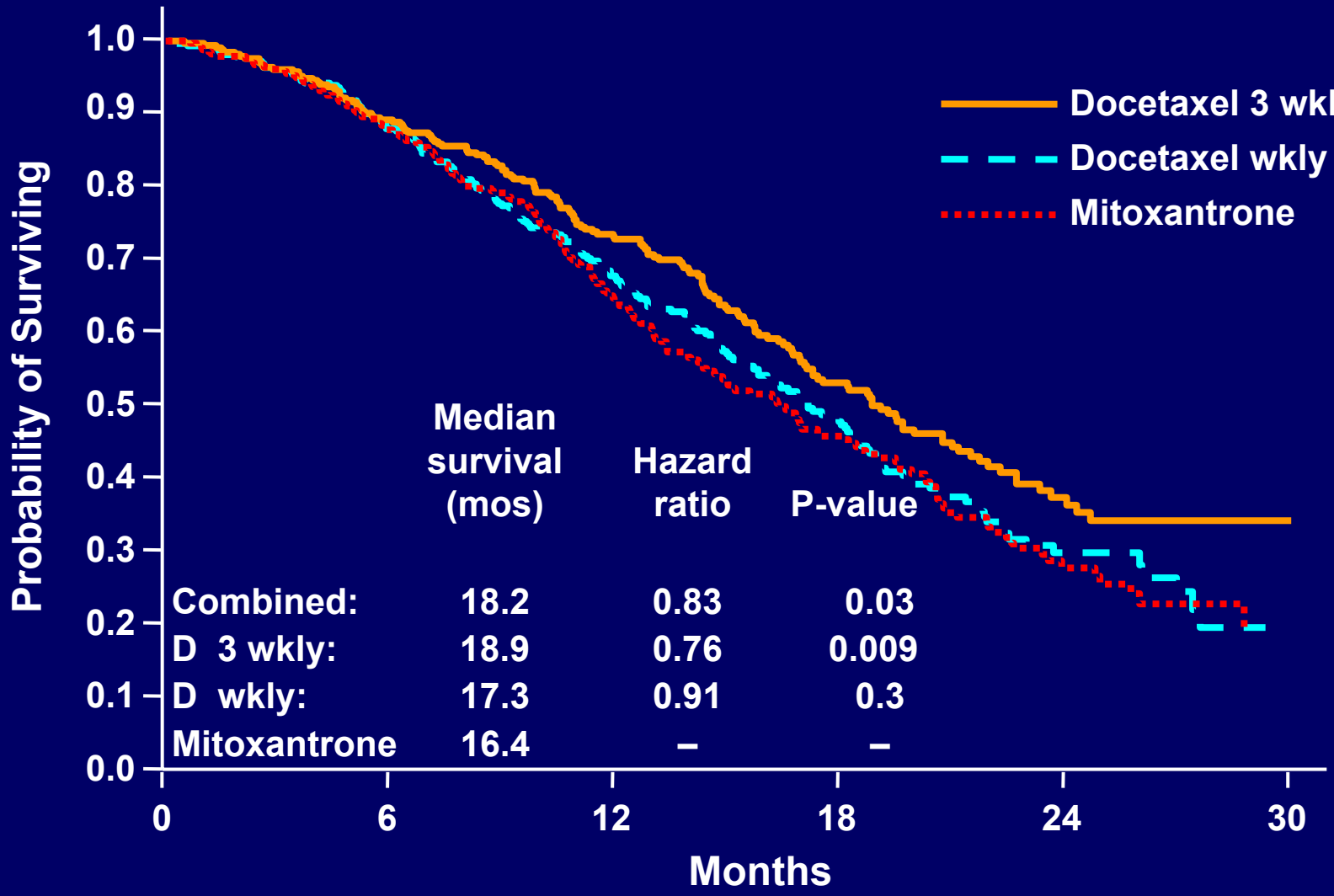


	# at Risk	# of Deaths	Median in Months
D+E	338	217	18
M+P	336	235	16

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

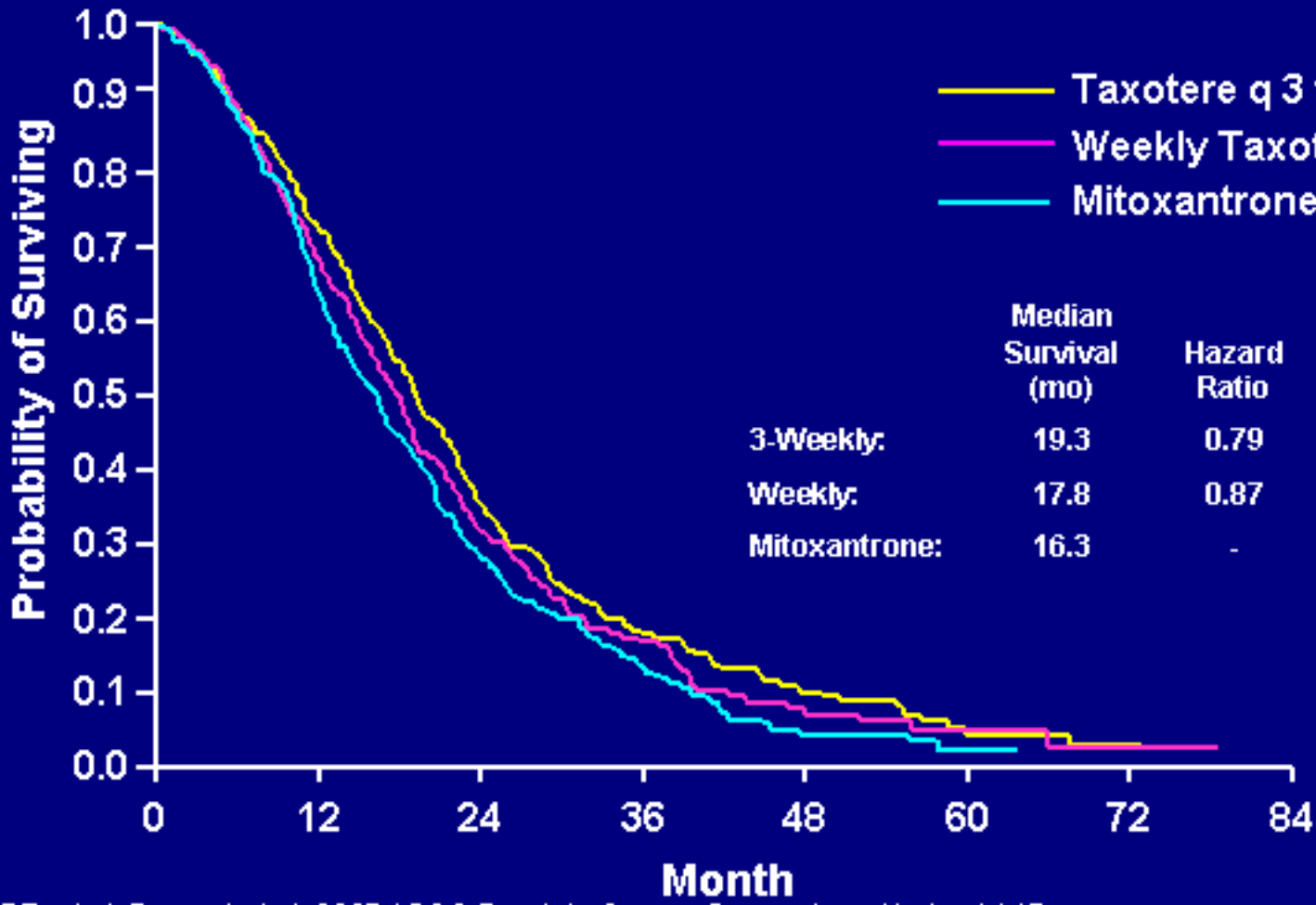
Petrylak et NEJM 2004

Overall Survival — TAX 327



Tannock et al. *N Engl J Med* 2004:351;1502-1512.

Long-Term Overall Survival (October 2006)



	Median Survival (mo)	Hazard Ratio	*P*-Value
3-Weekly:	19.3	0.79	.005
Weekly:	17.8	0.87	.10
Mitoxantrone:	16.3	-	

Berthold DR, et al. Presented at: 2007 ASCO Prostate Cancer Symposium. Abstract 147.

This information is not included in the Taxotere Package Insert.

tax2007apr25mis

Long-Term Survival (October 2006) (cont.)

	Taxotere q 3 wk (n=335)	Weekly Taxotere (n=334)	Mitoxantrone (n=337)
No. (%) deceased	256 (76.4)	257 (76.9)	282 (83.7)
Median survival (95% CI), mo	19.2 (17.6-21.3)	17.8 (16.2-19.2)	16.3 (14.4-18.2)
Hazard ratio (95% CI)	0.88 (0.81-0.96)	0.94 (0.86-1.02)	
3-year survival rate, %	17.2% (12.8-23.0)	16.4% (12.1-22.4)	12.8% (9.1-17.8)
P-value	.005	.14	

Berthold DR, et al. Presented at: 2007 ASCO Prostate Cancer Symposium. Abstract 147.

This information is not included in the Taxotere Package Insert.

Docetaxel HRPC Trials
Toxicity Data

	TAX 327[1]			SWOG 9916[2]	
	Docetaxel 3-weekly	Docetaxel weekly	M+P	DE Q 3 wk	M+P
≥ Gr 3 ANC	32	1.5	22	20	16
Infection	3% (fANC)	0%	2%	14%	7%
GI Toxicity Diarrhea ≥ Gr 3	 32% 2.1%	 34% 4.8%	 10% 1.2%	20%*	5%*
Neurosensory	30%	24%	7%	7%*	2%*
Other: Tearing CV Edema Nail changes	 10% 19% 30%	 21% 12% 37%	 1% 1% 7%	15%	7%

*Grade 3-4 toxicity only

1. Tannock et al. *N Engl J Med* 2004:351;1502-1512. 2. Petrylak et al. *N Engl J Med* 2004;351:1513-1520.

Are These toxicities Manageable?

Neutropenia	Short lived, CSF Antibiotics
Edema	Monitor weights, diuretics
Diarrhea	Loperimide
Lacrimation	Stenting of tear ducts
Nail Bed Changes	Nail polish, immersion in cold
Fatigue	Intermittent therapy?

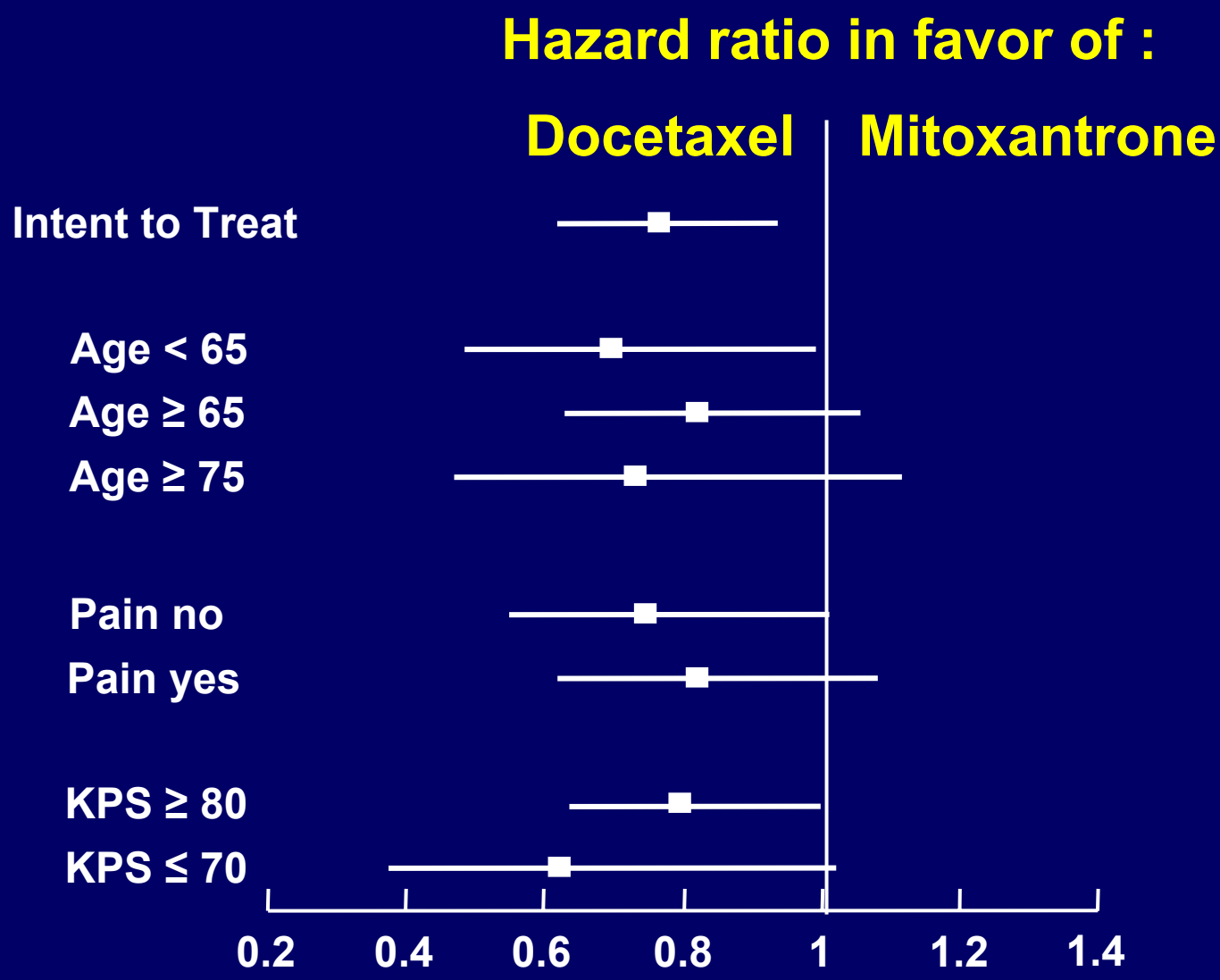
Quality of Life Response

> 16 points FACT-P score compared to baseline

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

*Compared to mitoxantrone

Survival in Subgroups
Docetaxel 3 wkly vs Mitoxantrone



Docetaxel as an Immune Modulator

- Apoptotic bodies removed by macrophages
  - Docetaxel: LPS mimetics
- Increase in helper/inducer T-lymphocytes and natural killer cells by 27% in murine tumors treated with docetaxel

Immune Therapies

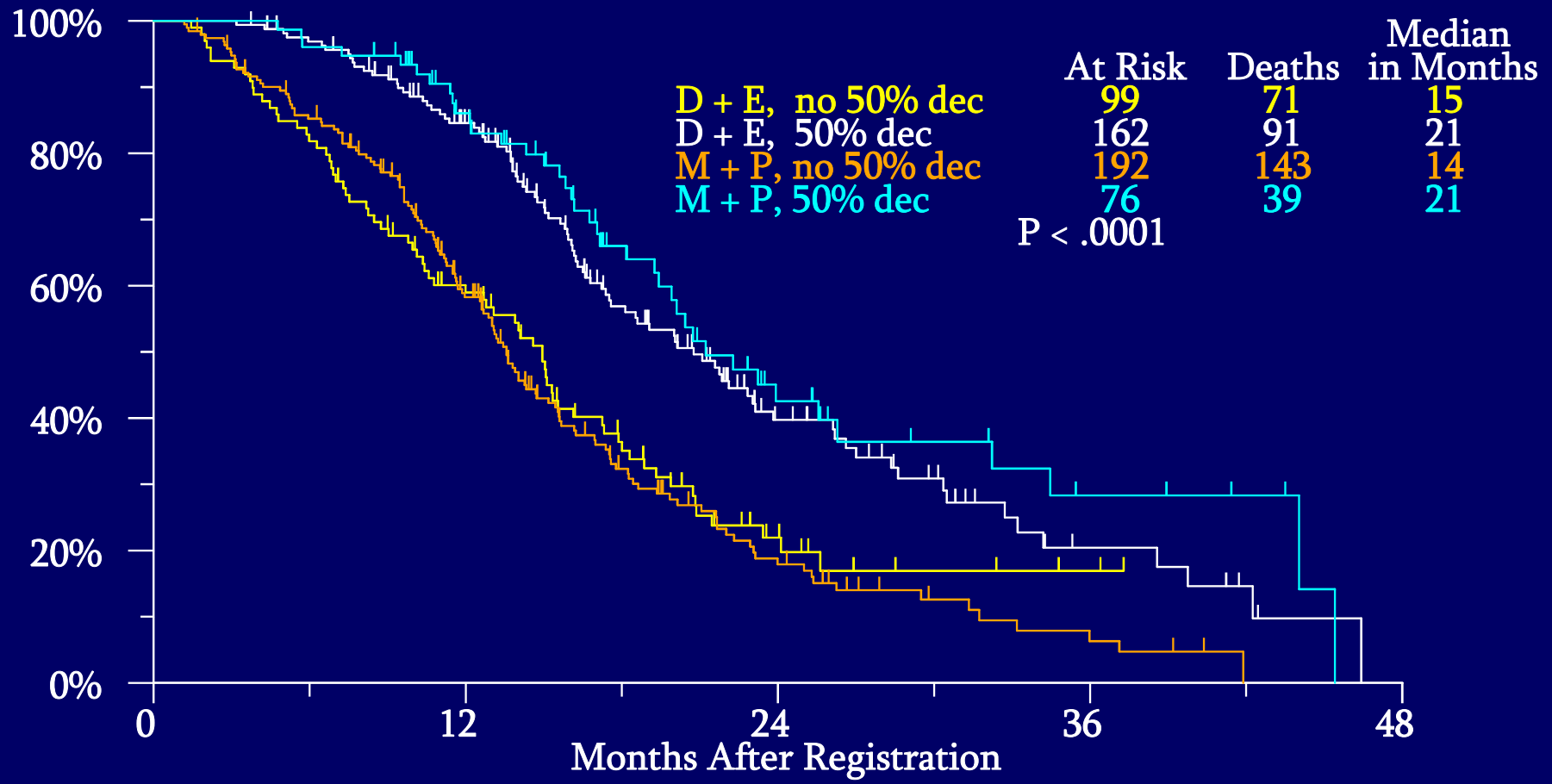
- Vaccines
  - GVAX
  - Prostvax
- Dendritic Cells
  - Provenge

Docetaxel Treated Patients who Received Sipuleucel-T Have Extended Survival

Study Treatment	Post-Study Chemotherapy	N	Median Survival (Months) Predicted+	Observed
Sipuleucel-T	Docetaxel	51	20.9	34.5
Placebo				
Placebo + Crossover	Docetaxel	21	20.3	25.7
Placebo only	Docetaxel	10	19.1	20.2

+ Median of predicted survivals, as calculated using model of Halabi et al., JCO 2003

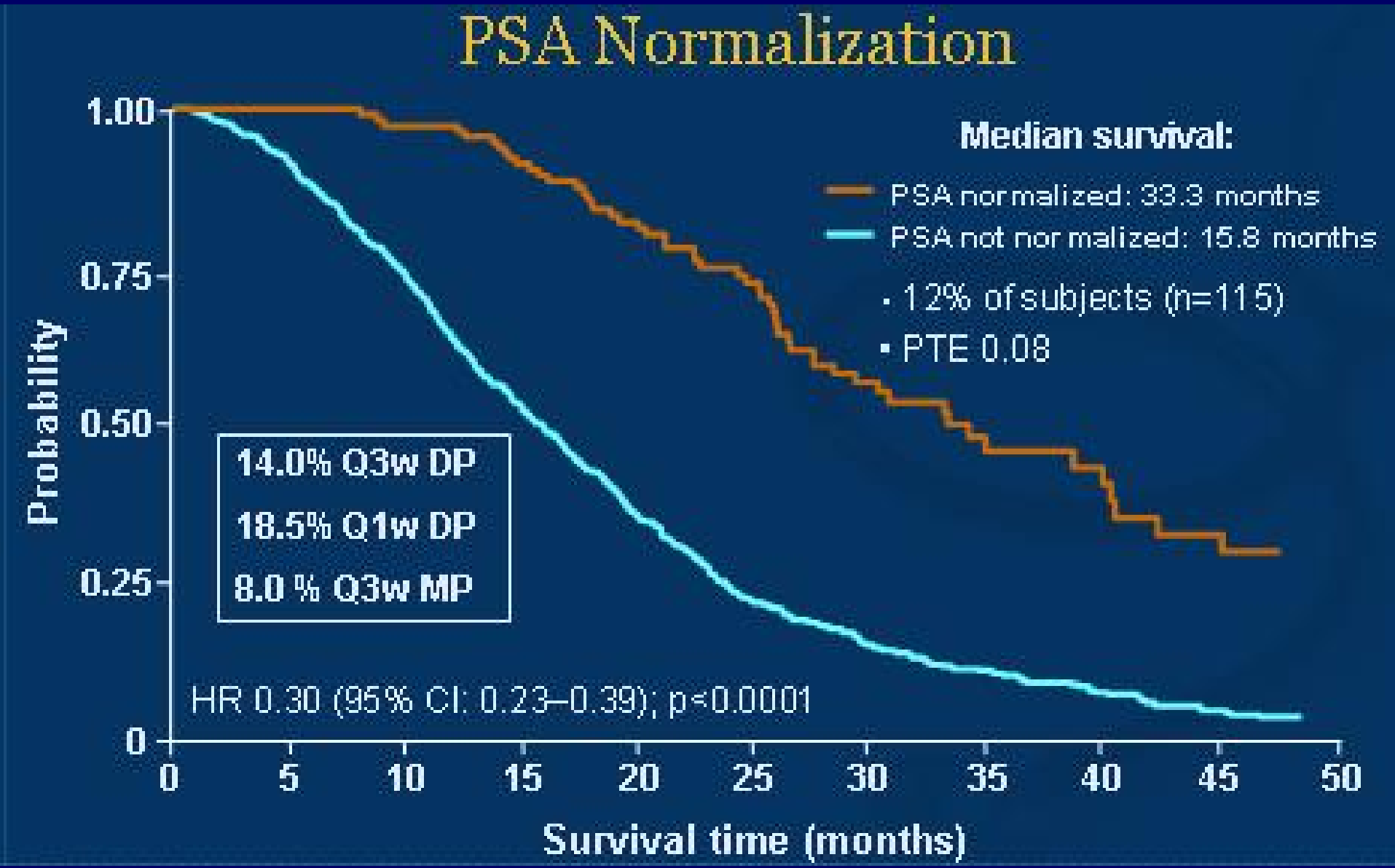
Criterion 1c: Survival by Treatment and Surrogate



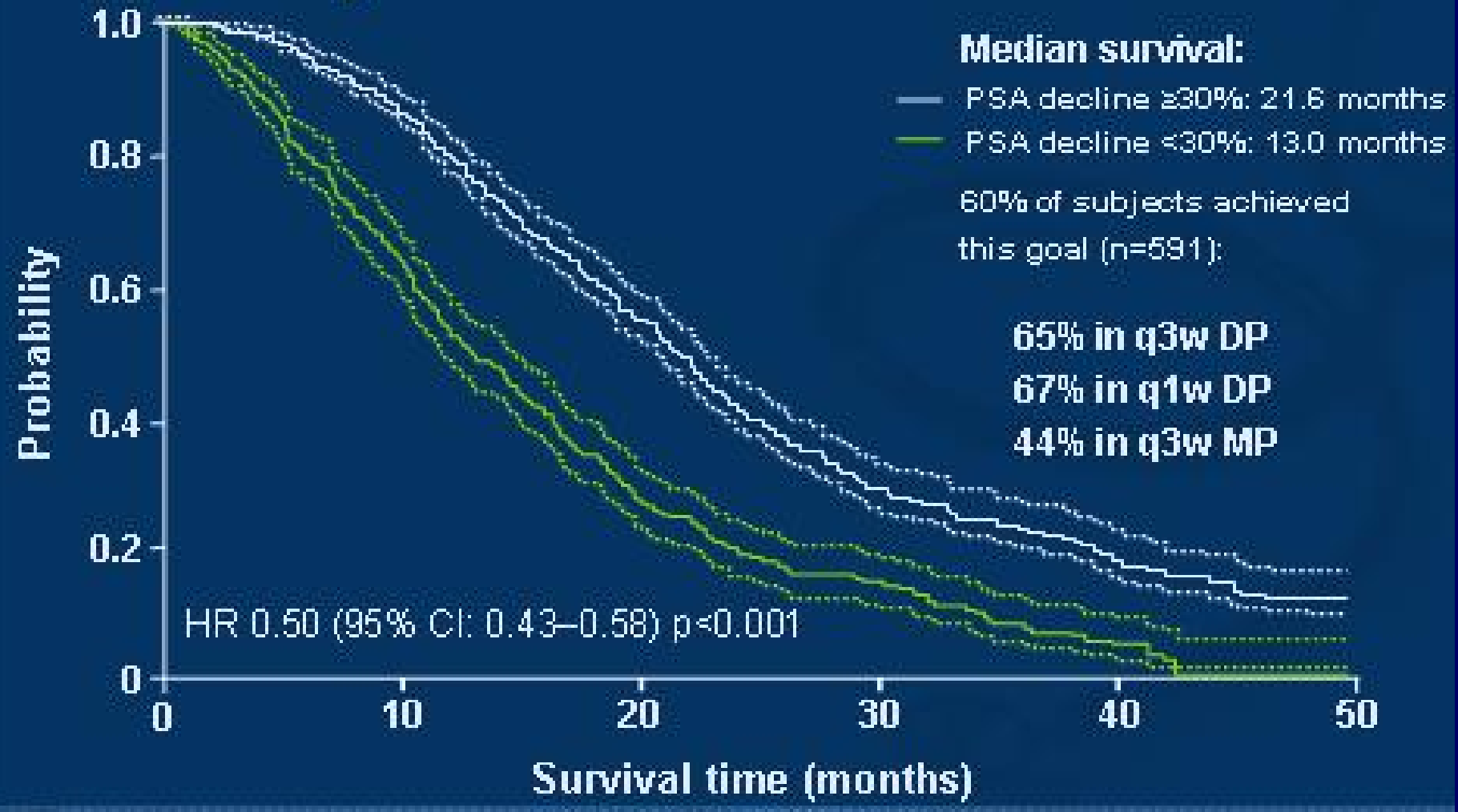
Summary: Surrogates

- 50% decrease in PSA over 3 months barely failed one of the surrogate criteria.
- 30% decrease satisfied all criteria for 3 and 2 months.
- Slope (Velocity) also satisfied all criteria for 3 and 2 months, but is less easily interpreted.
- Prostate cancer endpoints based on response require measurable disease.
- Change in PSA is a viable surrogate for chemo trials in advanced hormone refractory prostate cancer.

PSA Normalization



Surrogate Effect for ≥30% PSA Decline



Predictors of PSA Normalization

Variable	No PSA Normalization	PSA Normalization	P-value
Age, median in years	68 (66-70)	69 (68-69)	0.45
Visceral metastases (% yes)	23	15	**0.04**
Pain (% yes)	48	40	0.13
Performance status (% ≤ 70)	14	10	0.22
No. metastatic sites (% > 2)	14	8	0.09
PSA (median), ng/dl (95% CI)	177 (161-203)	57 (51-67)	
PSA (mean), ng/dl	518	478	0.85
PSADT, days	74 (66-82)	91 (66-116)	0.14

Pain Response as a Surrogate

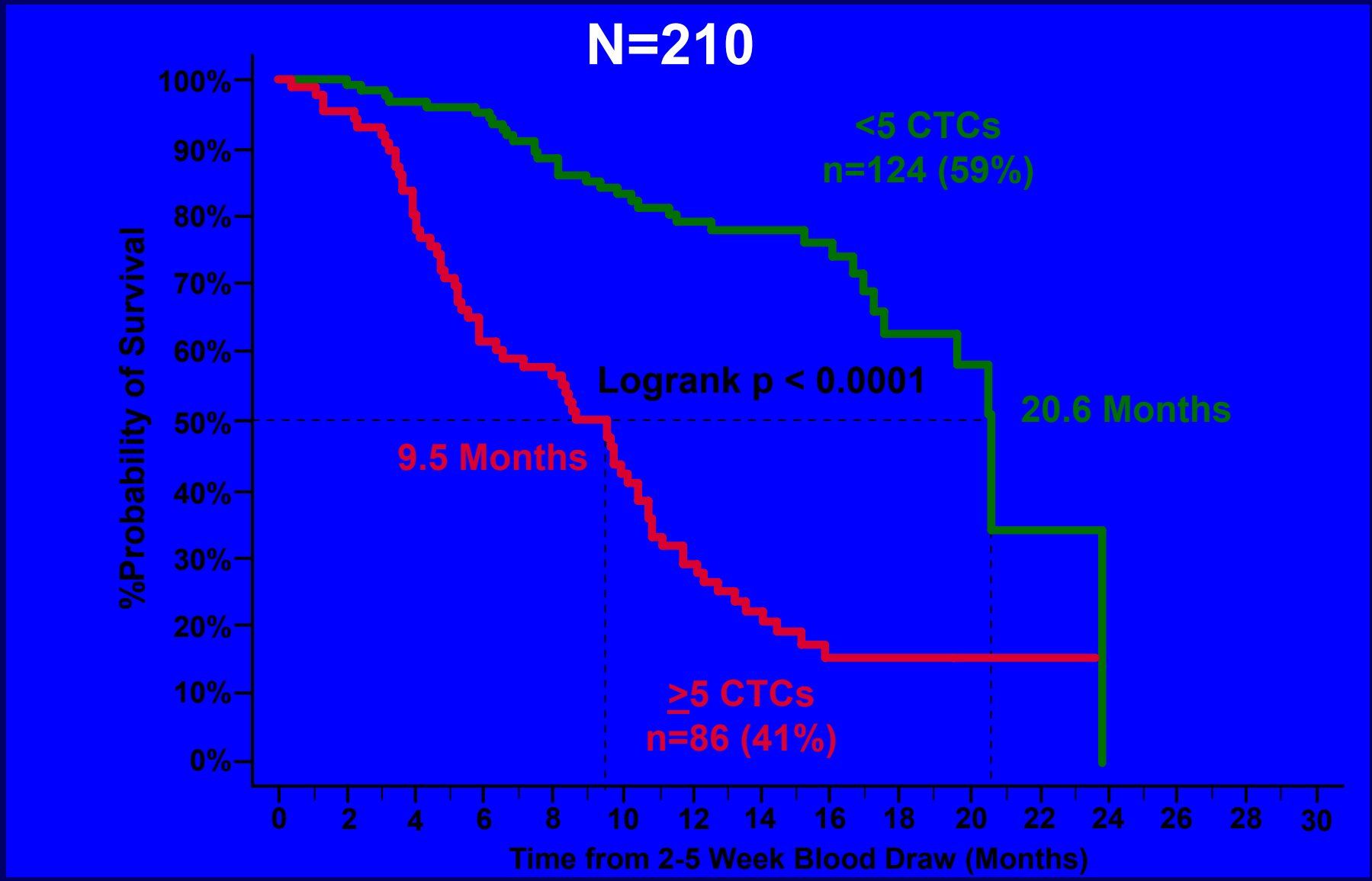
- Pain response identified in 29% of 466 evaluable subjects
- Pain response defined as:
  - 2-point reduction in present pain inventory score (PPI) without an increase in analgesic score (AS)
  - ≥50% reduction in AS without an increase in PPI

	Pain response (n=135)	No pain response (n=331)
Median survival, months (95% CI)	18.6 (16.4–20.3)	12.5 (11.3–14.3)

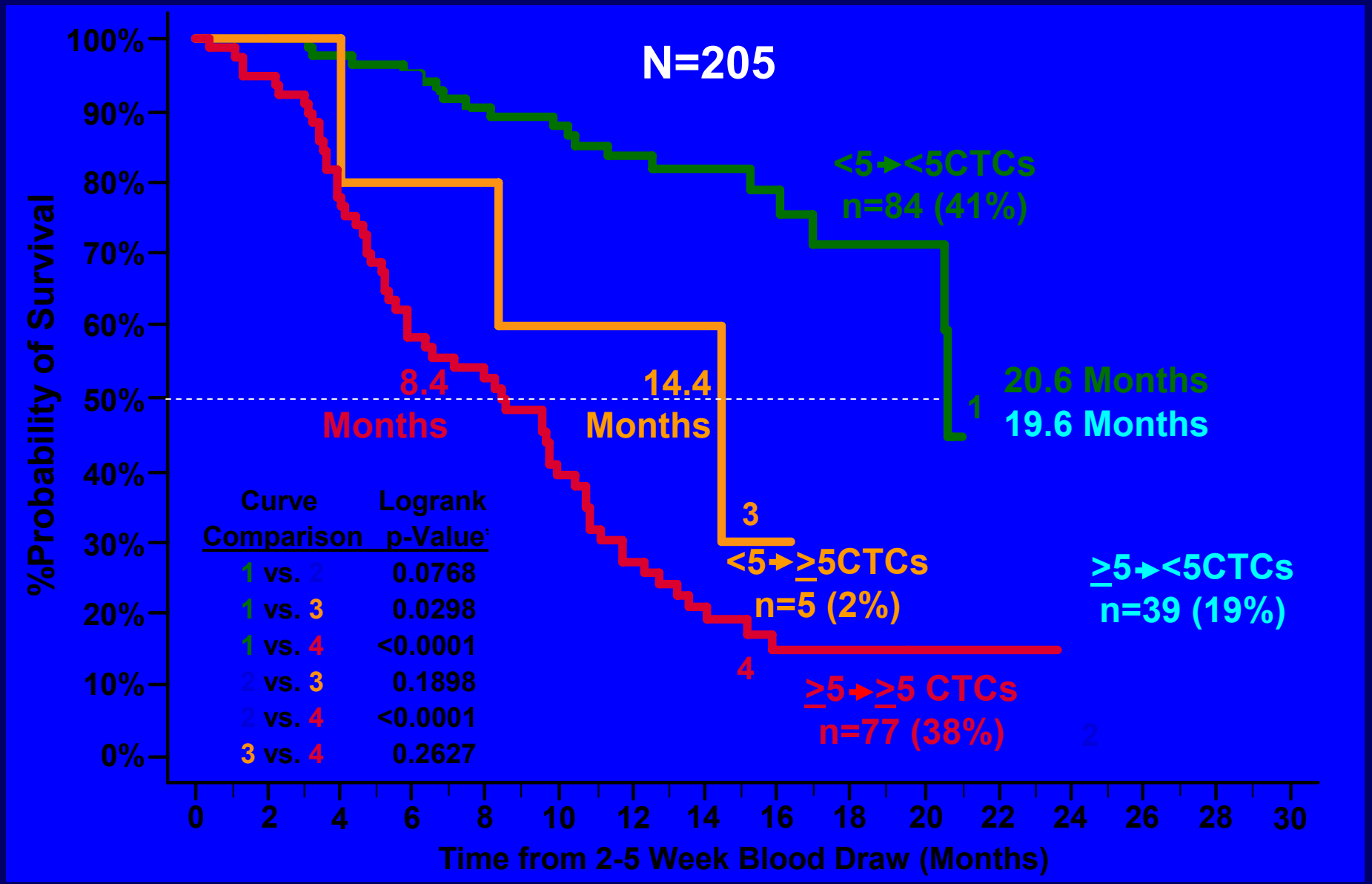
HR = 0.60 (95% CI: 0.48–0.75) for overall survival

PTE = 0.64 (95% CI: 0.22–1.0)

<5 VS. ≥5 CTC 2-5 WEEKS AFTER START OF TREATMENT PREDICTS SURVIVAL

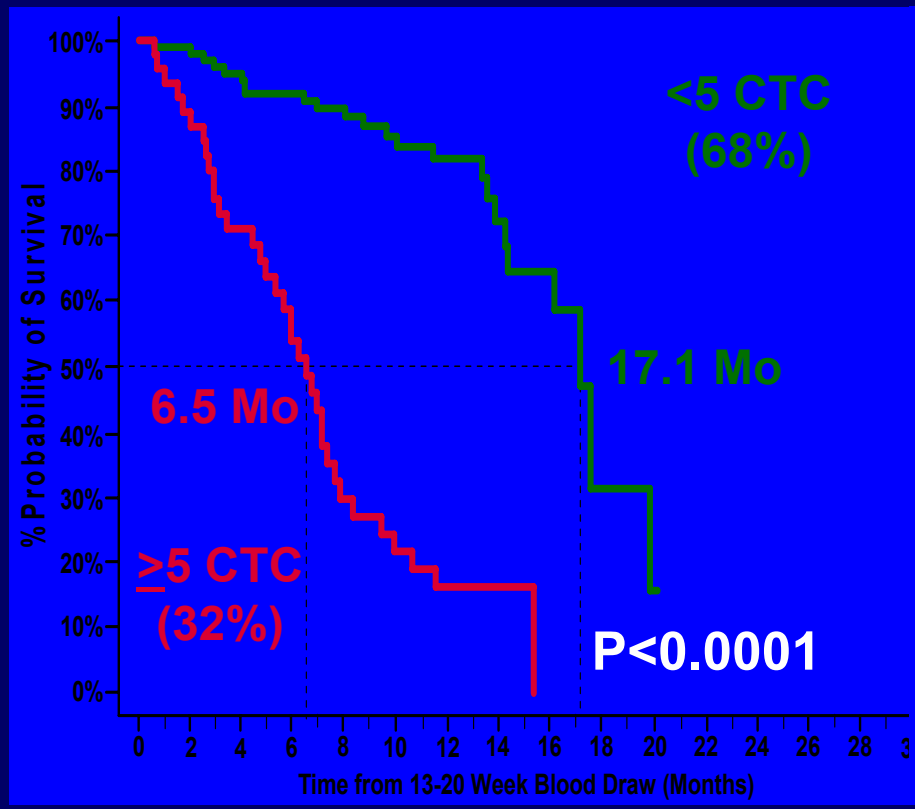


CHANGES IN CTC AT 2-5 WEEKS FROM BASELINE IS ALSO PREDICTIVE

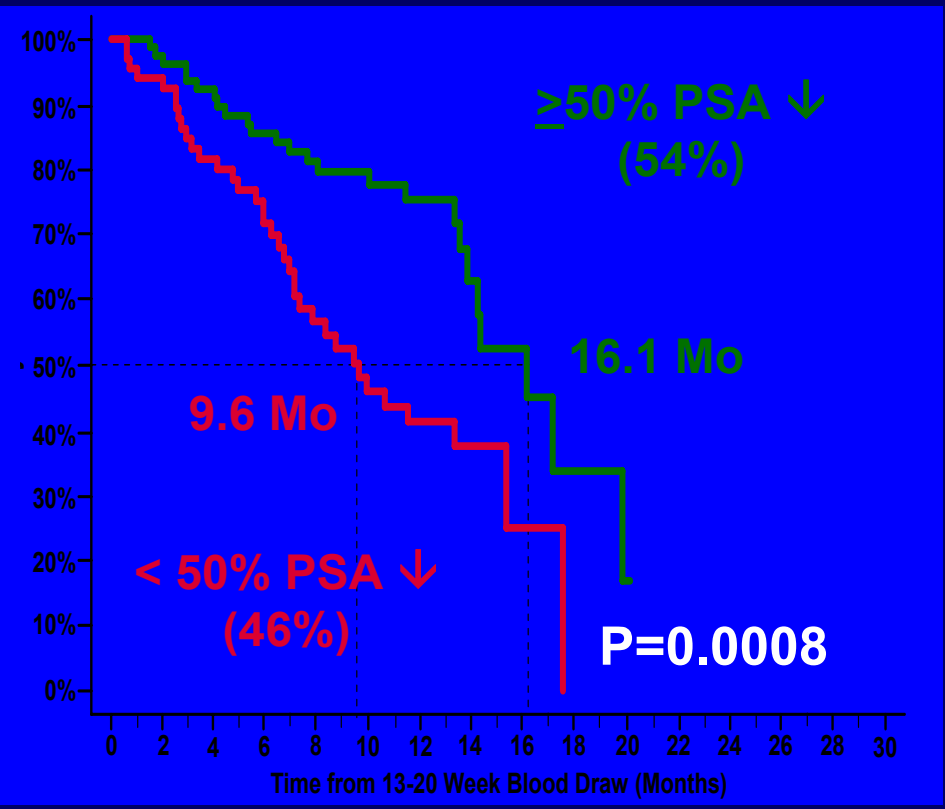


POST-TREATMENT CTC NUMBER WAS MORE PREDICTIVE THAN A PSA RESPONSE AT 13-20 WEEKS (>50% DECLINE FROM BASELINE)

CTC (n=145)



PSA (n=144)

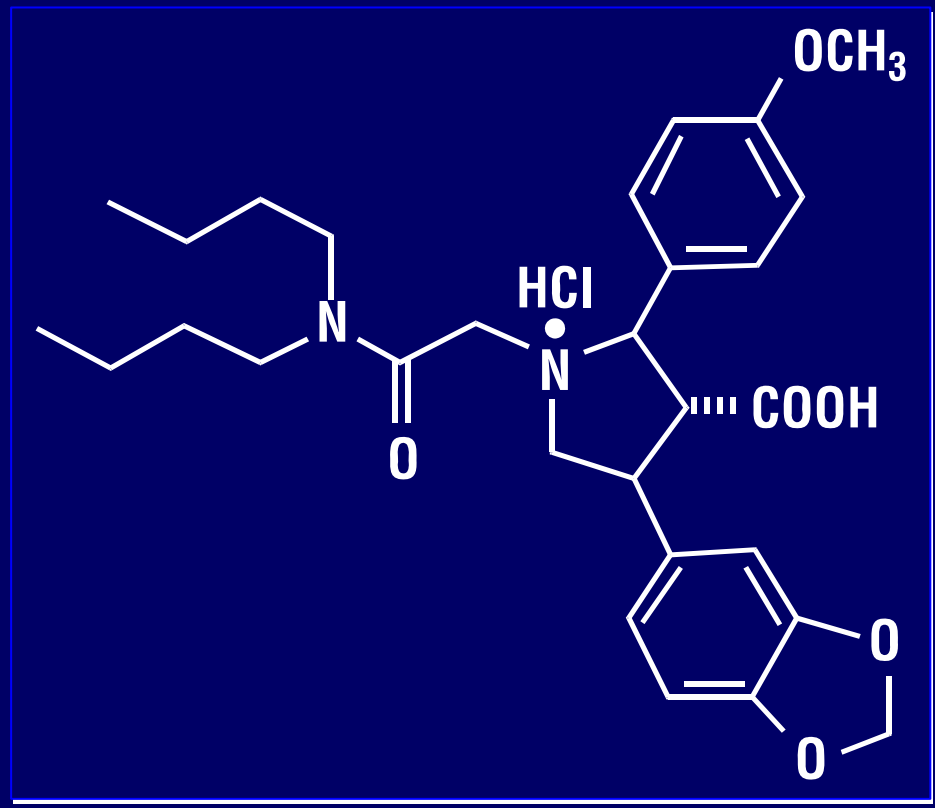


What is the best combination to pursue?

- Endothelins
- Angiogensis
- Calcitriol

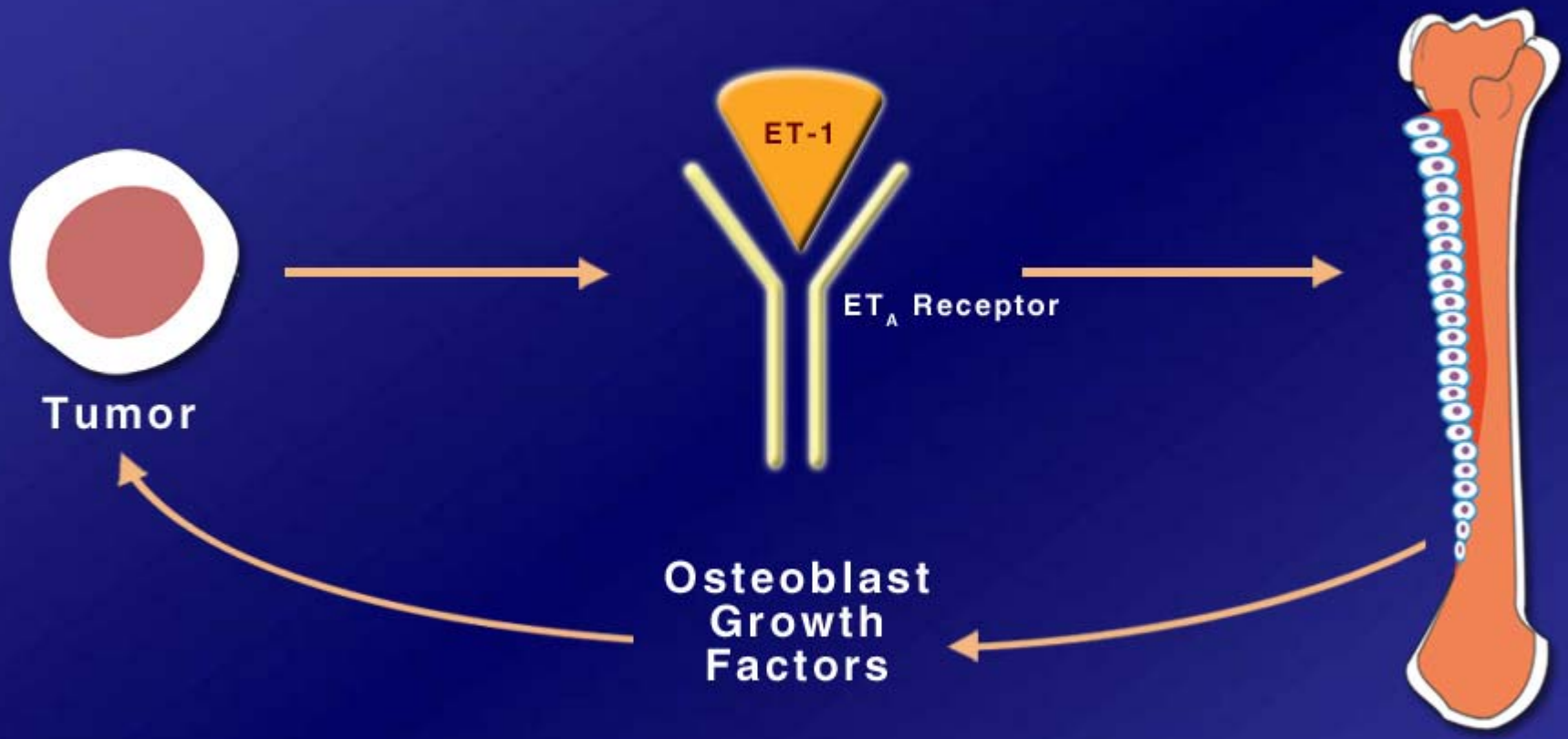
Atrasentan

- A potent, selective ET_A receptor antagonist
- Orally bioavailable
- Once daily dosing
  t ½ = 25 hours
- 1800 x more selective
  for ET_A than ET_B
  - ET_A binding constant
    = 34 pM



Opgenorth et al, Pharm Exp Ther 1996: 276
Verhaar et al, Br. J Clin Pharm 2000: 562

Endothelin-1 and the *Vicious Cycle* of Osteoblastic Bone Metastases



Adapted from Guise TA, et al. Cancer. 2003 Feb 1;97(3 Suppl):779-84. Copyright © 2003 American Cancer Society. This material is used by permission of John Wiley & Sons, Inc.
Kopetz ES, et al. Invest New Drugs. 2002 May;20(2):173-82.

Phase III Study of Docetaxel + Placebo VS Docetaxel + Atrasentan in Patients with Hormone-Refractory Prostate Cancer (S0421)

Stratification:

- Type of progression
- PS:0-1 vs 2-3
- Prior RP
- Total ALK-PO4
  < 5 vs. ≥ 5 XULN
- Bisphos.

RANDOMIZE

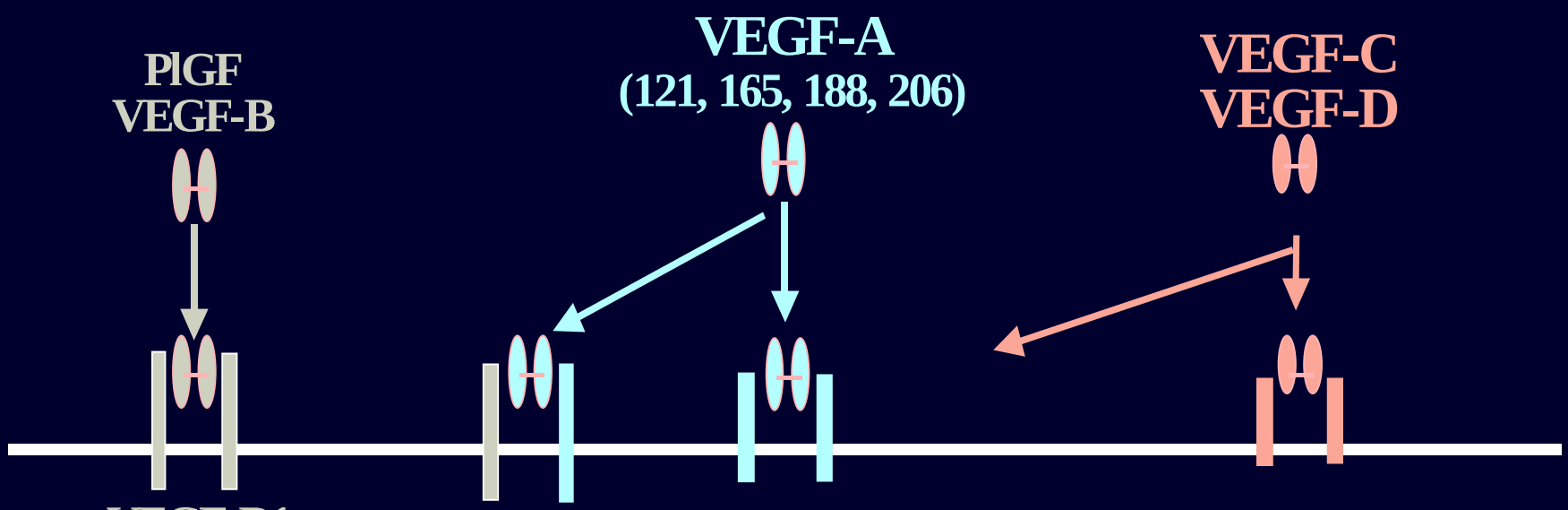
- **Docetaxel 75 mg/m2 Q3 wks**
- **Prednisone 10 mg**
- **Placebo**

- **Docetaxel 75 mg/m2 Q3 wks**
- **Prednisone 10mg**
- **Atrasentan 10 mg**

Phase III Study of Docetaxel + Placebo VS Docetaxel + Atrasentan in Patients with Hormone-Refractory Prostate Cancer (S0421)

- **Primary endpoint:**
  - **PFS**
- **Secondary endpoints:**
  - **Survival**
  - **Pain**
  - **QOL**
  - **PSA response**
  - **Objective response**
  - **Alk. Phos. (total & bone), osteocalcin, procollagen I & III, N-telopeptide**
- **706 pts, 4 years of accrual:**
  - **Power 96% to detect 33% increase in PFS (6 to 8 m)**
  - **Power 85% to detect 30% increase in MS**

VEGF family of angiogenic factors convey signals through Tyrosine kinase receptor homo- and hetero-dimerization



Motility, survival

Mitogen, Survival,

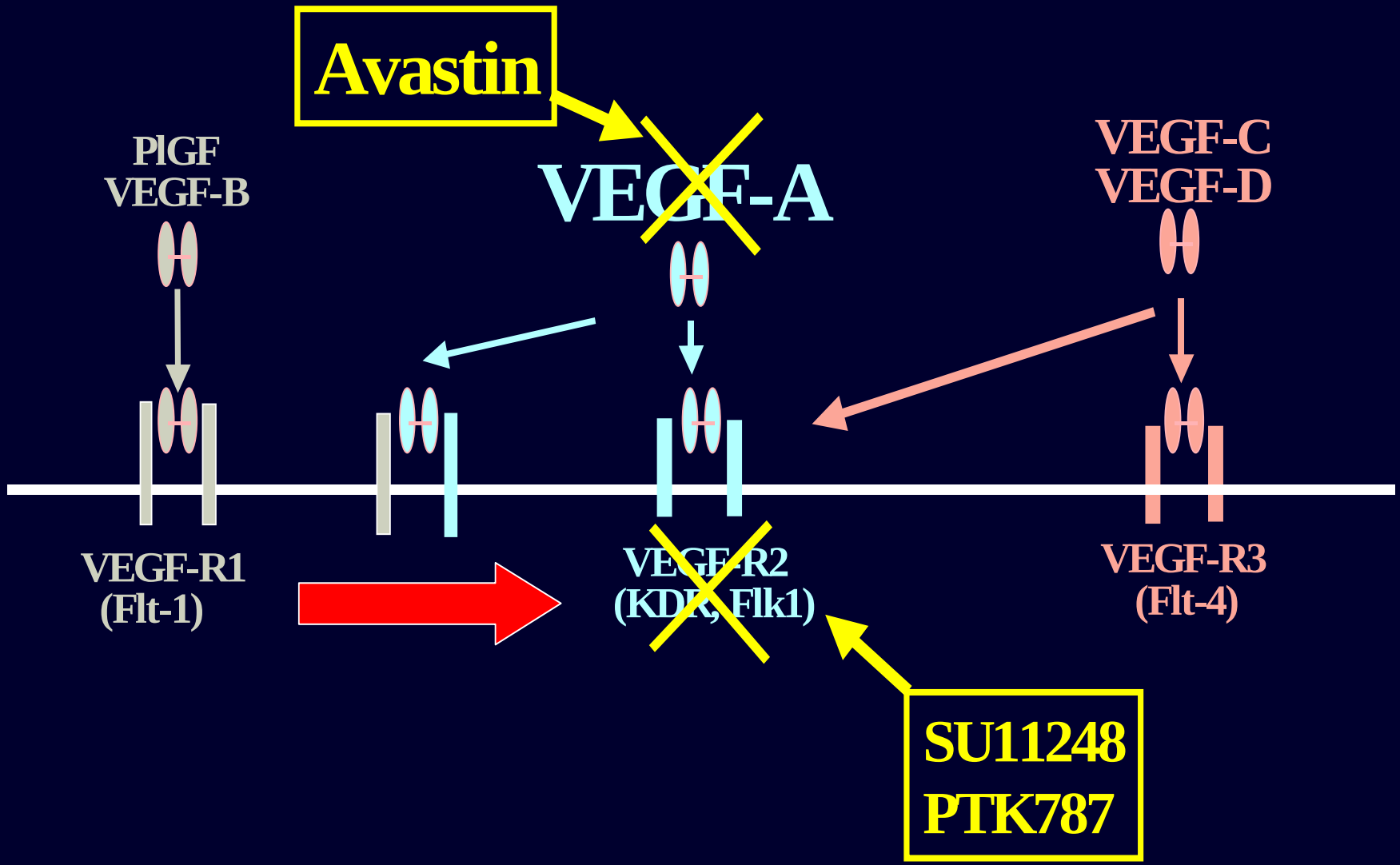
Mitogen,Survival

Hemangiogenesis
?Invasion
Vessel stabilization

Angiogenesis

Lymphangiogenesis
Invasion

Inhibition of VEGF-A may be insufficient to completely block the autophosphorylation of VEGFR2 tyrosine kinase



CALGB 9040: Randomized Double Blinded Placebo controlled Phase III Trial Comparing Docetaxel + Prednisone with or without Bevacizumab in men with HRPC

Eligibility

- Metastatic PC
- T <50 ng/ml
- No prior chemo
- Adequate hem, renal & liver function

Stratification

Halabi nomogram

RANDOMIZE

Arm A	
Dexamethasone	8 mg po x 3 doses
Docetaxel	75 mg/m^2 on d1 q21d
Prednisone	10 mg po daily
Placebo*	IV on day 1 q 21 days

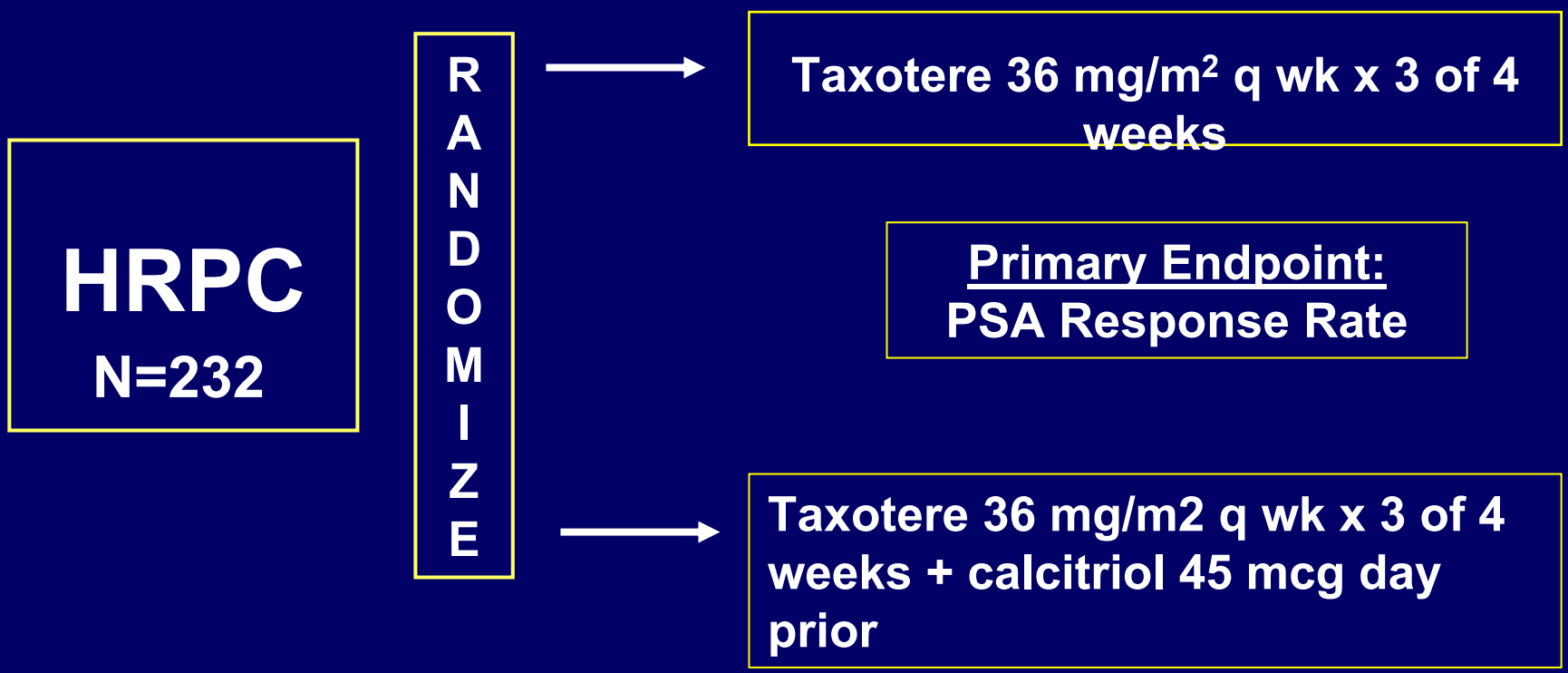
Arm B	
Dexamethasone	8 mg po x 3 doses
Docetaxel	75 mg/m^2 on d1 q 21d
Prednisone	10 mg po daily
Bevacizumab*	15 mg/kg IV on day 1q 21d

N = 1020 patients
CALGB, ECOG, NCIC

CALGB 90401: Statistical considerations

- **Endpoint:** primary: OS
  secondary: PSA RR; PFS
- **Stratification:** Halabi Nomogram (HANG)
  - » Predicted 2 year survival
  - » <10%, 10-29%, >= 30%
- **Power:** Two-sided alpha of 0.05
  Exponential distribution
  Hazard Ratio = 1.26
  (19 months to 24 months)
  Power = 90%
- **Accrual:** N= 1020
  - » 29 pts/mo. Over 36 months and follow-up 24 months
- **Interim analysis:** **19% (18 mo); 32% (24 mo); 48% (30 mo); 63% (36 mo); 75% (42 mo); 85% (48 mo); 93% (54 mo); 100% (60 mo)**

ASCENT Trial in HRPC



ASCENT: Toxicity

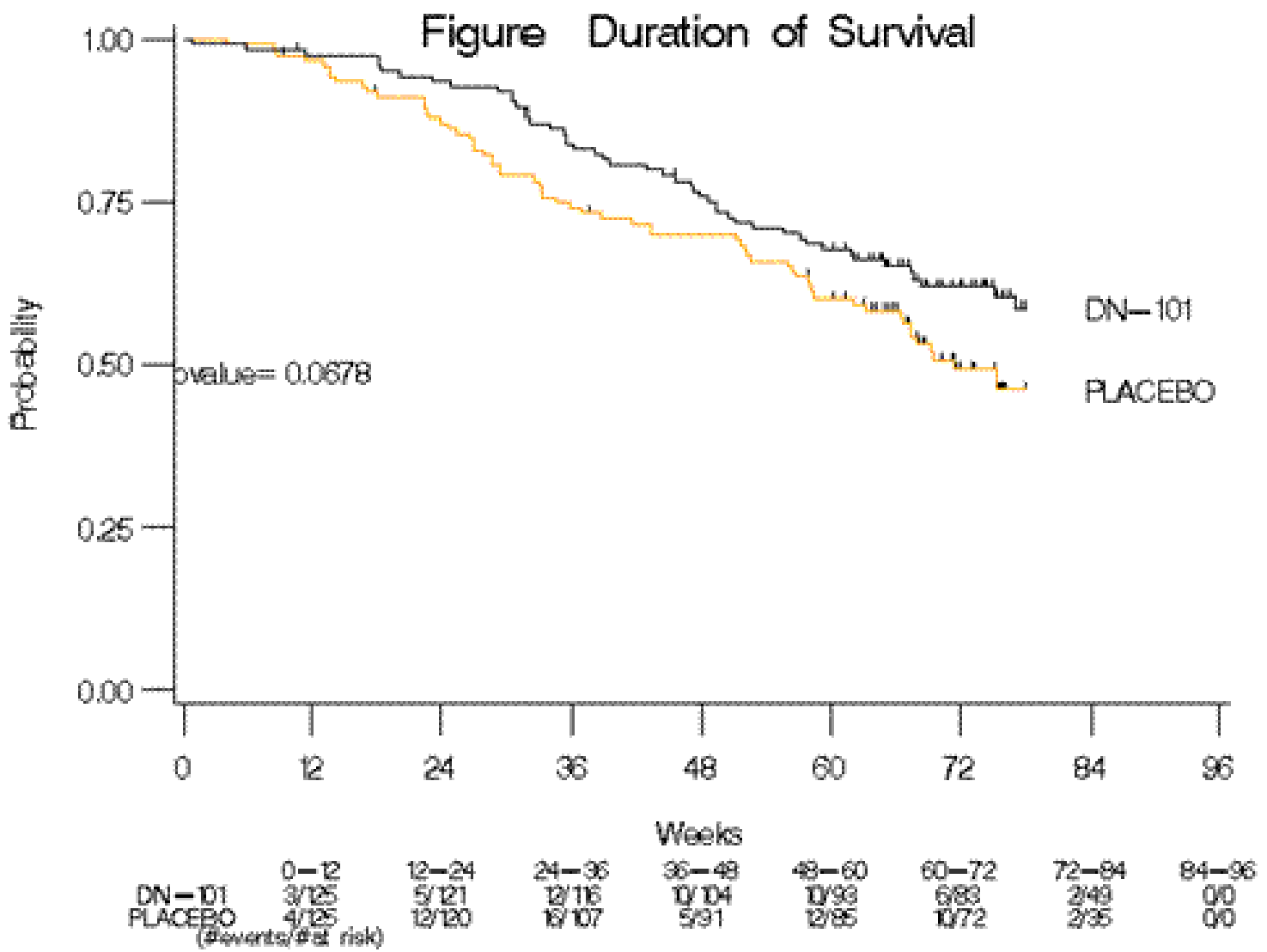
	Docetaxel	Doc/DN101
SAE	41%	27%
Any Grade 3 or 4 AE	70%	58%
AE leading to treatment Discontinuation	28%	22%

ASCENT: Exploratory Safety Analysis

Gastrointestinal Adverse Events Summary

AE Class	Placebo + Docetaxel (n = 125)	DN-101 + Docetaxel (n = 125)	*P* value
SAEs	**12** (9.6%)	**3** (2.4%)	**.017**
Grade 3/4 AEs	**19** (15.2%)	**16** (12.8%)	**.580**
All AEs	**118** (94.4%)	**107** (85.6%)	**.020**

Novacea, Inc.
Protocol DN101–002



Source: /u1/stat/dn101/002/f22apr/prog/g_surv78.sas jpyV8.2 27APR2005:17:39 db:22APR2005

ASCENT Overall Survival

Method	DN-101 + Docetaxel vs. Placebo + Docetaxel Hazard Ratio (95% CI)	P
Cox Model	0.70 (0.48-1.028)	0.070
MV Cox	0.67 (0.45-0.97)	0.035

So what are we going to do with this?

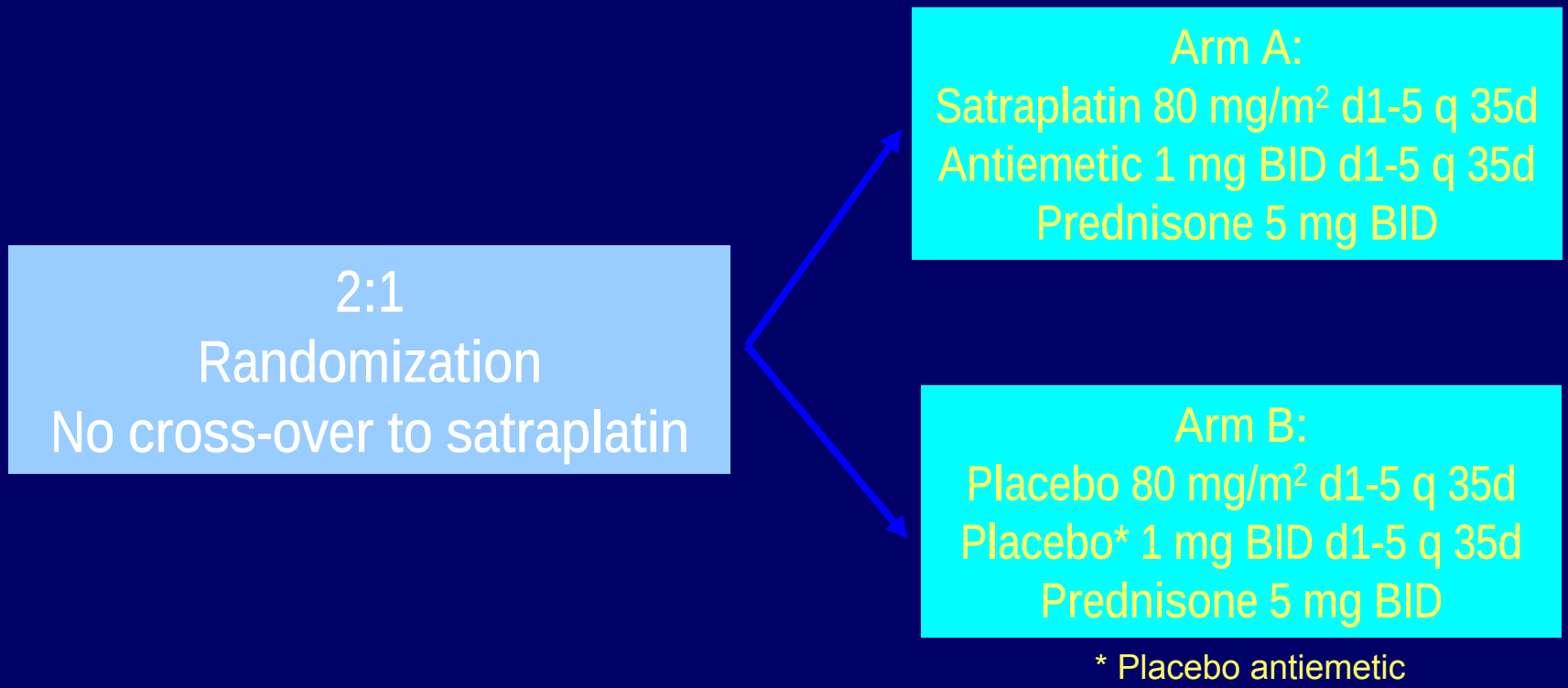
- Weekly vs every 3 weeks
  - Will DN 101 given with every 3 week docetaxel have the same effect?
- Not powered to detect toxicity differences but preliminary observations are intriguing
- ASCENT II Docetaxel/Prednisone Q 3 weeks vs Docetaxel DN101 Weekly

Satraplatin

- Novel oral platinum compound
- Acceptable safety profile in >500 patients treated in Phase I and II studies
- No cross resistance in taxane or anthracycline resistant cell lines
- Satraplatin significantly prolonged PFS for patients with chemotherapy-naïve HRPC in the EORTC trial*

*Sternberg CN, Oncology 2005;68:2-9

SPARC: Study Schema



- All patients treated until progression, intolerable toxicity or death

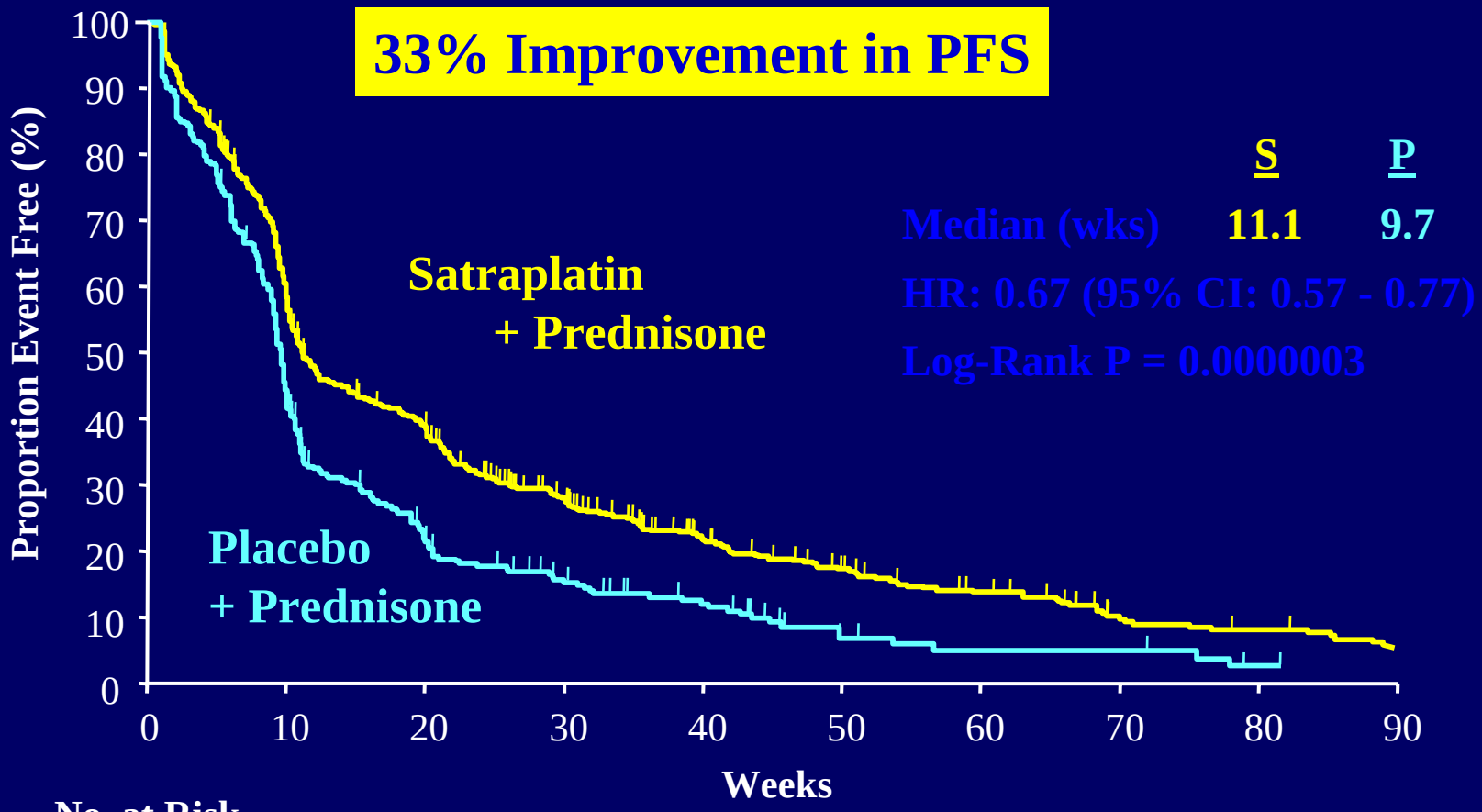
Baseline Patient Characteristics

	Satraplatin n=635	Placebo n=315
Pain Index		
0-1	64.6%	64.8%
2-5	35.4%	35.2%
Progression at Entry		
Tumor	61.7%	61.9%
PSA only	38.3%	38.1%

Baseline Patient Characteristics

	Satraplatin n=635	Placebo n=315
Prior Chemotherapy		
Docetaxel	51.5%	50.8%
Paclitaxel	2.7%	2.9%
Mitoxantrone	20.2%	20.3%
Others	25.6%	26.0%
Bisphosphonates	30.7%	27.3%

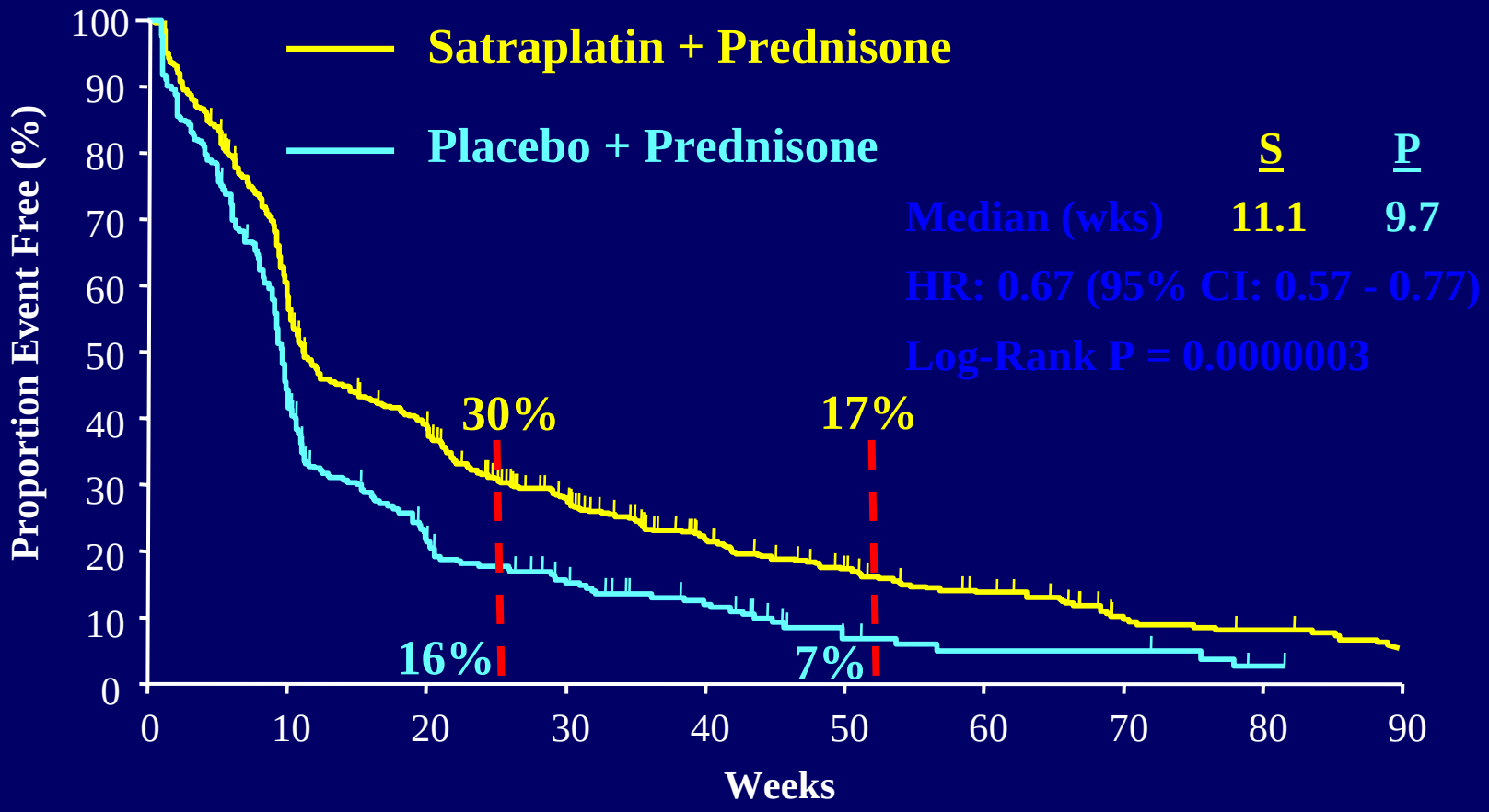
Progression Free Survival
ITT Population (per IRC)



No. at Risk

Satraplatin	635	363	229	143	90	63	43	24	18	12
Placebo	315	140	63	37	24	11	5	5	1	0

Progression Free Survival
ITT Population (per IRC)



33% Improvement in PFS

Other Pre-specified Endpoints Response Rates

	Patients, %		
Endpoint	**Satraplatin**	**Placebo**	**P value**
Pain	**24.2** (n=85/351)	**13.8** (n=25/181)	0.005
Tumor Response (RECIST)	**6.5** (n=23/352)	**0.6** (n=1/177)	0.001
PSA	**25.4** (n=121/476)	**12.4** (n=28/225)	< 0.001

Median duration of pain response was 39.1 weeks as compared to 24.1 weeks

Hematologic Toxicity

	Satraplatin, % (n=629)	Placebo, % (n=313)	P value
WBC			
Grade 3/4	13.7	0.6	<0.001
Grade 4	1.0	0.0	NS
Neutrophils			
Grade 3/4	21.1	0.6	<0.001
Grade 4	4.1	0.0	<0.001
Febrile neutropenia	0.6	0.0	NS
Platelets			
Grade 3/4	21.1	1.3	<0.001
Grade 4	0.2	0.0	NS
Hb			
Grade 3/4	9.4	3.2	<0.001
Grade 4	1.6	0.6	NS

Non Hematologic Adverse Events Grade 3/4

	Satraplatin, % (n=629)	Placebo, % (n=313)	P value
Bilirubin	0.5	0.0	ns
Serum Creatinine	0.8	0.3	ns
Nausea	1.3	0.3	ns
Vomiting	1.6	0.0	0.036
Diarrhea	2.1	0.0	0.007
Constipation	2.1	1.0	ns
Fatigue/Asthenia	4.9	2.6	ns
Neuropathy	0.3	0.3	ns
DVT	0.6	0.0	ns

Satraplatin was discontinued in 2.5% vs. placebo in 0.6%

Satraplatin demonstrates important clinical benefits

- 33% reduction in the risk of disease progression
- 36% reduction in the time to pain progression
- A significant improvement in pain, tumor and PSA response rates
- Well tolerated in this elderly population

Conclusions

- Standard of care for HRPCA is docetaxel/prednisone
- Novel phase IIII studies are combining docetaxel with novel targeted agents
- The role of second line chemotherapy and immune therapy are currently being defined.