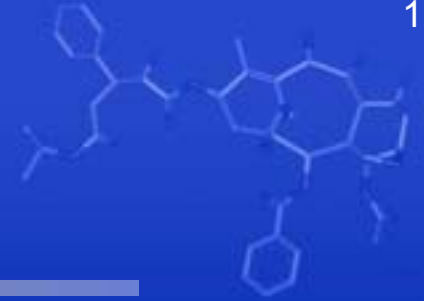


**Lloyd A. Shabazz, MD, FACP**  
**President and Medical Director**  
**Delta Hematology/Oncology Associates**

---



---

**MANAGEMENT OF METASTATIC PROSTATE CANCER  
BY  
LLOYD A. SHABAZZ, MD, FACP**

# Program Outline

A faint, light blue chemical structure diagram is visible in the upper right corner of the slide. It consists of several interconnected rings and lines, representing a complex organic molecule. The structure includes a central ring system with various substituents and branches, typical of a pharmaceutical or chemical structure.

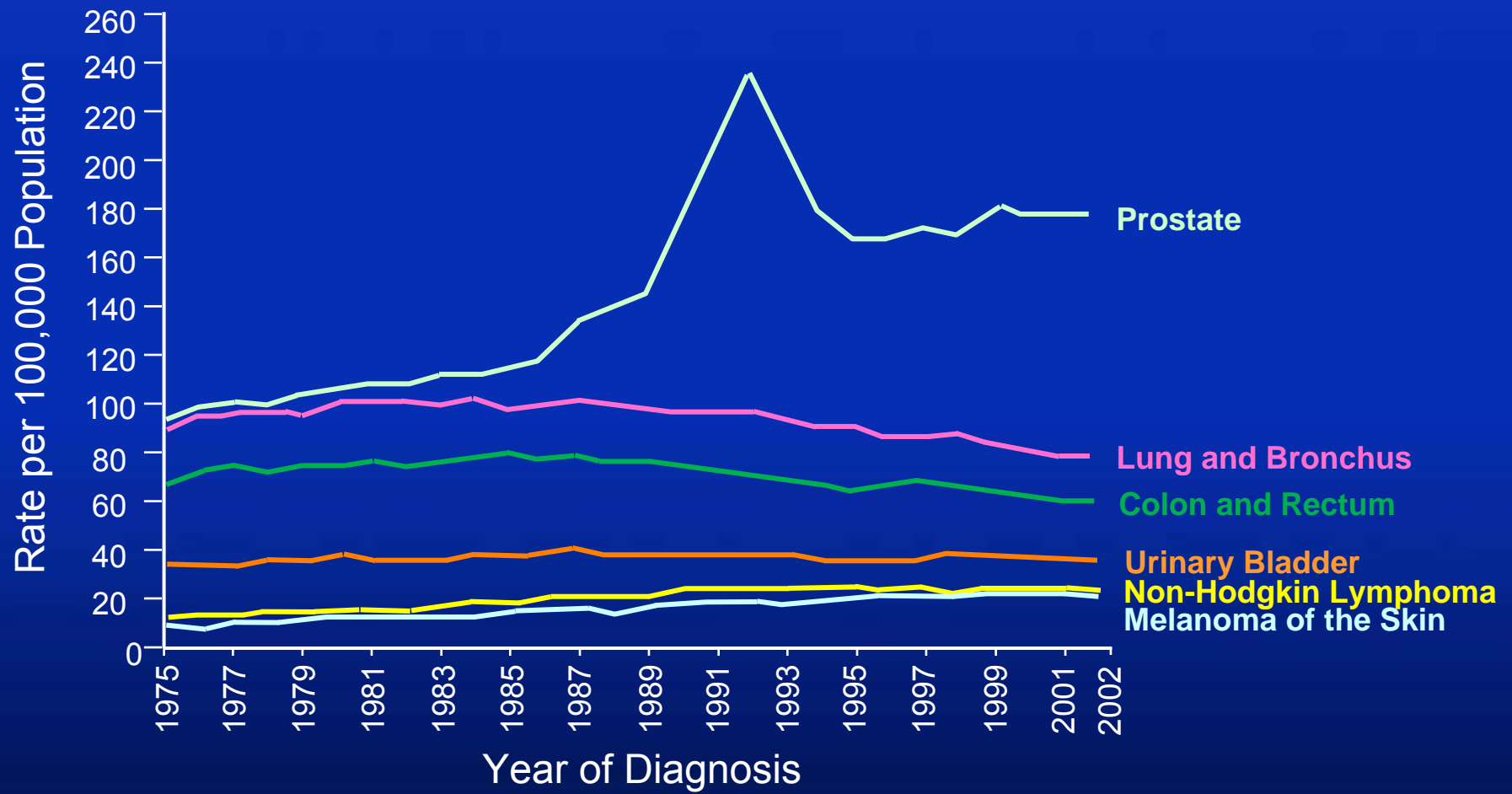
- Epidemiology Trends and Natural History
- Importance of the Multidisciplinary Team
- Chemotherapy in Prostate Cancer
- Important Safety Information

# Prostate Cancer (2008)

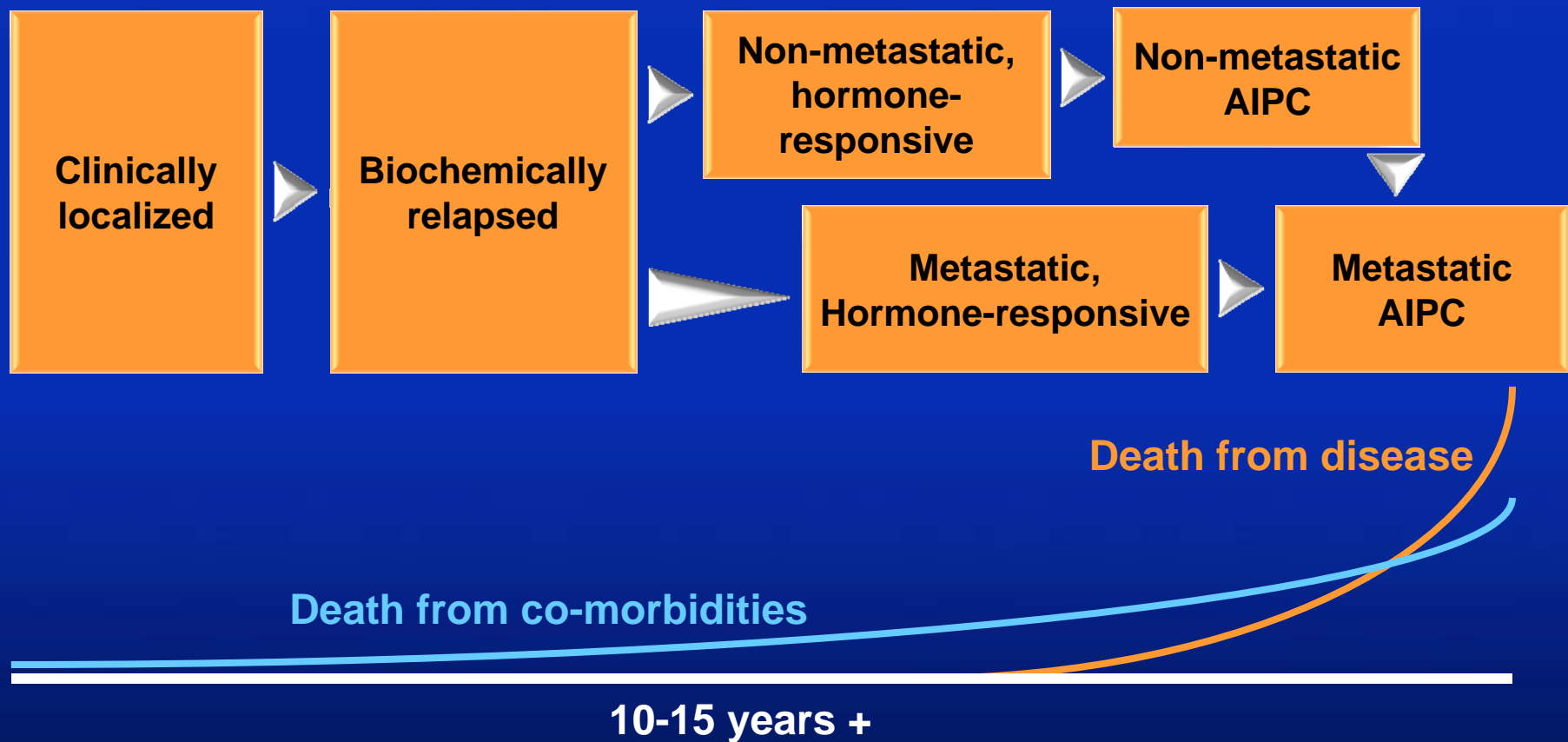


- Prostate cancer is the most common male cancer and the second leading cause of cancer death in men
  - 186,320 new cases (US, 2008)
  - 28,660 deaths (US, 2008)
- Established risk factors include age, race, and family history of prostate cancer
  - About 64% of all cases are diagnosed in men >65 years old
  - African American men have highest incidence rates worldwide
- More than 90% of all cases are discovered in the local or regional stages

# Annual Age-Adjusted Cancer Incidence Rates Among Males for Selected Cancers, 1975-2002



# Clinical States of Prostate Cancer



# Disease Progression and Clinical Management

## *Localized Disease*

### **Prognostic factors**

PSA level  
Gleason score  
Clinical stage

### **Management options**

Watchful waiting  
Surgery  
Radiation

Average  
7 years



- Clinical staging
- Gleason score
- PSA monitoring

## *Recurrent Disease*

### **Prognostic factors**

PSA DT  
Time to recurrence  
Gleason score

### **Management options**

Hormone therapy  
Watchful waiting until metastasis

Average  
3-5 years



- Clinical staging
- PSA monitoring

## *Advancing Disease*

### **Prognostic factors**

PSA DT  
Visceral metastases  
Bone metastases  
Anemia  
Alk phos, LDH

### **Management options**

Chemotherapy  
Bisphosphonates

# Hormonal Therapy



- Types of hormone therapies include:
  - LHRH analogs and LHRH antagonists
  - Anti-androgens
  - Estrogens
  - Orchiectomy
- Over time both adaptive and selective pressures result in development of disease progression in the setting of systemic castrate level testosterone suppression

# Evolution of Hormonal Therapy



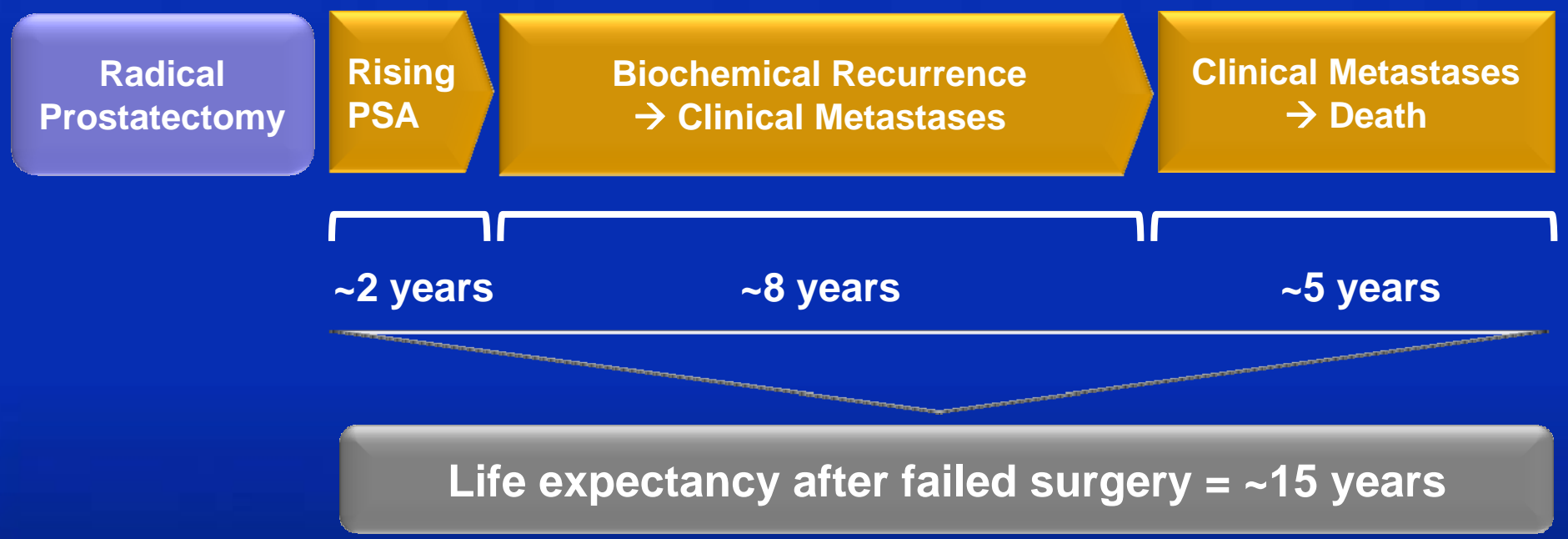
- Pre-PSA Era
  - Therapy should be delayed
  - Hormonal therapy not curative
  - Significant side effects
- Post-PSA Era
  - Hormonal therapy is a palliative treatment of choice for advanced prostate cancer
  - Androgen suppression can be achieved through surgical or medical castration

# Available LHRH Agents



Brand Name	Administration	Company
<b>Eligard®</b> (leuprolide acetate for injectable suspension)	<b>Subcutaneous Injection</b> <b>1,3,4,6-month formulations</b>	<b>sanofi-aventis</b>
<b>Lupron Depot®</b> (leuprolide acetate for depot suspension)	<b>Intramuscular Injection</b> <b>1,3,4-month formulations</b>	<b>TAP Pharmaceuticals Inc.</b>
<b>Trelstar® Depot</b> (injectable triptorelin pamoate) <b>Trelstar® LA</b> (triptorelin pamoate for injectable suspension)	<b>Intramuscular Injection</b> <b>28-day formulation</b> <b>84-day formulation</b>	<b>Watson Pharma, Inc.</b>
<b>Vantas®</b> (histrelin implant)	<b>Subcutaneous Implant</b> <b>12 month formulation</b>	<b>Indevus Pharmaceuticals</b>
<b>Viadur®</b> (leuprolide acetate implant)	<b>Subcutaneous Implant</b> <b>12 month formulation</b>	<b>Bayer Pharmaceuticals Corporation</b>
<b>Zoladex®</b> (goserelin acetate implant)	<b>Subcutaneous Implant</b> <b>1,3-month formulations</b>	<b>AstraZeneca Pharmaceuticals LP</b>

# Natural History of a Rising PSA after Surgery as Primary Therapy in Select Patient Subset



# Definition of Castrate-resistant Prostate Cancer (CRPC)



- CRPC defined as disease progression on androgen deprivation therapy, although there is no accepted standard
  - Presence of progressive metastatic measurable disease (by RECIST)
  - Progression of bone metastases (by bone scan)
  - Biochemical progression: 2 consecutive increases in PSA (>5 ng/mL or >10 ng/mL)
  - Castrate testosterone levels (<50 ng/mL or <20 ng/mL)
  - Progression despite anti-androgen withdrawal (up to 4-6 weeks earlier)

Sternberg C, et al. *BJU Intl.* 2006;99:22-27.

Bubley G, et al. *J Clin Oncol.* 1999;17:3461-3467.

Winqvist E, et al. *BMC Cancer.* 2006;6:112.

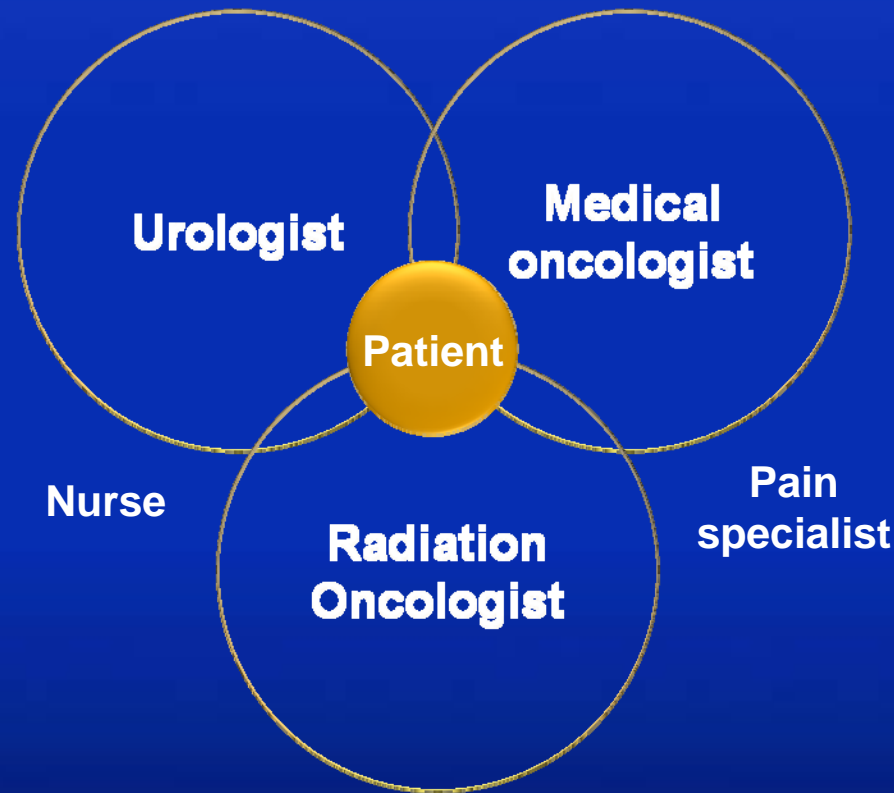
# Prostate Cancer Management and the Multidisciplinary Team

# Multidisciplinary Team (MDT) Approach to Prostate Cancer Management



- The survival benefit of chemotherapy has changed standard of care of CRPC
  - Greater involvement of medical oncologists
- Communication can optimize MDT relationships
  - Early interaction at the training level
  - Overcoming existing barriers
    - Limited interaction between urologists and medical oncologists
    - Late referral of prostate cancer patients to oncologists
    - Difference in opinions regarding beneficial survival advantage

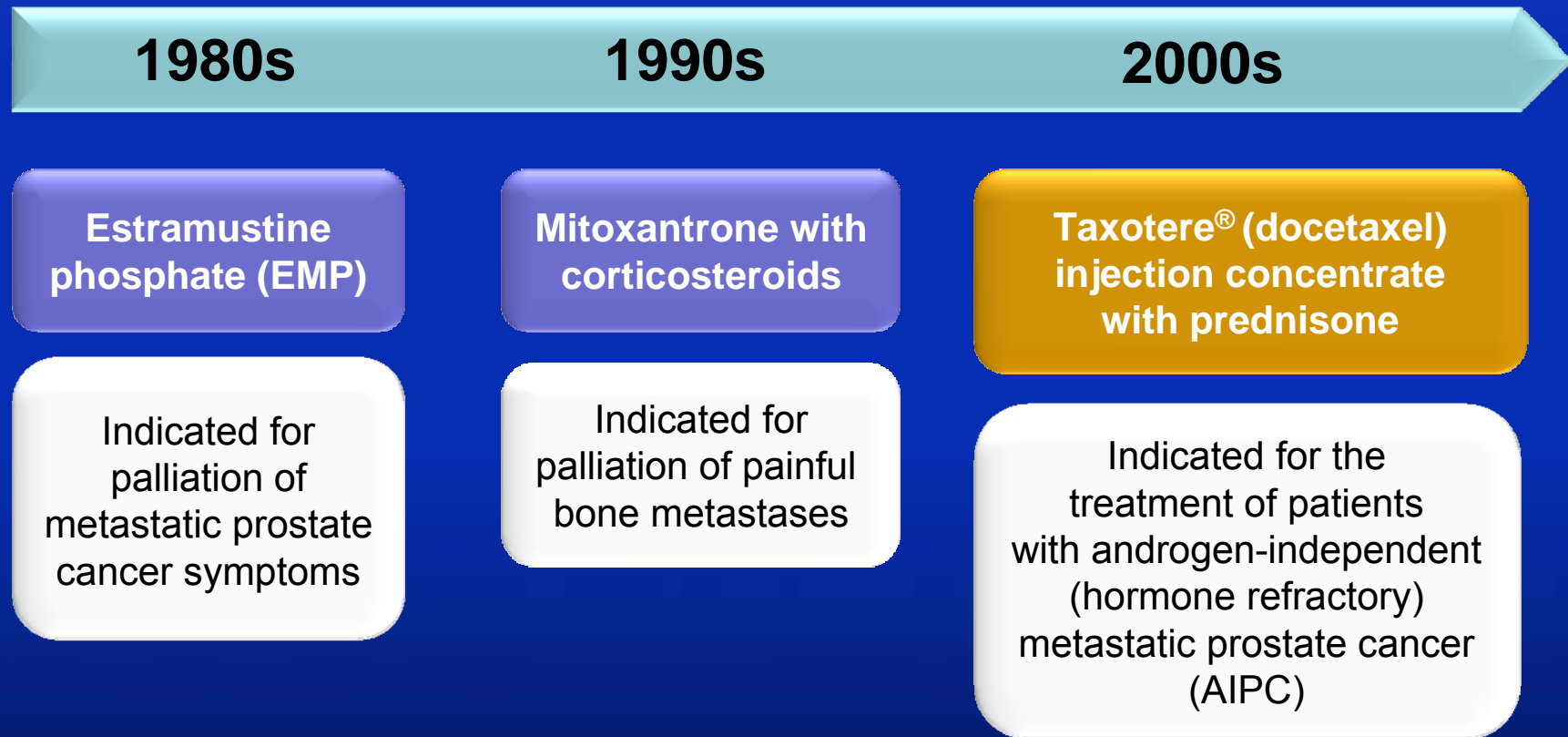
# Multidisciplinary Team (MDT) Approach to Prostate Cancer Management



*An MDT approach offers patients **optimal care** from the **most appropriate specialist** at a given time*

# Chemotherapy in Prostate Cancer

# FDA-Approved Chemotherapy Options for AIPC (HRPC)

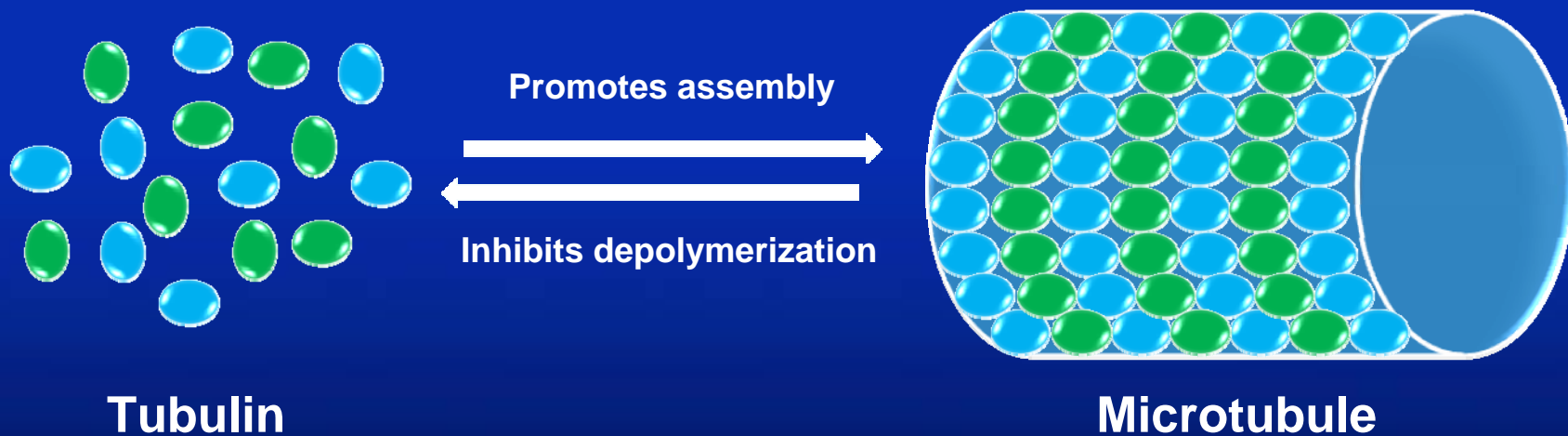


Please see important safety information on slides 40-43 and accompanying full prescribing information including boxed WARNING

# Mechanism of Action

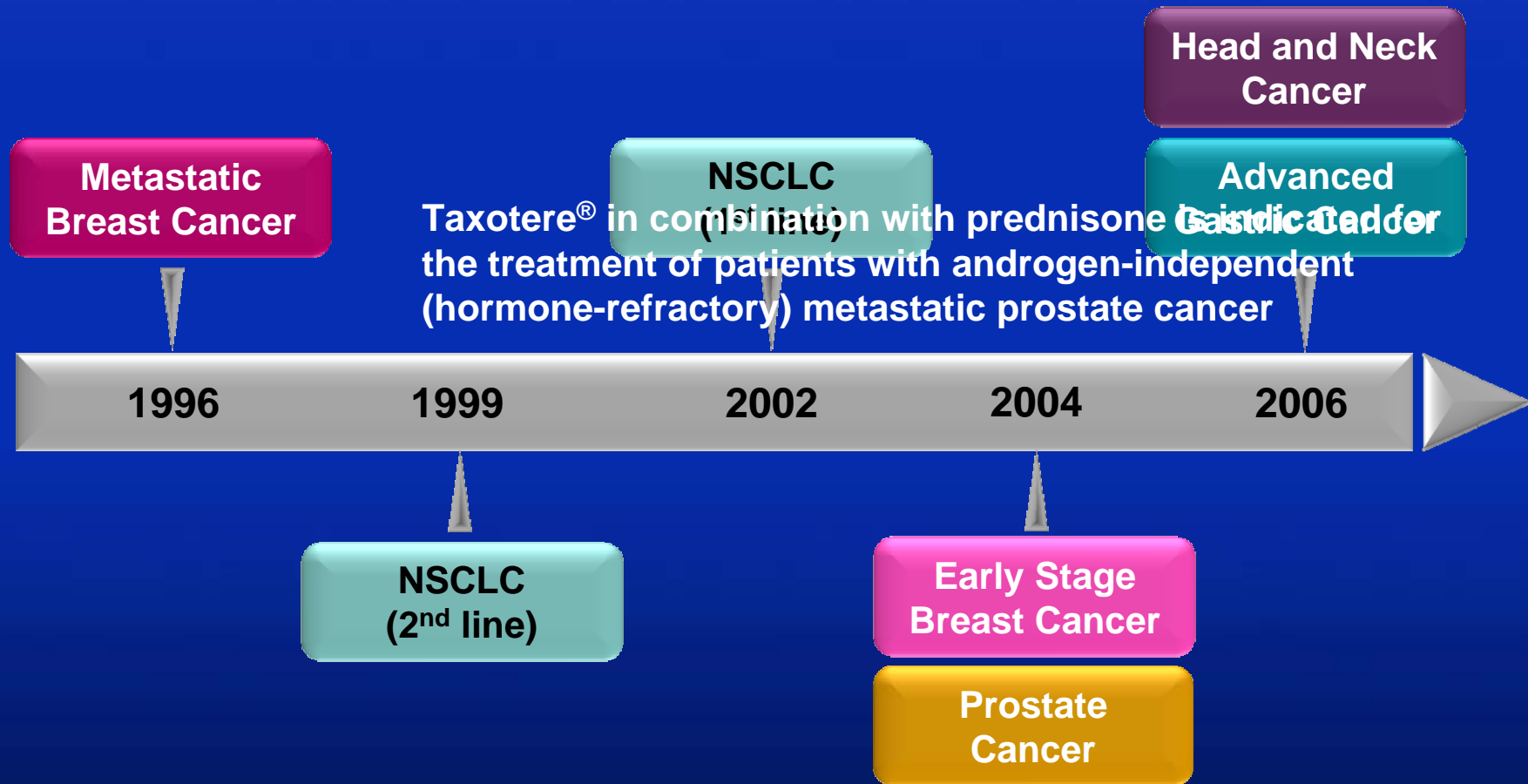
## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

- Disrupts the intracellular microtubular network by binding to free tubulin and promoting its assembly into stable microtubules
- Leads to the production of microtubule bundles without normal function, inhibiting mitosis



# Timeline of FDA Approvals

## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate





# **Taxotere<sup>®</sup> (docetaxel) Injection Concentrate Clinical Studies in Prostate Cancer**

Please see important safety information on slides 40-43 and accompanying full prescribing information including boxed WARNING

# TAX 327: Study Design

## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

- N=1006
- Patients with metastatic AIPC
- Karnofsky performance status  $\geq 60$
- Randomized, multicenter active control trial

R  
A  
N  
D  
O  
M  
I  
Z  
E

Taxotere<sup>®</sup> 75 mg/m<sup>2</sup>  
q3w x 10 cycles  
+ prednisone 5 mg bid  
(n=335)

Taxotere<sup>®</sup> 30 mg/m<sup>2</sup>  
qw for first 5 weeks in a  
6-week cycle for 5 cycles  
+ prednisone 5 mg bid  
(n=334)

Mitoxantrone 12 mg/m<sup>2</sup>  
q3w x 10 cycles  
+ prednisone 5 mg bid  
(n=337)

### Primary endpoint

- Overall survival (OS)

### Secondary endpoints

- Pain response
- 50% PSA decline
- Measurable response
- Quality of life

# TAX 327: Patient Characteristics

## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

	Taxotere <sup>®</sup> q3w (N=335)	Mitoxantrone (N=337)
<b>Median age (range)</b>	<b>68 (42-92)</b>	<b>68 (43-86)</b>
<b>≥ 75 years (%)</b>	<b>20</b>	<b>20</b>
<b>Pain level ≥ PPI 2 or analgesic score (AS) ≥ 10 (%)</b>	<b>45</b>	<b>46</b>
<b>Hormonal manipulations (%)</b>		
1-2	77	75
>2	23	25
<b>Median PSA (ng/mL)</b>	<b>114</b>	<b>123</b>
<b>Bone metastases (%)</b>	<b>90</b>	<b>92</b>
<b>Visceral disease (%)</b>	<b>22</b>	<b>22</b>

*All patients had androgen independent metastatic prostate cancer*

Please see important safety information on slides 40-43 and accompanying full prescribing information including boxed WARNING

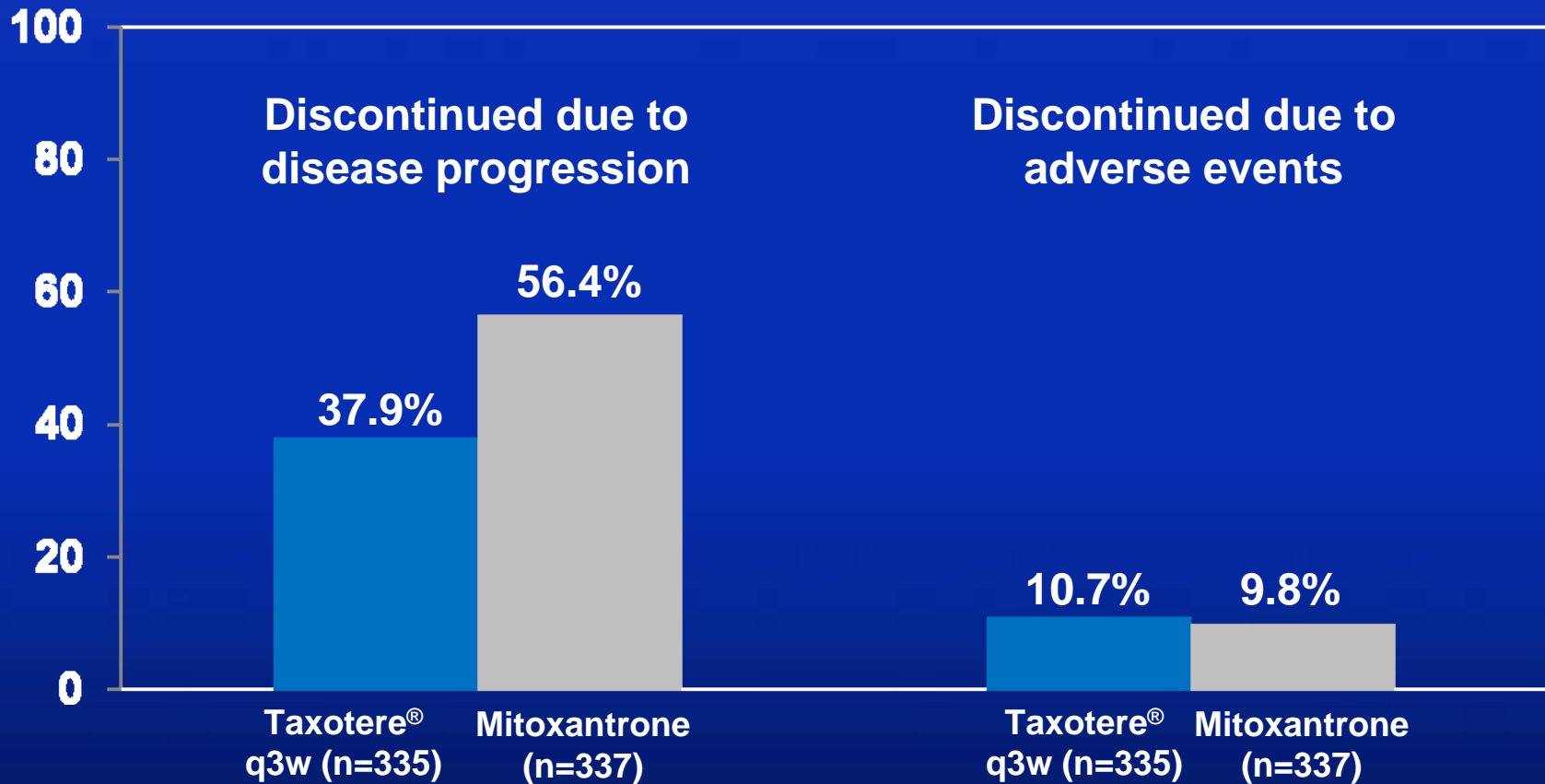
# TAX 327: Treatment

## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

	Taxotere <sup>®</sup> q3w (N=335)	Mitoxantrone (N=337)
<b>Completed treatment (%)</b>	<b>46</b>	<b>25</b>
Median number of cycles	9.5	5.0
<b>Reasons for discontinuation</b>		
Progression (%)	38	56
Adverse reaction (%)	11	10
Withdrawal of consent (%)	1	3
Death	1	2
Other (%)	4	5

# TAX 327: Regimen Tolerability

## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate



Data on file, Aventis Pharmaceuticals, Inc.  
Clinical study report (TAX 327).

Please see important safety information on slides 40-43 and  
accompanying full prescribing information including boxed WARNING

# TAX 327: Selected Adverse Event Profile

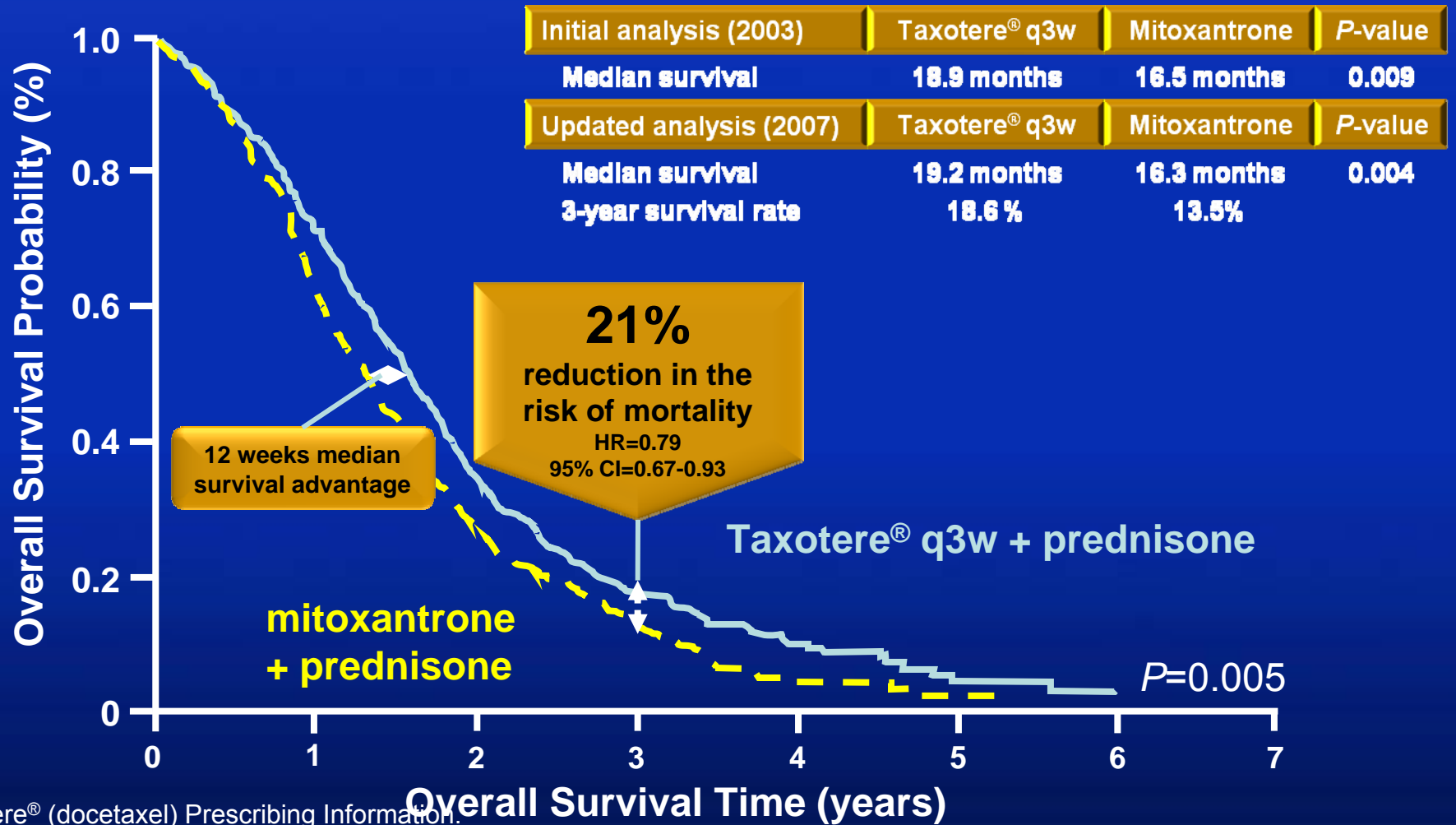
## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

Grade 3-4 Adverse Events*	Taxotere <sup>®</sup> 75 mg/m <sup>2</sup> + prednisone (n=332) %	Mitoxantrone 12 mg/m <sup>2</sup> + prednisone (n=335) %
<b>Neutropenia</b>	<b>32.0</b>	<b>21.7</b>
<b>Febrile neutropenia</b>	<b>2.7</b>	<b>1.8</b>
<b>Infection</b>	<b>5.7</b>	<b>4.2</b>
<b>Anemia</b>	<b>4.9</b>	<b>1.8</b>
<b>Fatigue</b>	<b>4.5</b>	<b>5.1</b>
<b>Nausea</b>	<b>2.7</b>	<b>1.5</b>
<b>Dyspnea</b>	<b>2.7</b>	<b>0.9</b>
<b>Diarrhea</b>	<b>2.1</b>	<b>1.2</b>

*\*Events reported in  $\geq 2\%$  of patients in Taxotere<sup>®</sup> arm*



# Overall Survival Advantage Maintained at 3 Years Taxotere<sup>®</sup> (docetaxel) Injection Concentrate



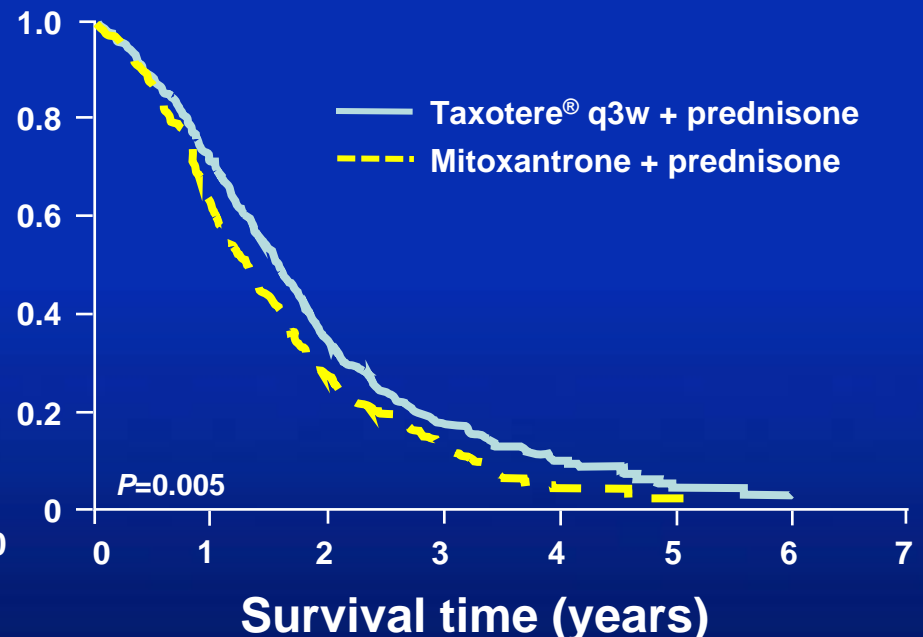
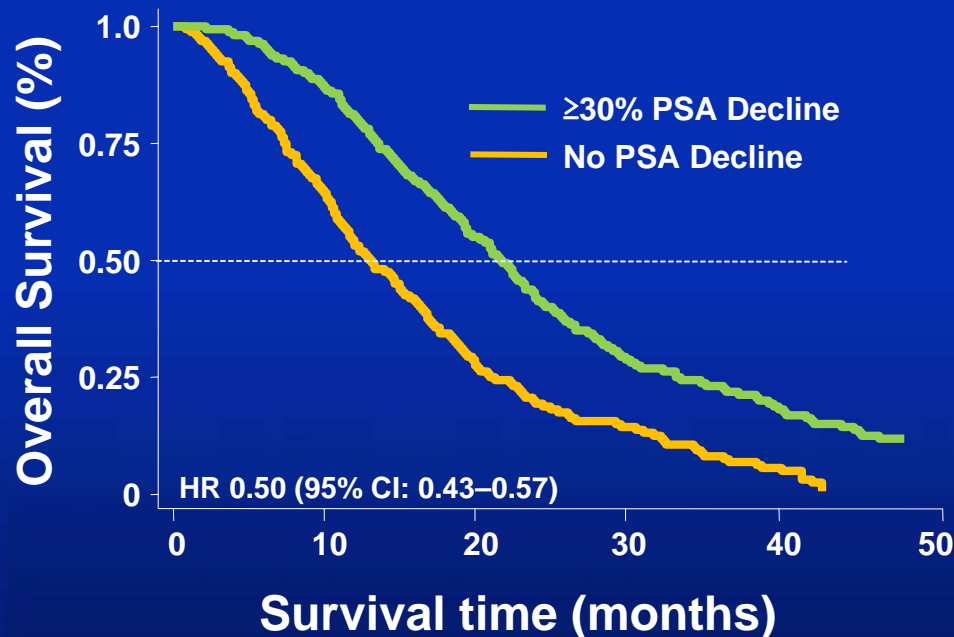
Taxotere<sup>®</sup> (docetaxel) Prescribing Information.  
Bridgewater, NJ: sanofi-aventis U.S. LLC; November 2007.  
Berthold DR, et al. *J Clin Oncol.* 2008;26:242-245.

Please see important safety information on slides 40-43 and accompanying full prescribing information including boxed WARNING

# Overall Survival by 30% PSA Decline

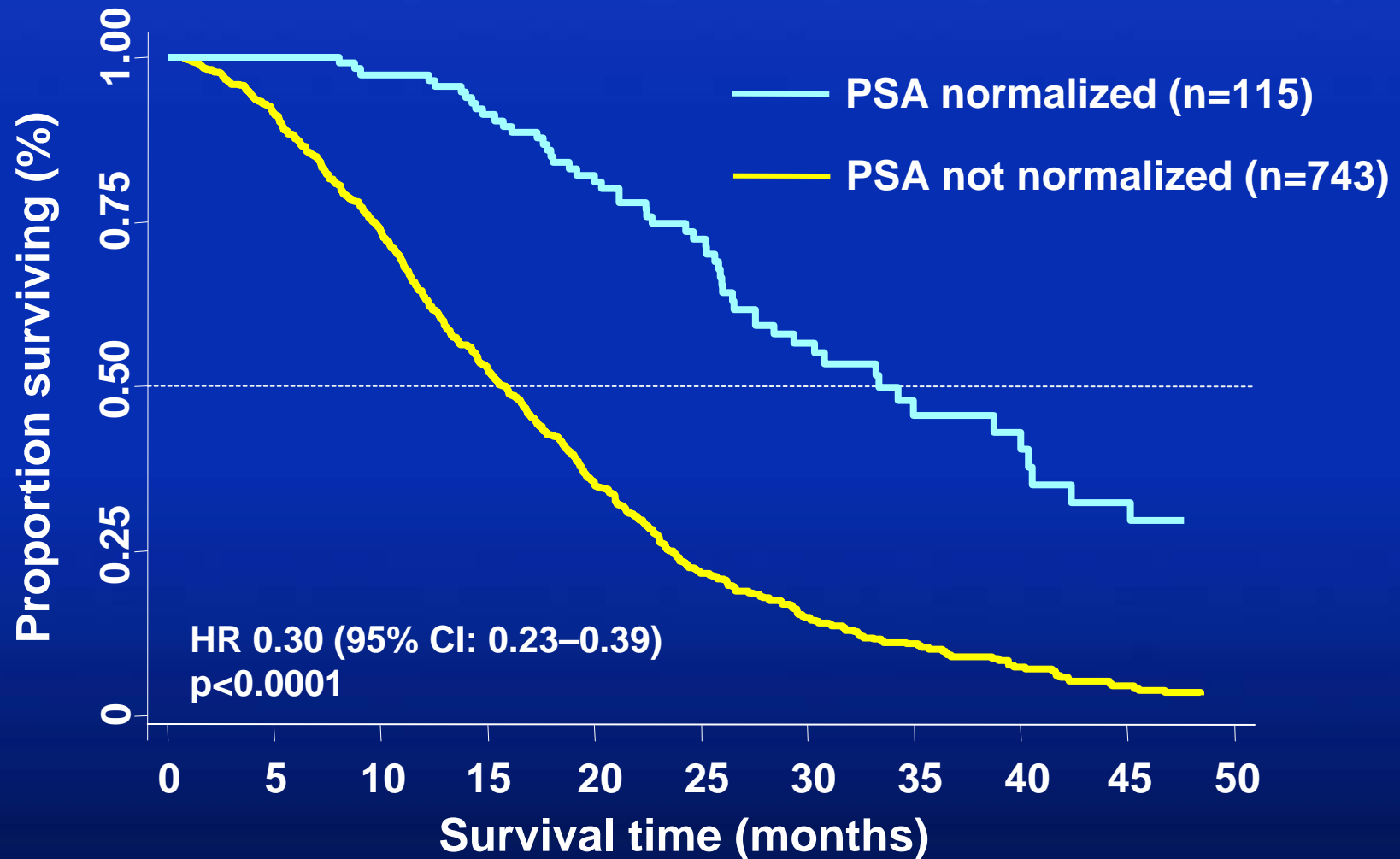
## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

- PSA is a strong surrogate predictor for OS (confirms SWOG 99-16 analysis)
- Two-thirds of patients in TAX 327 had >30% PSA decline within 3 months
- Administration of Taxotere<sup>®</sup> as prescribed is important for overall survival



Adapted from Armstrong AJ, et al. ASCO Prostate 2007; abstract 148. Please see important safety information on slides 40-43 and Berthold DR, et al. *J Clin Oncol*. 2008;26:242-245. accompanying full prescribing information including boxed WARNING

# Overall Survival by PSA Normalization



Adapted from Armstrong AJ, et al.  
ASCO Prostate 2007; abstract 148.

Please see important safety information on slides 40-43 and  
accompanying full prescribing information including boxed WARNING

# What is the Optimal Management for Metastatic CRPC Patients?

- To treat or not to treat?

## Timing

- Do I wait until patients have dramatic symptoms or do I treat a minimally-asymptomatic patient?

## Duration

- If tolerated, do I stop at first PSA rise or treat for 10 cycles (30 weeks) or longer?

# Guideline Recommendations



- Several guidelines recommend Taxotere<sup>®</sup> (docetaxel) Injection Concentrate plus prednisone as chemotherapy for HRPC
  - American Society of Clinical Oncology
  - European Association of Urologists
  - European Society of Medical Oncologists
  - National Comprehensive Cancer Network
  - Society of Urologic Oncology

Loblaw DA, et al. *J Clin Oncol*. 2007;25(12):1596-1605.

Heidenreich A, et al. EAU Guidelines on Prostate Cancer.

Available at: [http://www.uroweb.org/fileadmin/user\\_upload/Guidelines/Prostate%20Cancer.pdf](http://www.uroweb.org/fileadmin/user_upload/Guidelines/Prostate%20Cancer.pdf).

Accessed 22 May 2008.

Kataja V and Bergh J. *Ann Oncol*. 2005;16(Suppl.1):i34-i36.

NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. V1.2008.

Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/prostate.pdf](http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf).

Accessed 21 May 2008.

Chang S, et al. *Cancer*. 2005;103:11-21.

Please see important safety information on slides 40-43 and accompanying full prescribing information including boxed WARNING

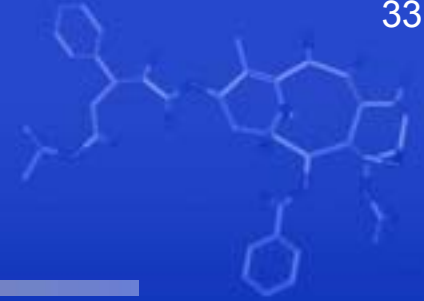
# Dose Adjustments in Prostate Cancer

## Taxotere<sup>®</sup> (docetaxel) Injection Concentrate

Taxotere<sup>®</sup> 75 mg/m<sup>2</sup> IV infusion over 1 hour, administered every 3 weeks  
Prednisone 5 mg orally twice daily is administered continuously

Side Effect	Taxotere <sup>®</sup> Dose Adjustment
<b>Febrile neutropenia, or ANC &lt;500 cells/mm<sup>3</sup> &gt;7 days, or severe/cumulative cutaneous reactions, or moderate neurosensory side effects</b>	
First episode	Reduce dose to 60 mg/m <sup>2</sup>
Second episode	Discontinue

# Case Study



- 68-year-old male
- Presents with locally advanced disease
  - T3N1M0
  - PSA = 9; Gleason 8 (4+4)
  - Pelvic CT reveals positive nodes
  - Bone scan negative
- Patient receives radical prostatectomy
  - Post-op PSA <0.02
- Referred to medical oncologist; declines enrollment in adjuvant study
- Starts treatment with LHRH (plan 2 years)

# Case Study Recap



- 68-year-old male initially presented with locally advanced disease
  - T3N1M0; PSA = 9; Gleason 8 (4+4)
  - Pelvic CT reveals positive nodes
- Received radical prostatectomy (post-op PSA <0.02)
- 2.5 years later (now 70 years old)
  - Castrate resistant
  - PSA 27 with positive bone scan
  - Asymptomatic, but increased fatigue, abnormal alkaline phosphatase and increased LDH

*How would you treat this patient?*

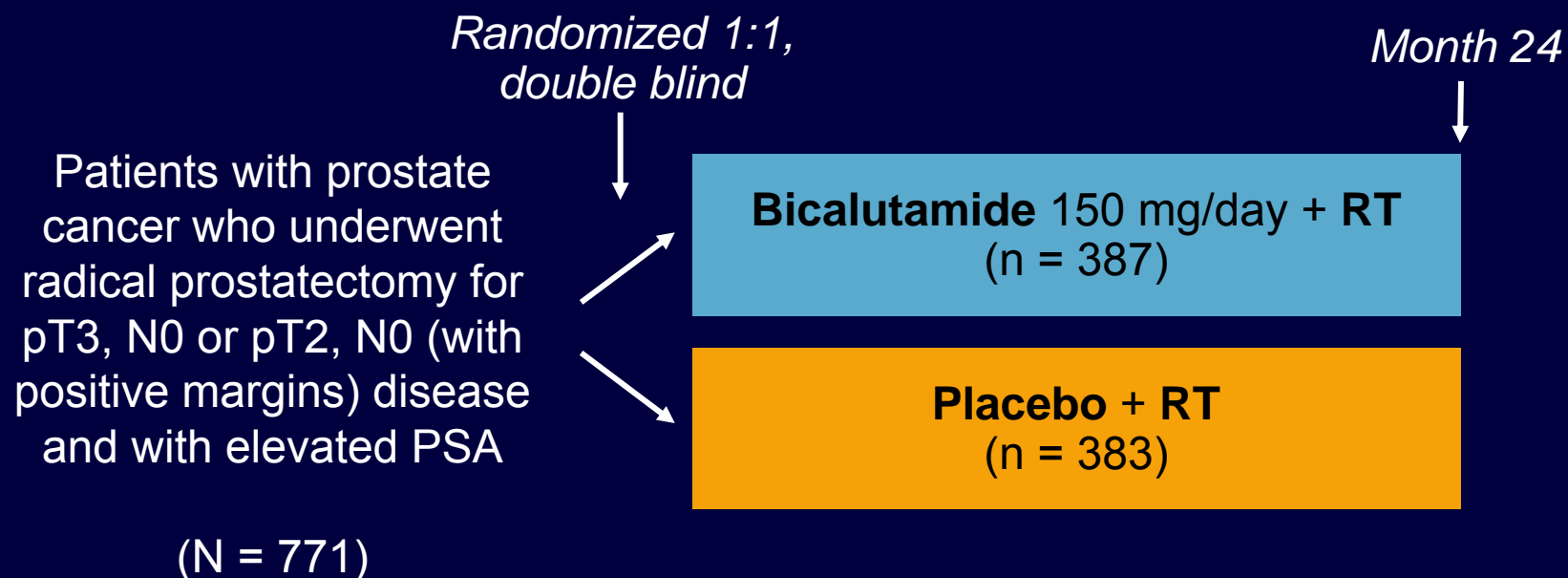
*What if the patient was 85 years old?*

# Case Study (continued)

- Over next 18 months, PSA rises to 0.2 → 0.4 → 1.0
  - Bone scan negative
  - CT negative
  - Bicalutamide added
- 5 months later PSA rises to 6.4
  - Bone scan negative, decrease in BMD
  - Referral to medical oncologist; starts zoledronic acid q6 months
- 6 months later PSA rises to 27
  - Bicalutamide withdrawn; bone scan positive
  - Patient still asymptomatic, but increased fatigue, abnormal alkaline phosphatase and increased LDH

*How would you treat this patient?*

# Addition of Bicalutamide to RT in Pts With Elevated PSA: Phase III RTOG 9601 Study



- Primary endpoint: OS
- Median follow-up: 7.1 yrs

## RTOG 9601: Efficacy

7-Yr Outcome, %	Bicalutamide + RT (n = 387)	Placebo + RT (n = 383)	P Value
OS	91	86	--*
FFP	57	40	< .0001
▪ GS < 7	63	50	< .02
▪ GS 7	55	39	< .0006
▪ GS 8-10	56	26	< .0008
Metastatic PC	7	13	.041

\*Too few primary endpoints occurred to allow statistical comparison of OS between groups.

## RTOG 9601: Adverse Events

Late Grade 3/4 Toxicity, %	Bicalutamide + RT (n = 387)	Placebo + RT (n = 383)
Bladder	6	5
Cardiac	3	2
Bowel	2	1

- Gynecomastia (mostly grade 1/2) differed significantly
  - 86% with bicalutamide vs 15% with placebo
- Liver toxicity with bicalutamide did not exceed grade 3
  - Occurred in 3 patients

# Intermittent vs Continuous Androgen Suppression: Phase III Noninferiority Study

Patients who underwent radical RT (initial or salvage) for localized prostate cancer and who had rising PSA > 3.0 ng/mL after > 1 yr

(N = 1386)

**Intermittent Androgen Suppression\***

(n = 690)

*Stratified by time since radical RT, initial PSA, previous radical prostatectomy, and previous ADT*

**Continuous Androgen Deprivation**

(n = 696)

\*Delivered in 8-mo cycles; restarted when PSA > 10 ng/mL off treatment.

- Primary endpoint: OS
- Secondary endpoints: time to hormone-refractory state, QoL, lipid levels, duration of treatment/nontreatment intervals, time to testosterone and potency recovery

# Intermittent vs Continuous Androgen Suppression: Results

- Median follow-up: 6.9 yrs
- IAS patients received median of two 8-month cycles (range: 1-9)
- IAS noninferior to CAD by statistical criteria
  - OS HR: 1.02 (95% CI: 0.86-1.21)
  - *P* for noninferiority (HR  $\geq$  1.25) = .009
- Time to hormone-refractory state improved with IAS vs CAD
  - HR: 0.80 (95% CI: 0.67-0.98; *P* = .024)

Outcome	IAS (n = 690)	CAD (n = 696)
Median OS, yrs	8.8	9.1
Deaths, n	268	256
▪ Disease related	122	97
▪ Unrelated	134	146

- No difference in AEs between arms, except for fewer hot flashes with IAS
  - Includes similar incidence of myocardial events and osteoporotic fractures

# Addition of Docetaxel to ADT in Pts With Metastatic PC: Phase III GETUG 15 Study<sup>[1]</sup>

*Stratified by previous systemic therapy,  
Glass risk group<sup>[2]</sup>*

Patients with hormone-naive metastatic prostate cancer and ECOG performance score 0-2

(N = 385)



**Docetaxel 75 mg/m<sup>2</sup> Q3W for 9 cycles + ADT\***  
(n = 192)

**ADT\***  
(n = 193)

\*ADT: LHRH agonist, maximum androgen blockade, or orchiectomy

- Primary endpoint: 3-yr OS
- Secondary endpoints: biological and clinical PFS, QoL, toxicity

1. Gravis G, et al. ASCO GU 2011. Abstract 10.

2. Glass TR, et al. J Urol. 2003;169:164-169.

## GETUG 15: Efficacy

- OS data not yet mature
- PSA response and progression outcomes favored addition of docetaxel to ADT

Outcome, %	Docetaxel + ADT (n = 192)	ADT (n = 193)	P Value
PSA response (decrease $\geq$ 50%)			
▪ Month 3	91	80	.008
▪ Month 6	95	86	.01
PSA progression (increase $\geq$ 25%)			
▪ Month 3	3	8	.08
▪ Month 6	1	10	.002

# Robotic-Assisted Laparoscopic Prostatectomy: Surgical Learning Curve

- Retrospective, multicenter cohort study of patients undergoing RALP between 2003 and 2009 by 3 surgeons from 3 centers
  - Mean overall PSM rate and mean overall OT calculated for every 50 RALPs per surgeon
  - Learning curves fit for these means
- Large number of cases needed to minimize PSM rate and OT
  - 1600 cases needed to attain PSM rate < 10%
    - Learning curve plateaued after 1000-1500 cases when only pT3 patients evaluated
  - Mean OT plateaued after 750 cases
- Findings suggest RALP should be performed by high-volume surgeons to optimize patient outcomes

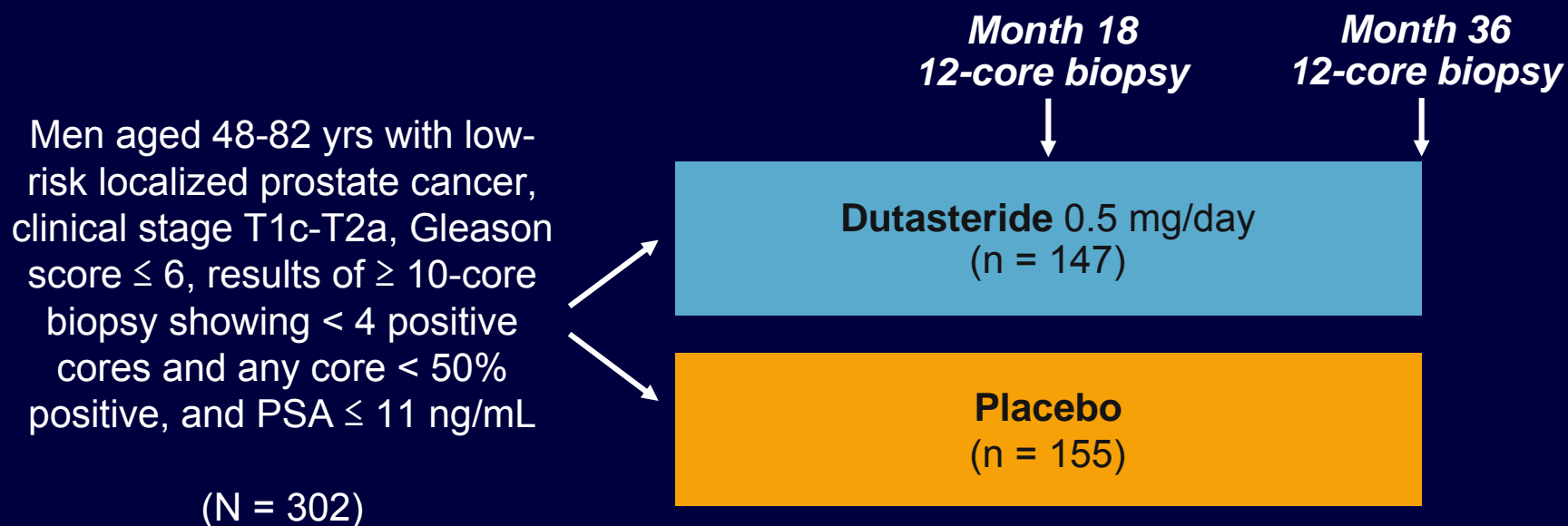
## Quantitative Gene Expression: Correlation With Clinical Recurrence After RP

- Observational study to determine whether tumor-derived gene expression profiling predicts for clinical recurrence after RP
- Cohort included 501 patients with T1/T2 prostate cancer treated with RP at Cleveland Clinic from 1987-2004
  - 127 patients with clinical recurrence after RP
  - 374 patients without clinical recurrence after RP
- Each patient had 2 separate tumor specimens sampled that included primary Gleason pattern and highest Gleason pattern
- RT-PCR used to quantify 732 cancer-related and reference genes
- Clinical recurrence-free interval analyzed with Cox regression analysis

## Quantitative Gene Expression: Correlation With Clinical Recurrence After RP

- Tumor samples from 441 patients evaluable
  - Median follow-up: 5.8 yrs
- Factors associated with cRFI ( $P < .05$ ): surgical Gleason pattern, biopsy Gleason pattern, pathological T stage, clinical T stage, baseline PSA level, yr of surgery
- 295 and 297 genes significantly associated with primary Gleason pattern and highest Gleason pattern, respectively ( $P < .05$ )
  - 235 genes associated with cRFI in both specimens
- 289 genes remained significantly associated with cRFI after multivariate analysis adjusted for AUA risk group
- Data can be used to develop biopsy-based assay that differentiates indolent vs aggressive disease

# REDEEM: Dutasteride in Active Surveillance



- Primary endpoint: TTP
  - Defined as earliest of either pathological progression (Gleason pattern  $\geq 4$ ,  $\geq 4$  positive cores, or any core  $> 50\%$  positive) or therapeutic progression (radical prostatectomy, radiation therapy, or hormonal therapy)

## REDEEM: Results

- Dutasteride reduced 3-yr TTP by 38.9% (95% CI: 12.4%-57.4%;  $P = .007$ )

Outcome at Year 3 or Based on Final Biopsy, %	Dutasteride (n = 147)	Placebo (n = 155)
Disease progression	38	49
▪ Pathologic	31	38
▪ Therapeutic	7	13
Gleason score		
▪ No cancer detected	36	23
▪ No change (Gleason score $\leq 6$ )	51	61
▪ Progression (Gleason score 7 or 8)	14	16

- Dutasteride significantly reduced disease-related anxiety by Year 3 ( $P = .036$ )
- Dutasteride-related AEs similar to those previously reported; incidence of AEs comparable to placebo

## New FDA Approved Treatment Modalities

- Provenge: Sipuleucel-T
- Autologous cellular immunotherapy indicated for asymptomatic or minimally symptomatic metastatic prostate cancer that is resistant to hormonal therapy.
- Jevtana:
- Abiraterone



**Q&A**