Prostate Cancer

Gurkamal Chatta, MD
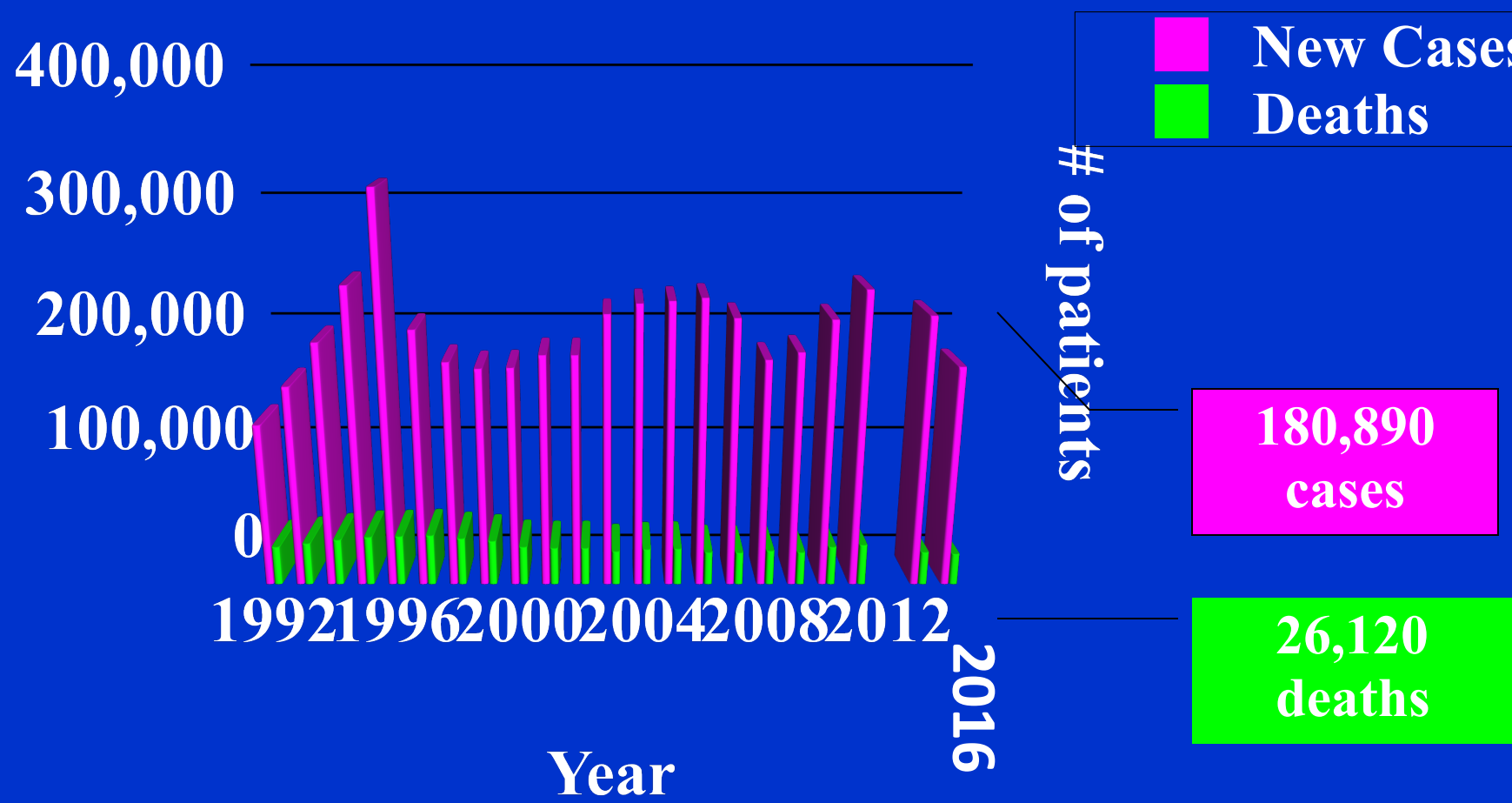
Professor of Oncology

Chief, GU Oncology

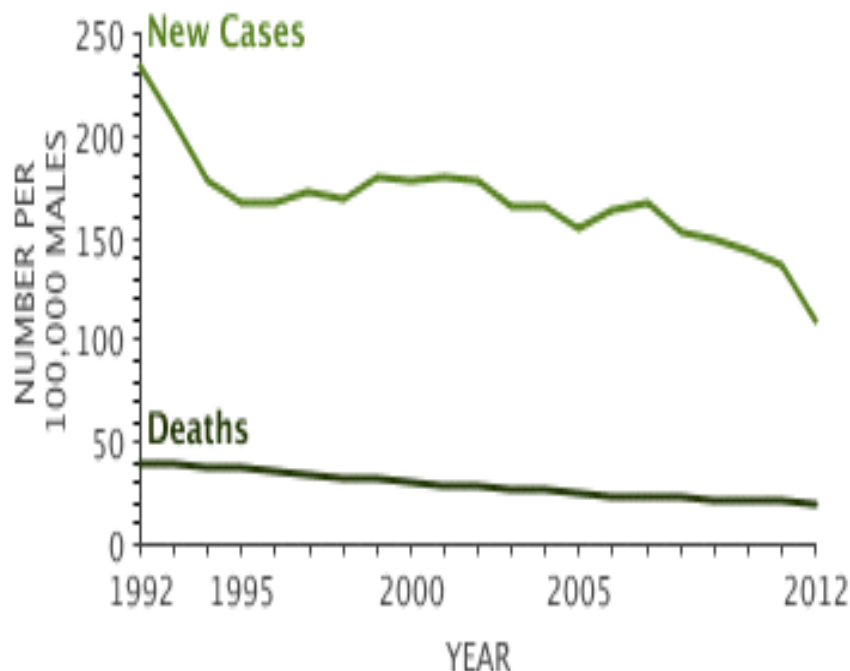Roswell Park Cancer Institute

GOALS

- Epidemiology, Screening and Prevention

- Risk Stratification

- Treatment of Early and High Risk Disease

- Hormonal Therapy

- Treatment of Advanced Disease

Estimated New Cases in 2015	220,800
% of All New Cancer Cases	13.3%
Estimated Deaths in 2015	27,540
% of All Cancer Deaths	4.7%

Percent Surviving 5 Years
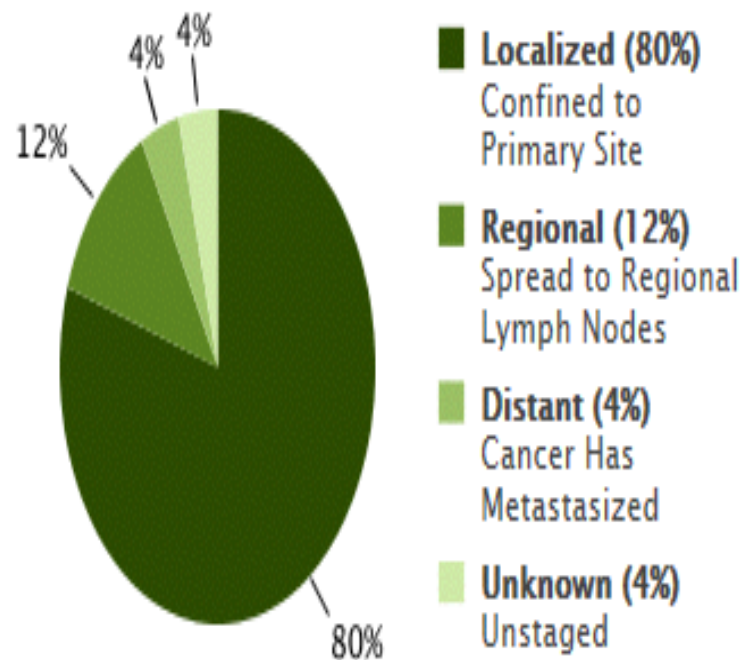
98.9%

2005–2011

Number of New Cases and Deaths per 100,000: The number of new cases of prostate cancer was 137.9 per 100,000 men per year. The number of deaths was 21.4 per 100,000 men per year. These rates are age-adjusted and based on 2008–2012 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 14.0 percent of men will be diagnosed with prostate cancer at some point during their lifetime, based on 2010–2012 data.
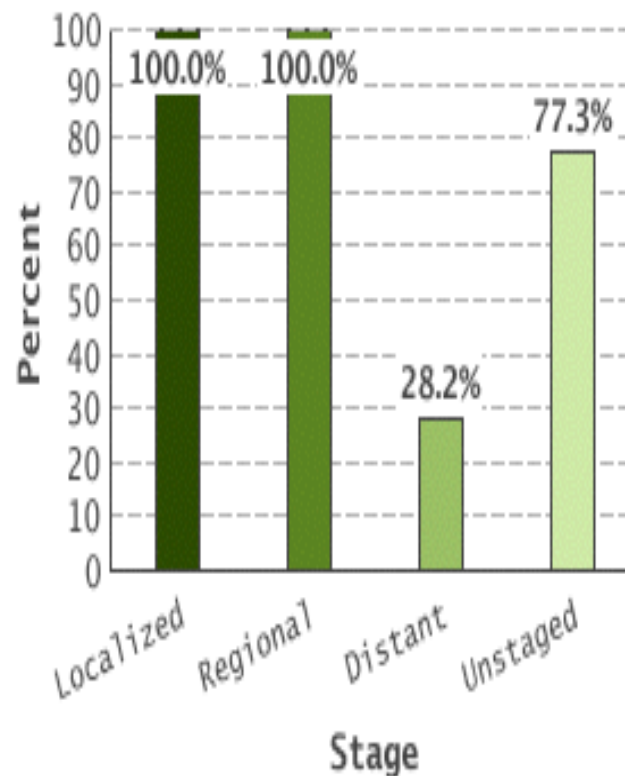
Prevalence of This Cancer: In 2012, there were an estimated 2,795,592 men living with prostate cancer in the United States.

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Prostate Cancer

Percent of Cases by Stage

- **Localized (80%)** Confined to Primary Site
- **Regional (12%)** Spread to Regional Lymph Nodes
- **Distant (4%)** Cancer Has Metastasized
- **Unknown (4%)** Unstaged

5-Year Relative Survival

- Localized: 100.0%
- Regional: 100.0%
- Distant: 28.2%
- Unstaged: 77.3%
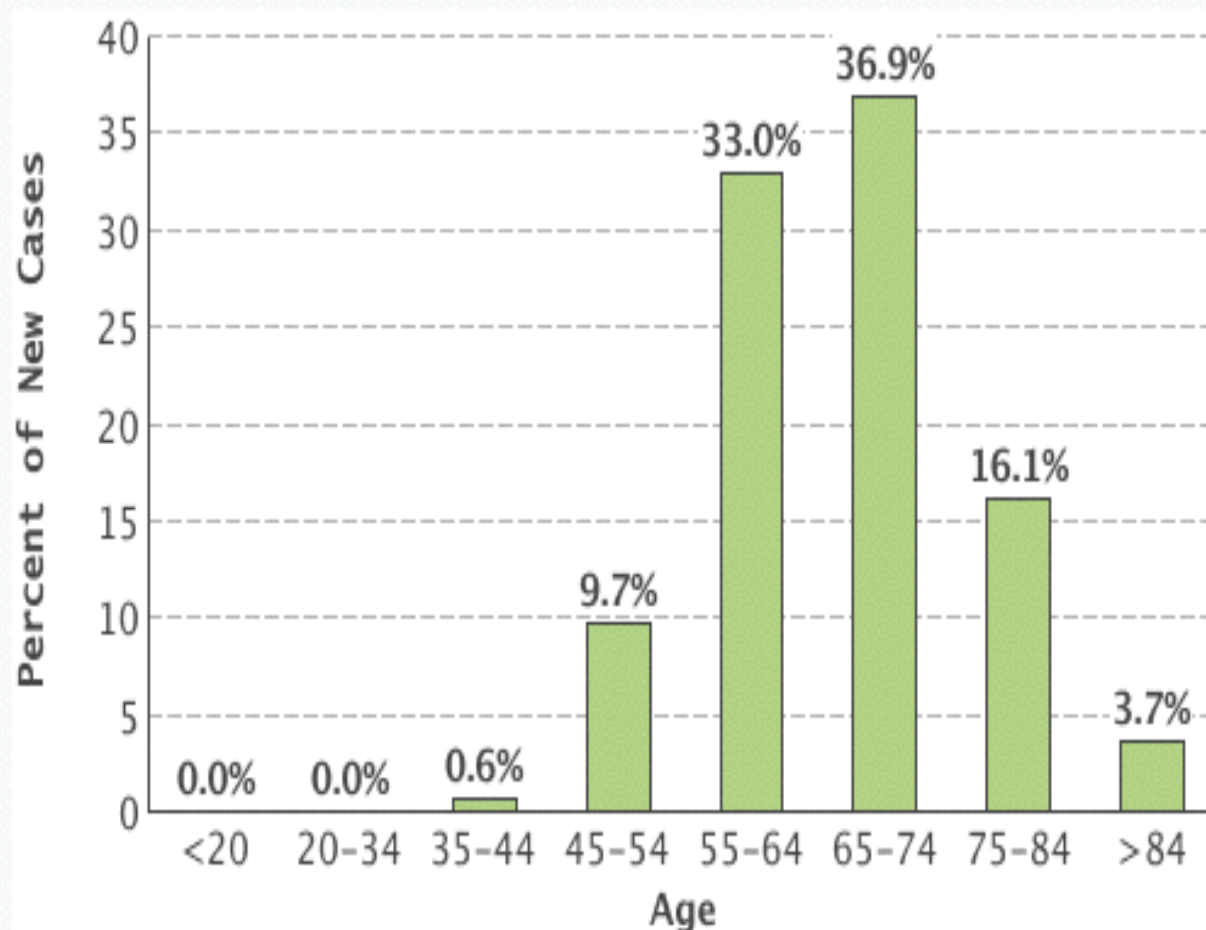
Risk Factors

- Male Gender
- Aging
- Race and Ethnic Background
- Dietary Factors
- Androgen levels
- Genetic Factors

Percent of New Cases by Age Group: Prostate Cancer
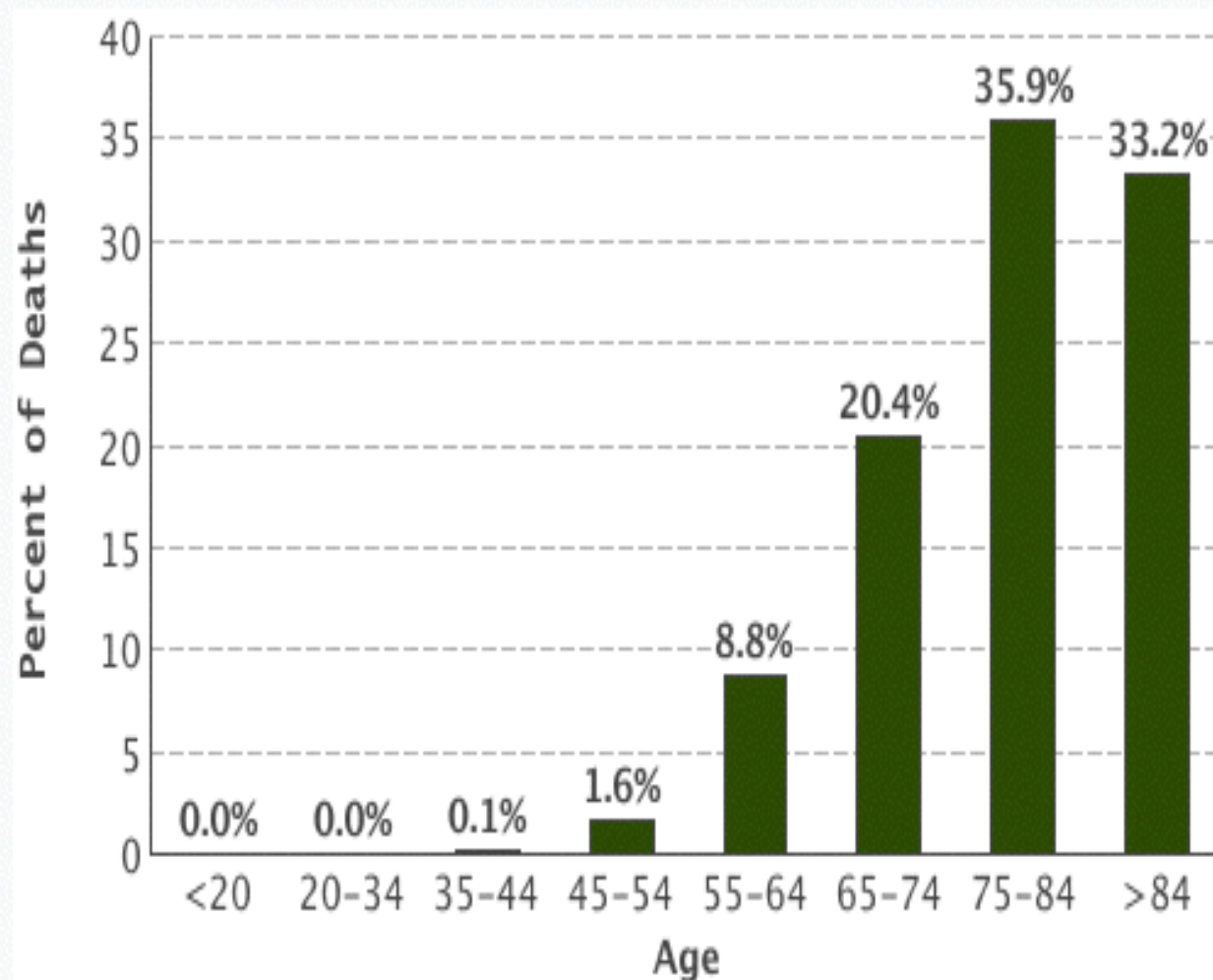

Prostate cancer is most frequently diagnosed among men aged 65–74.

Median Age At Diagnosis

66

SEER 18 2008–2012, All Races, Males

Percent of Deaths by Age Group: Prostate Cancer

U.S. 2008–2012, All Races, Males

Number of New Cases per 100,000 Persons by Race/Ethnicity: Prostate Cancer

MALE

		FEMALE
137.9	All Races	*Sex–Specific Cancer*
130.4	White	
214.5	Black	
74.0	Asian / Pacific Islander	
67.1	American Indian / Alaska Native	
114.7	Hispanic	
141.5	Non–Hispanic	
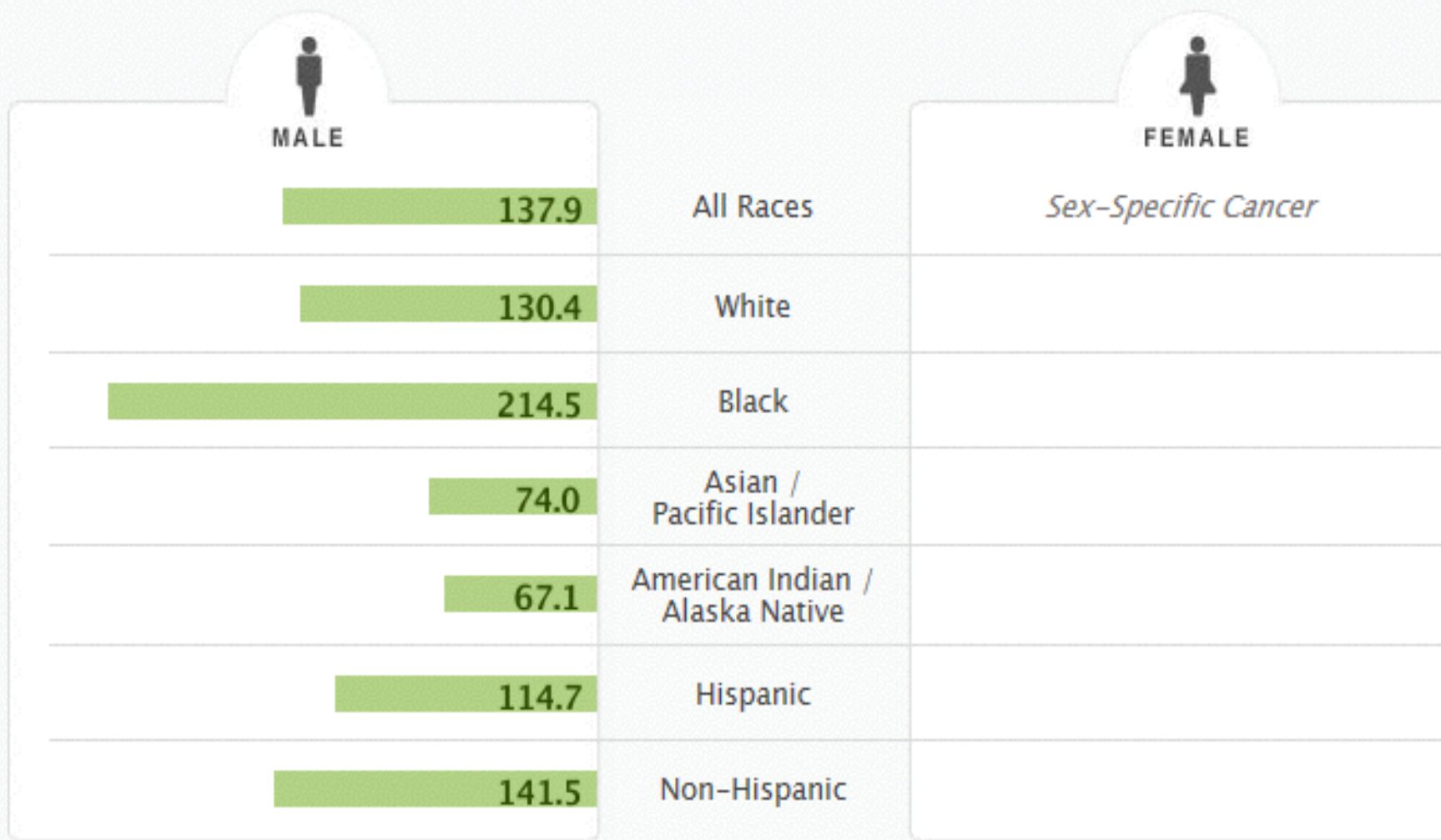
SEER 18 2008–2012, Age-Adjusted

Number of Deaths per 100,000 Persons by Race/Ethnicity: Prostate Cancer

MALE

	Race/Ethnicity	FEMALE
		Sex–Specific Cancer
21.4	All Races	
19.8	White	
46.3	Black	
9.4	Asian / Pacific Islander	
20.2	American Indian / Alaska Native	
17.8	Hispanic	
21.7	Non-Hispanic	
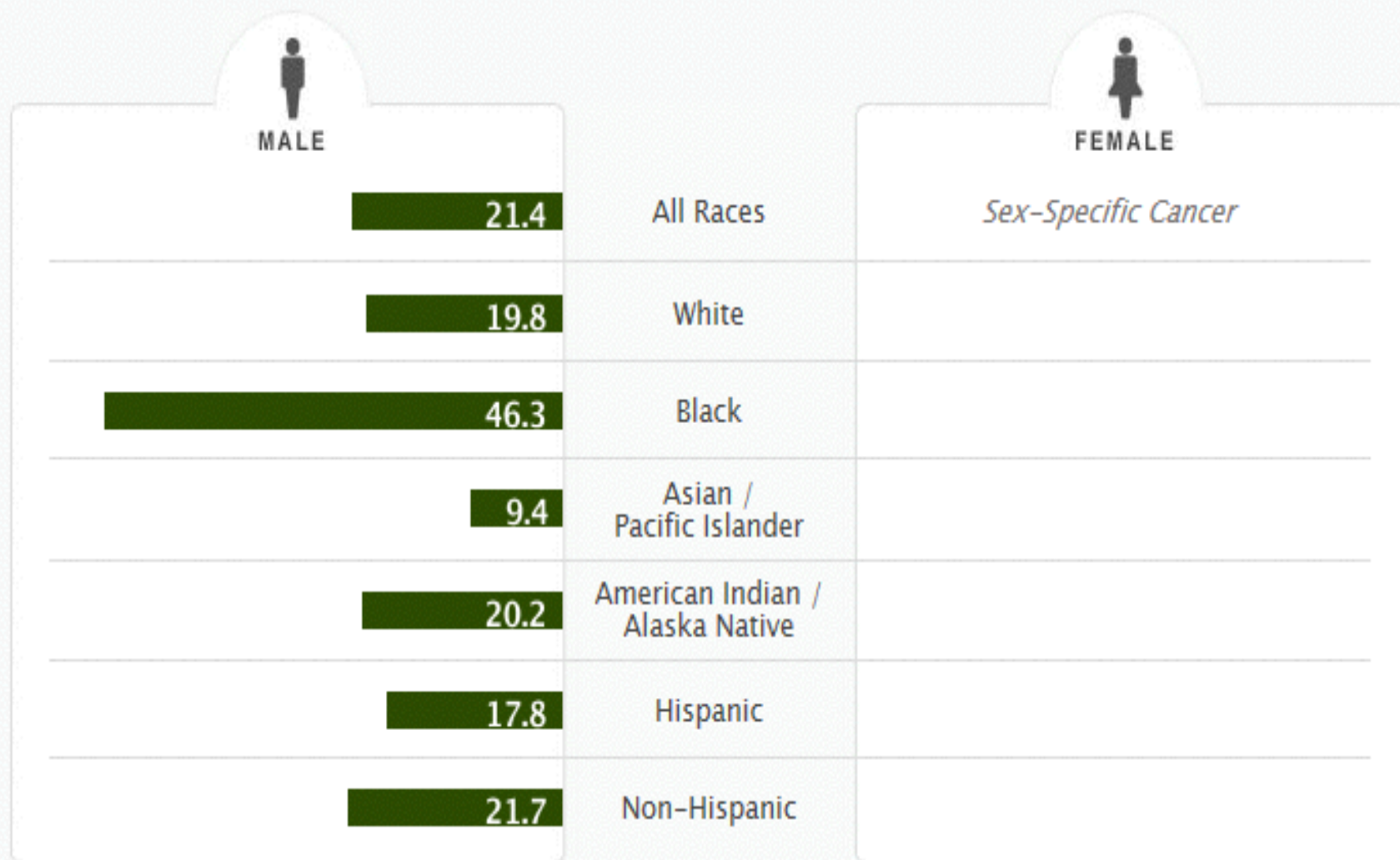
U.S. 2008–2012, Age-Adjusted
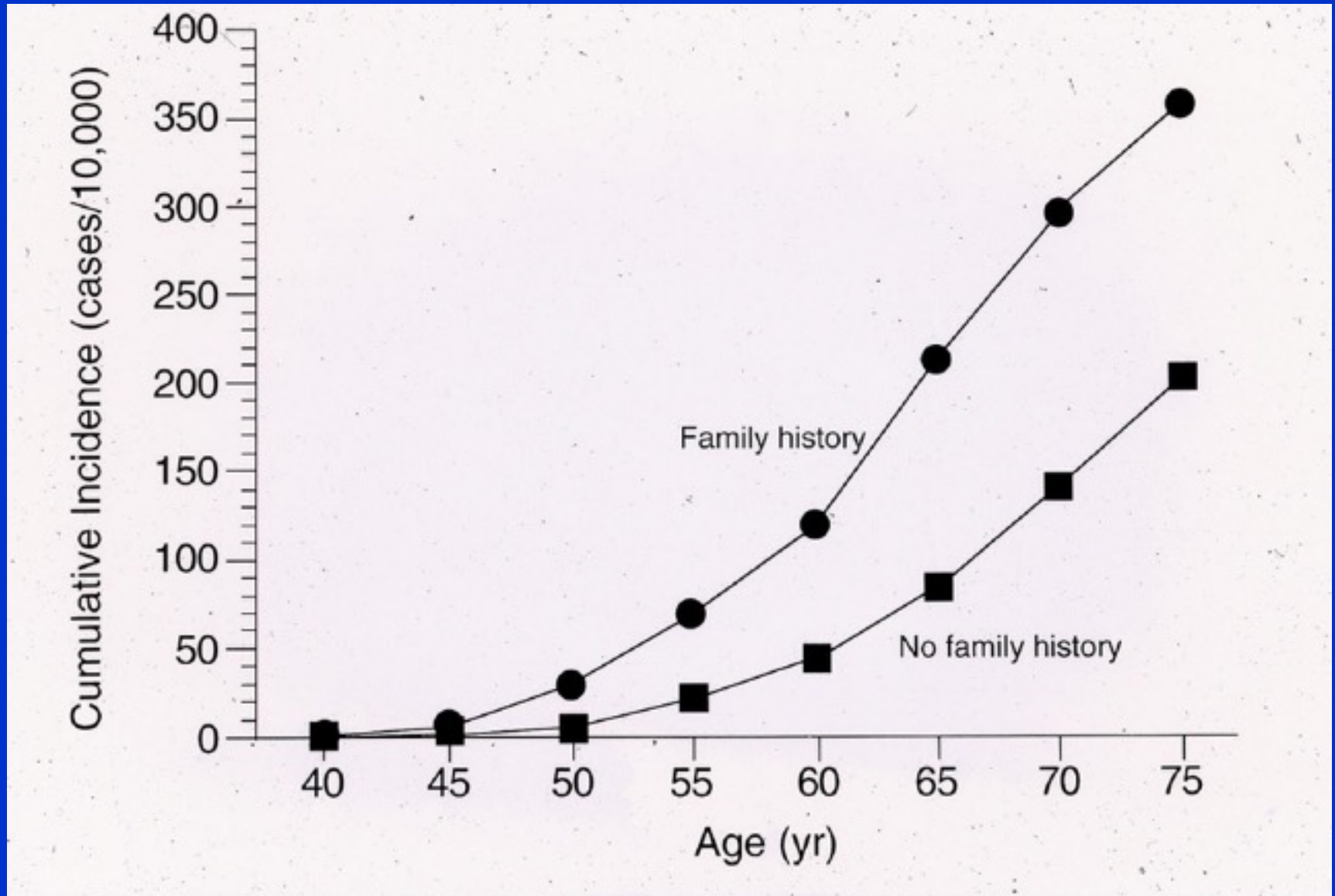
Dietary Factors

- **Increase Risk**
  - Fat

- **Decrease Risk**
  - Soy (isoflavones)
  - Vitamin E
  - Selenium
  - Vitamin D
  - Lycopene
  - Lipid lowering drugs including statins
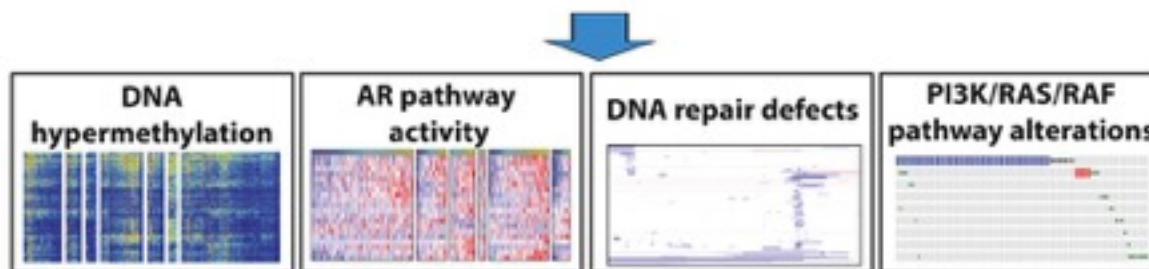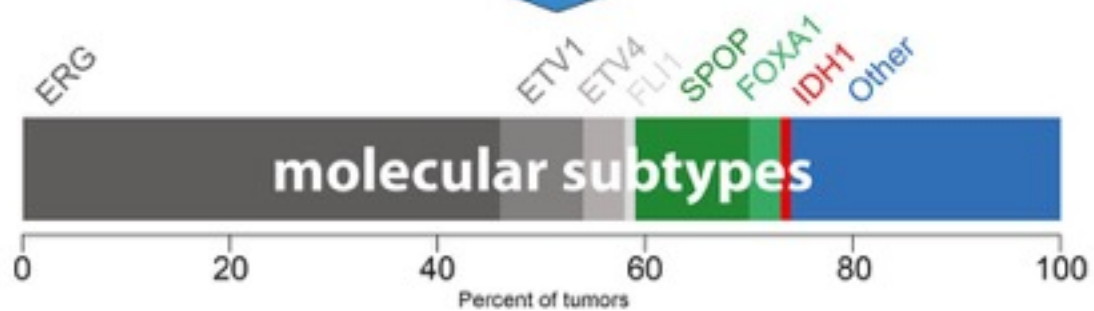
Risk as a Function of Family History

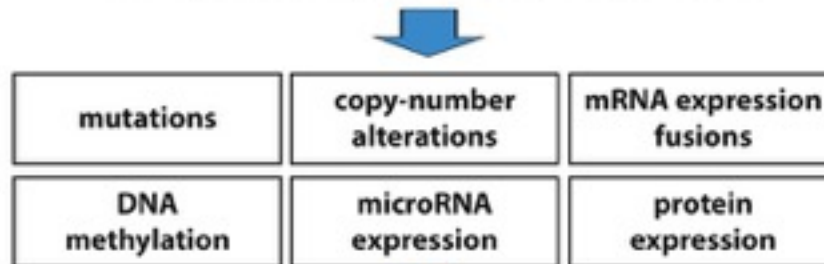# Familial Prostate Cancer Genes and Gene Regions

- 8q24 (MYC gene promoter region)

- Over 30 SNPs associated slight increased risk (HR1.1-1.5)

Molecular Pathways Relevant in Prostate Cancer

- **Androgen Receptor Signaling**
- **IGF-1/PTEN Pathway**
- **ETS Activation**
  - **Prostate cancers are predominated by genetic rearrangements. Point mutations appear less frequently than other malignancies**

333 primary prostate carcinomas – 74% associated with a molecular abnormality

Seven subtypes defined by ETS fusions or mutations in SPOP, FOXA1, and IDH1

Substantial epigenetic heterogeneity, including a hypermethylated IDH1 mutant subset

Presumed actionable lesions in the PI3K, MAPK, and DNA repair pathways
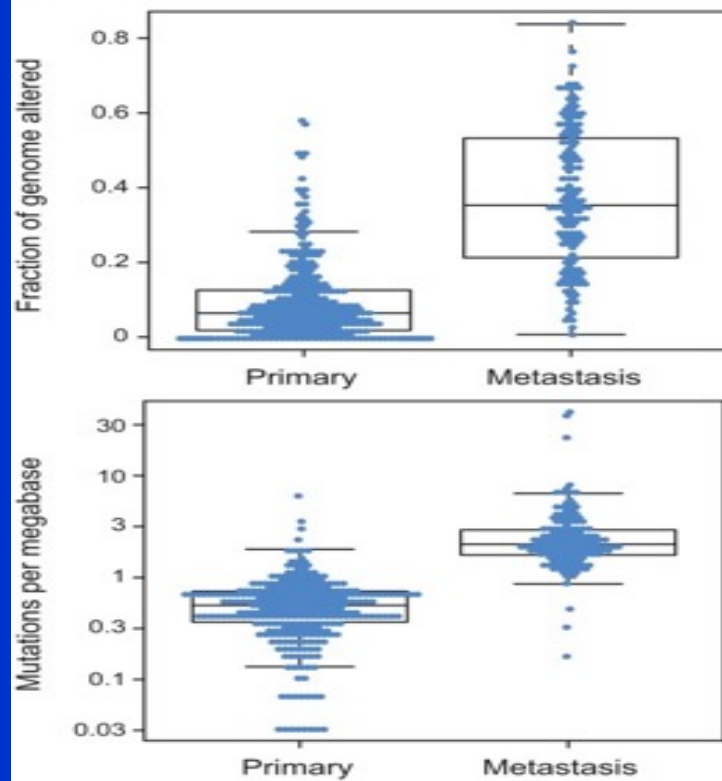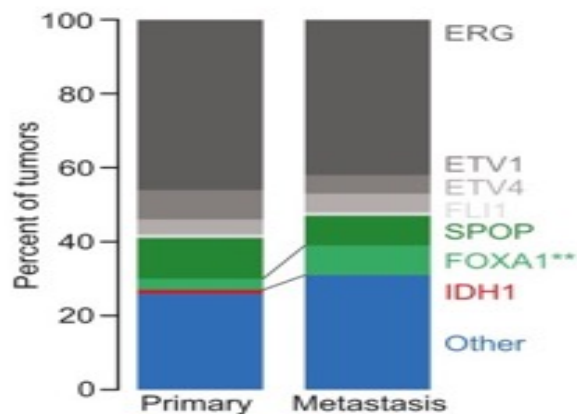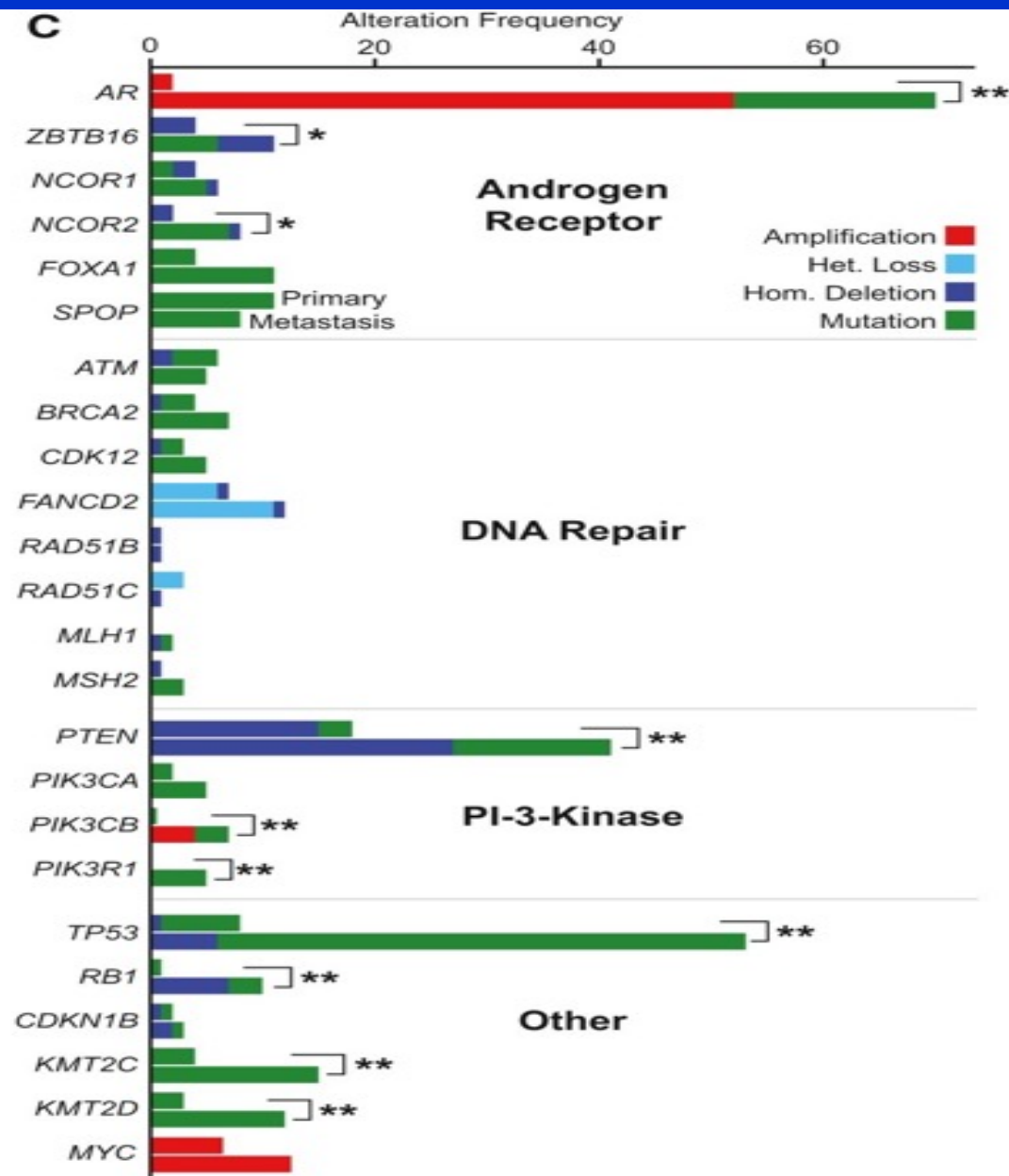
Chemoprevention

5 alpha reductase inhibitors for prostate cancer prevention

Finasteride Chemoprevention Study (PCPT)

18,000 Men>55 nl DRE and PSA<3

finasteride → CaP

placebo → CaP

PCPT-Conclusions

- Finasteride reduces risk of prostate cancer by 25%
- Morbidity is minimal-high in placebo arm
- 20% more Gleason 8-10
  - Possibly explained by a pathologic artifact

REDUCE Trial

- 8,200 men who had PSA between 2.5 ng/mL and 10 ng/mL (50 to 59 years old) or between 3.0 ng/mL and 10 ng/mL (60 to 75 years old) at initial screening

- All men had one negative prostate biopsy within six months prior to study entry

- Participants were randomly assigned to dutasteride or placebo; the study mandated 10 core biopsies at two and four years

- **Dutasteride was associated with a 23% reduction in prostate cancer cases compared with placebo**

- Dutasteride statistically did not increase the prevalence of high-grade disease

Chemoprevention

5 ARIs reduce risk of prostate cancer but long term effects are not yet known

- FDA has chosen not to approve
- Long term effect on survival and toxicity?

Does PSA based Screening Reduce Mortality?

- PLCO
- ERSPC study
- Göteborg study

Randomized Screening Studies for Prostate Cancer

- PLCO (NEJM 2009)
  - 150,000 men
  - 52% contamination
  - Median follow-up of 7 years
  - **No difference in prostate cancer mortality**
- European Screening Study (NEJM 2009)
  - 162,243 men
  - Median follow up of 9 years
  - **20% reduction in prostate cancer mortality p=0.04**
  - **NNT- 48 needed to be treated to prevent 1 death**
- Göteborg screening trial (Lancet Oncology 2010)
  - 20,000 men
  - Median follow-up of 14 years
  - **44% reduction in prostate cancer mortality (p=0.0002).**
  - **NNT-12 needed to be treated to prevent 1 death**

Conclusions

- Low mortality of prostate cancer in first 10 years (few events)

- PSA screening probably reduces mortality but longer follow-up needed

- Apparent large amount of over-diagnosis and overtreatment (at least as seen in first 10 years)

Impact of USPTF on Screening

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

National Prostate Cancer Screening Rates After the 2012 US Preventive Services Task Force Recommendation Discouraging Prostate-Specific Antigen–Based Screening

Michael W. Drazer, Dezheng Huo, and Scott E. Eggener

Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Decrease in screening
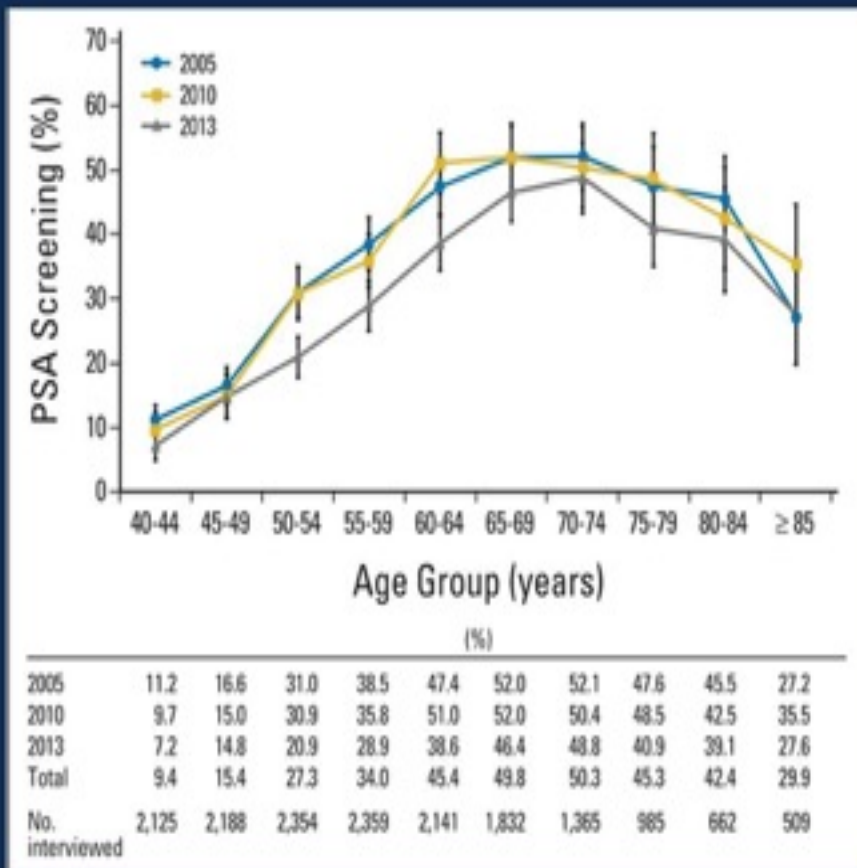
- Decrease in screening accross age groups
- 1/3 of men older than age 65 years with a high probability of death within the next 9 years were screened
- 1.4 million men at high risk of overdiagnosis and overtreatment.

Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Diagnosis Suspected

- Abnormal PSA
- Abnormal DRE
- CaP detected on TURP

T1

T2

T3

T4
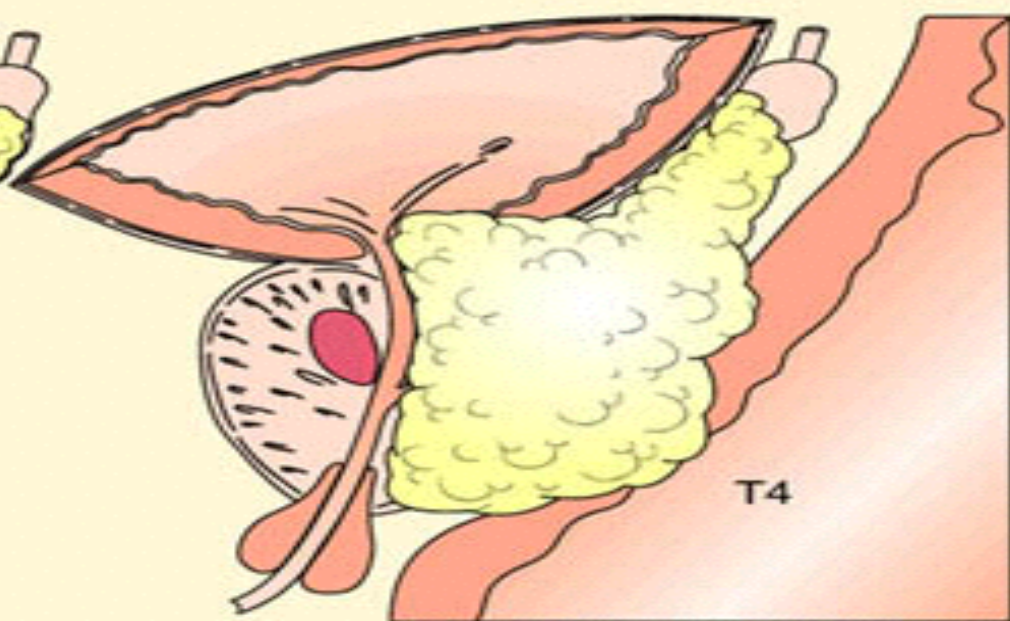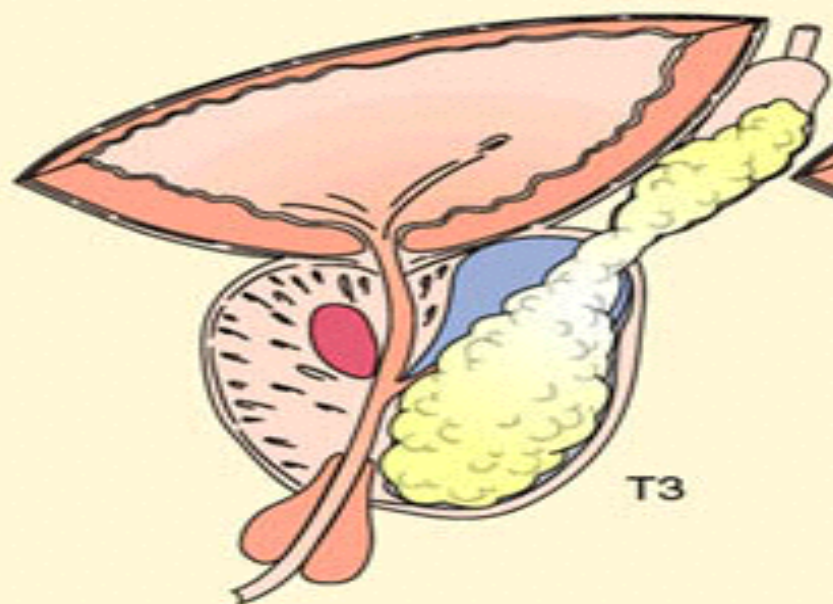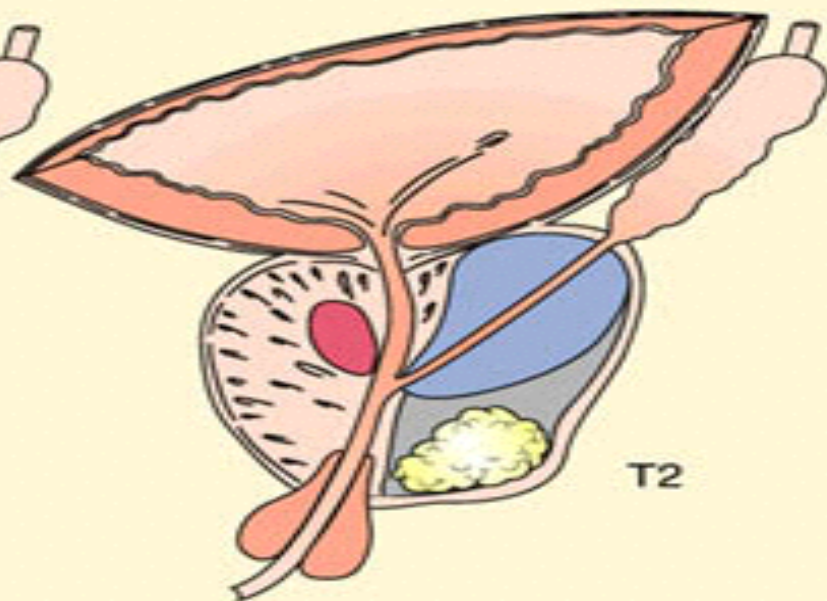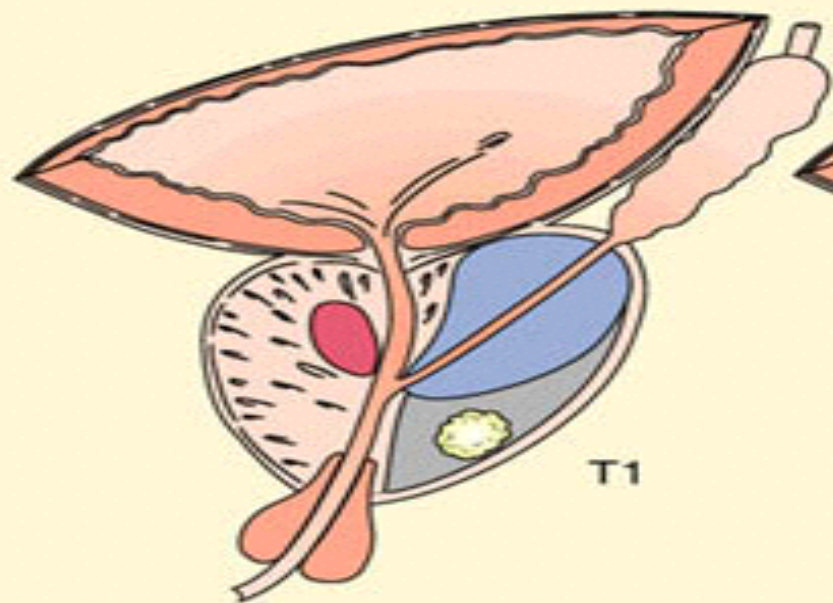
Gleason's Pattern

1. Small, uniform glands

2. More stroma between glands

3. Distinctly infiltrative margins

4. Irregular masses of neoplastic glands

5. Only occasional gland formation

Well differentiated

Moderately differentiated

Poorly diff./ Anaplastic

Risk Groups

Low Risk	PSA<10	and
	Gleason<7	and
	Stage T1c or T2a	
Intermediate Risk	PSA 10-20	or
	Gleason 7	or
	Stage T2b	
Poor Risk	PSA >20	or
	Gleason >7	or
	Stage T2c	

Staging-Metastatic vs Non-Metastatic

- Bone scan and CT scan
  - Only required in intermediate and poor risk patients

ONCOTYPE DX

- **Genomic Health**

- **17 gene signature**

- **Stratifying Low risk and Intermediate risk disease**

Treatment Choices

- No treatment-Active surveillance
- Radical prostatectomy
- Radiation
  - External beam-conformal
  - Brachytherapy-seeds
  - Neutrons
  - Protons
- Hormonal therapy
- Combination therapies

Outcome of Surgically Treated Patients

- The cohort: 24,441 patients who underwent RP between 1987-2005 at:
  - Cleveland Clinic
  - MSKCC
  - Baylor College of Medicine
  - University of Michigan
  - JHH

- All pathological specimens reviewed by genitourinary pathologists at each institution

- Endpoint: Prostate cancer mortality

Outcome of Treated Patients
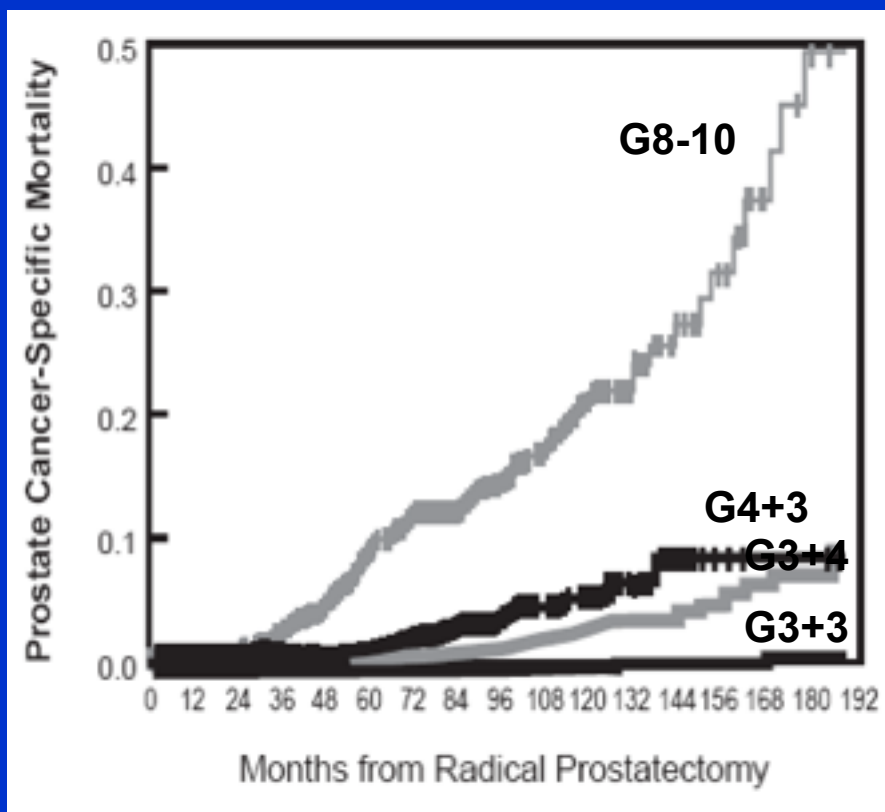
- **Gleason 8-10**: 10% of all cases
  - 49% 15-year PCSM
  - 45% of all cancer deaths
- **Gleason 7**: 40% of all cases
  - 8% 15-year PCSM
  - 50% of all cancer deaths
- **Gleason 6** 50% of all cases
  - <1% 15-year PCSM
  - 1 of 3756 patients with organ-confined, Gleason 6 cancer has died of prostate cancer

The PIVOT Trial

- First randomized controlled trial in the US to compare initial treatment to observation

- Initiated 1994

- Randomized 731 men to treatment with radical prostatectomy or watchful waiting

- Median age 67

- 75% screen detected; median PSA 7.8

Kaplan–Meier Plots of Mortality
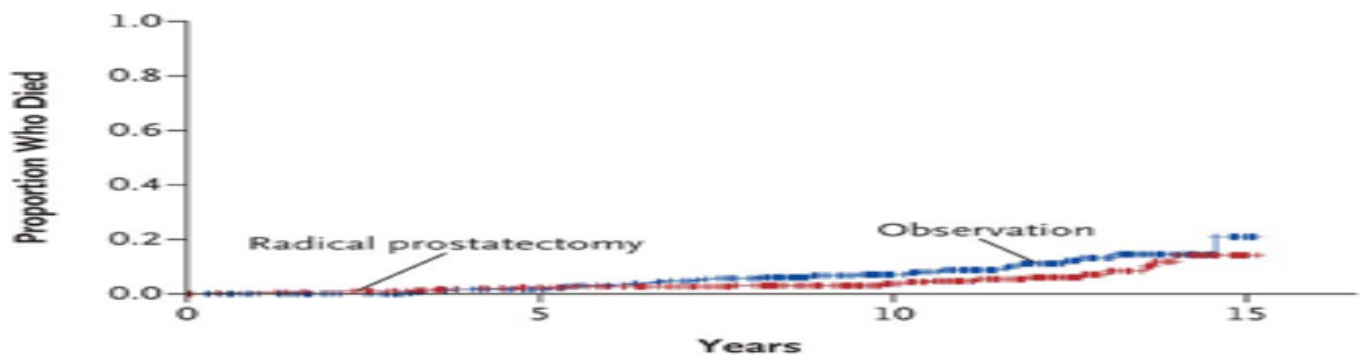
Wilt TJ et al. N Engl J Med 2012;367:203-213

Conclusions

- Among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up

- Absolute differences were less than 3 percentage points.

Randomized Study: Surgery Versus Watchful Waiting

- 695 Scandinavian men, 1989-1999
- Median f/u 8.2 years
- Mean age: 64.7 years
- Mean PSA: 12.8 ng/ml
- Stage T1b (12%), T1c (11%), T2 (76%)
- Gleason: 2-6 (61%), 7 (23%), 8-10 (5%)

Bill-Axelson NEJM 2011

Prostate Cancer Death
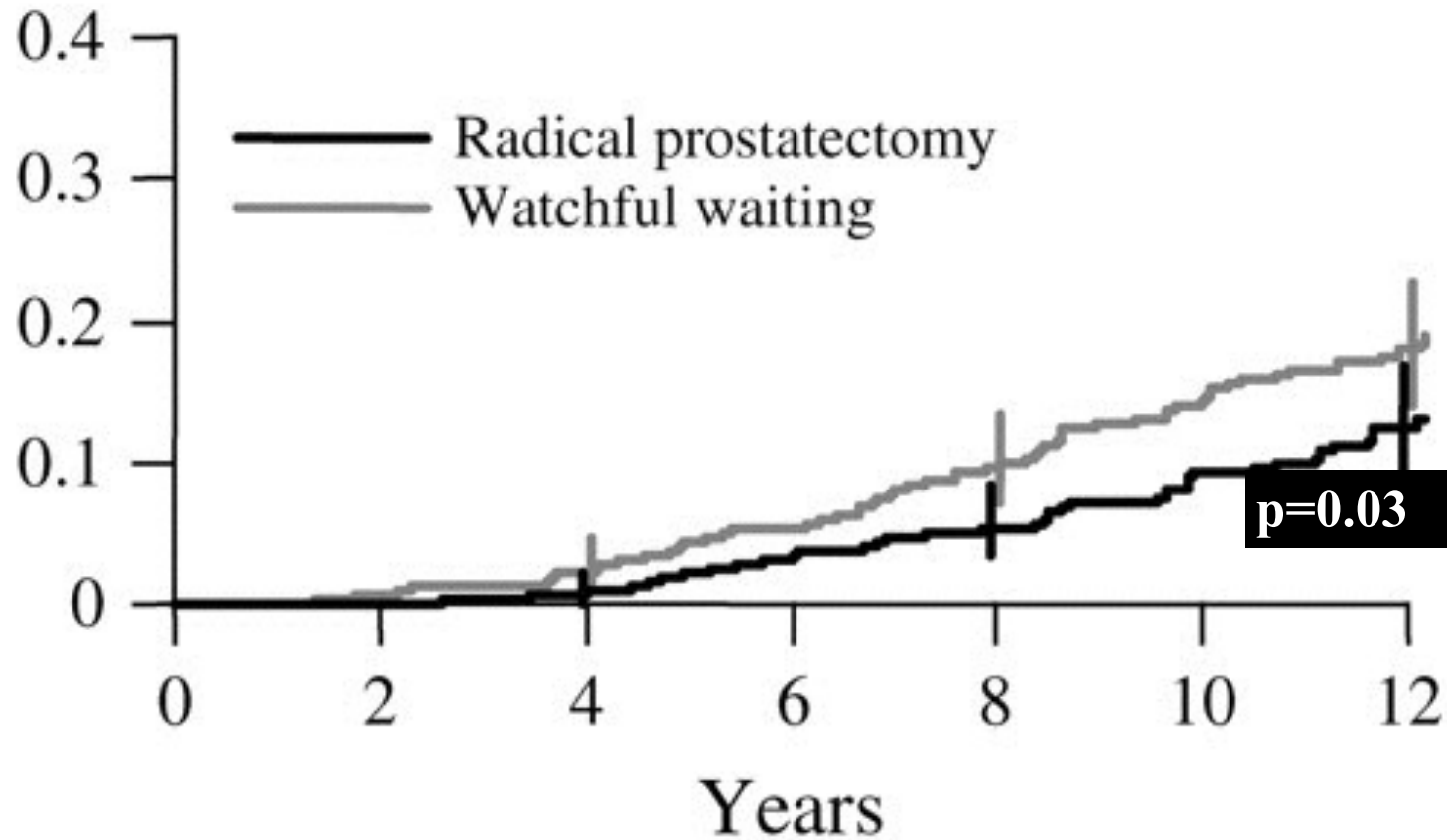
Long term outcome of AS

Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

Laurence Klotz, Danny Vesprini, Perakaa Sethukavalan, Vibhuti Jethava, Liying Zhang, Suneil Jain, Toshihiro Yamamoto, Alexandre Mamedov, and Andrew Loblaw

Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Remaining on AS

CS survival

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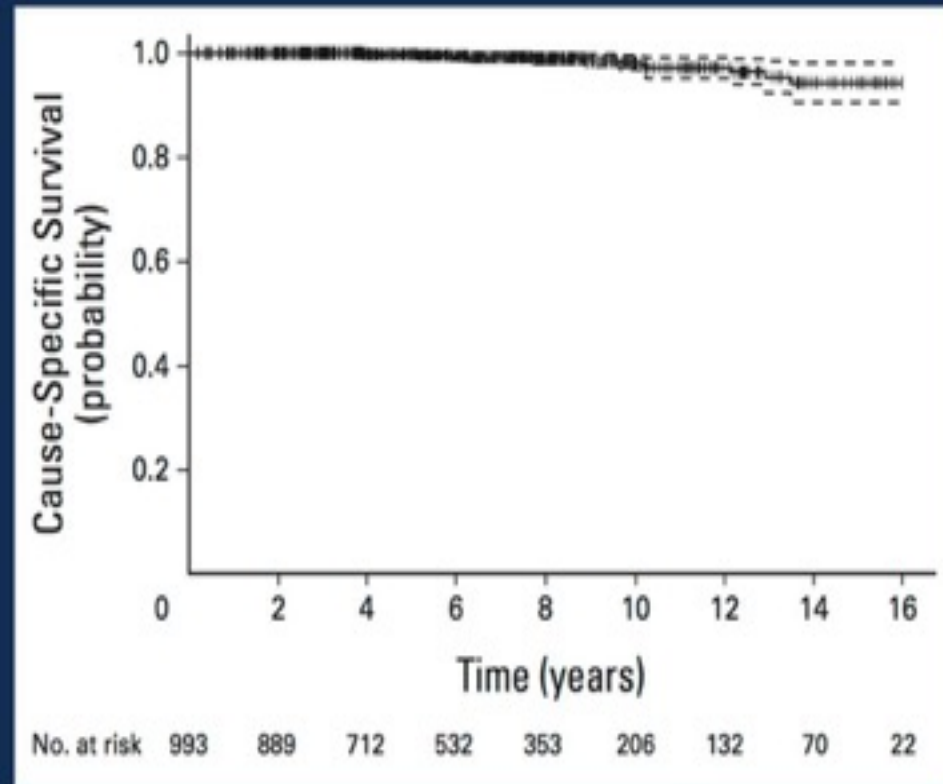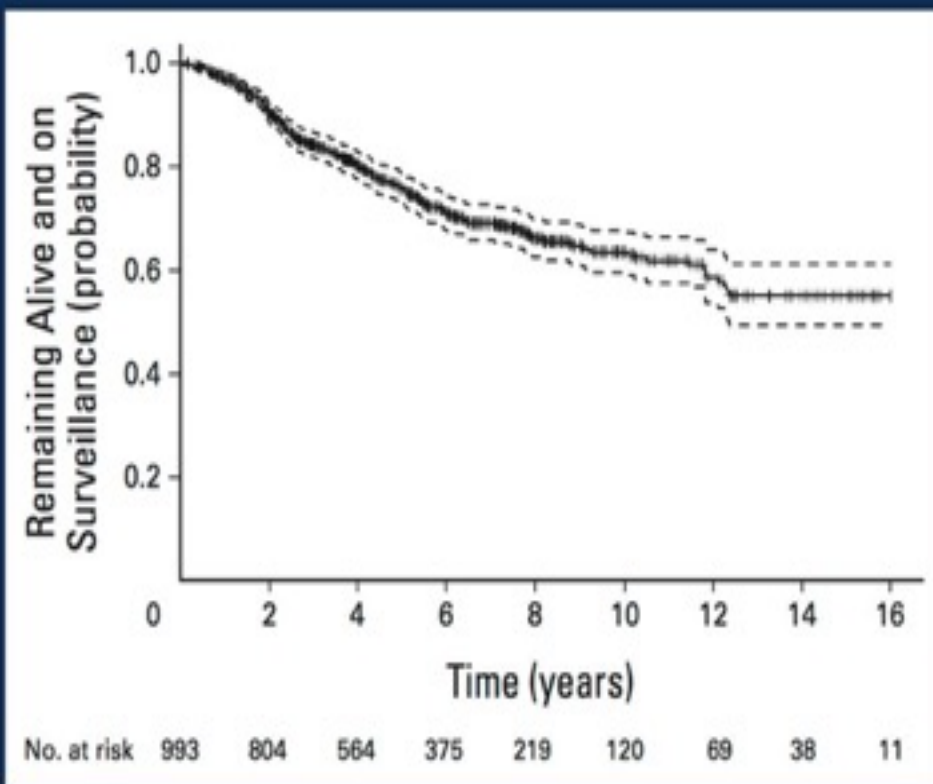
Conclusions

- Active surveillance for favorable-risk prostate cancer is feasible and seems safe in the 15-year time frame.

- 2.8% developped metastatic disease, 1.5% died of PCa

- Mortality rate is consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.

Active Surveillance catching on?

ACTIVE PRIME TIME

In US men diagnosed with low-risk prostate cancer, the number choosing active surveillance is rising.

— Active surveillance
— Radical prostatectomy
— Other therapy

CAPRA score range, 0-2

CAPRA score range, 0-2
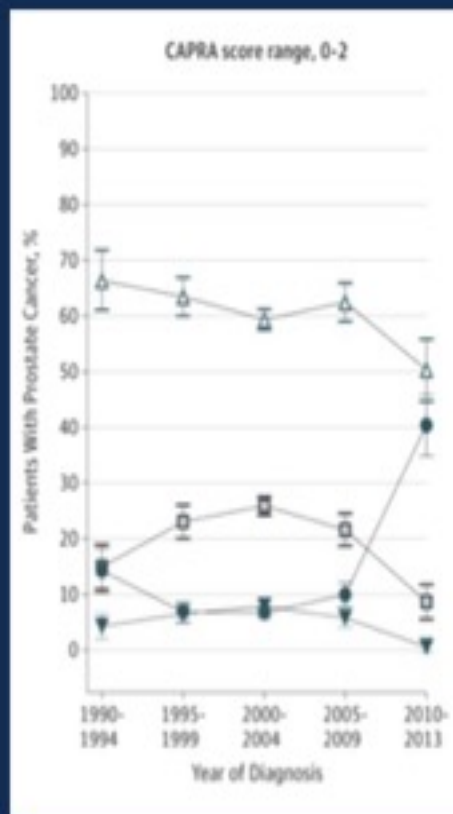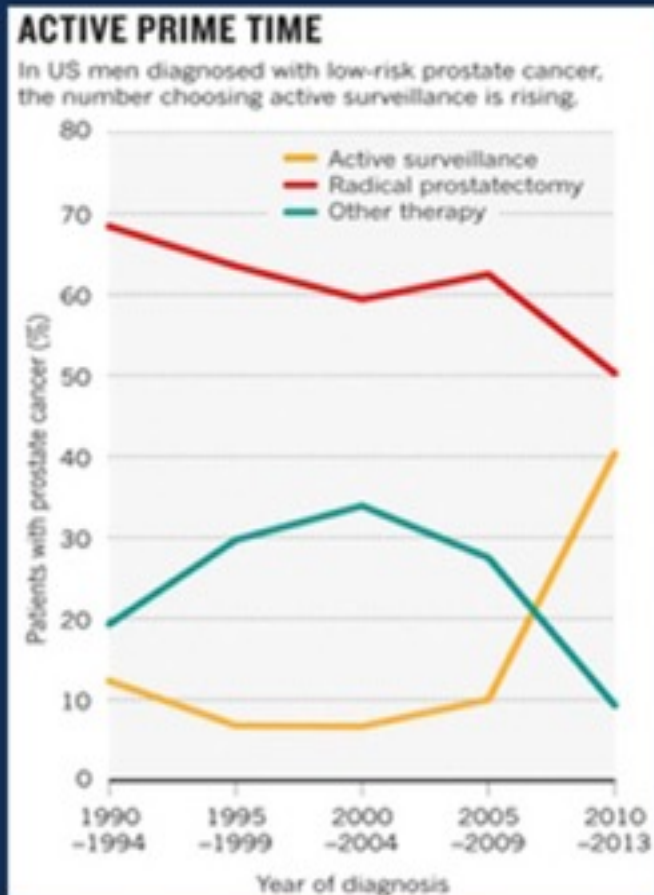
40% AS
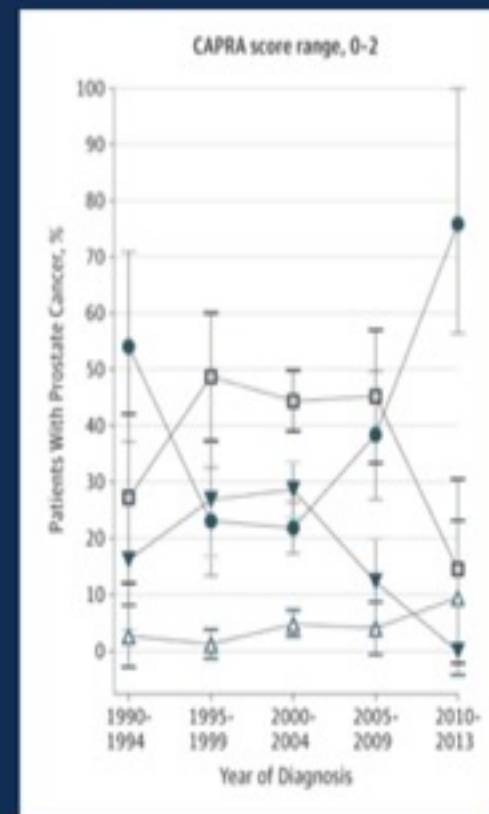
> 75 75%

Cooperberg, Carroll JAMA. 2015 Jul 7;314(1):80-2.

Multimodality Treatment:
High Risk Disease

EBRT vs EBRT + 3 Years HT: EORTC Trial 2002

Log-rank test *P*<.0001
Hazard ratio 0.51
(95% CI, 0.36–0.73)

Overall Survival (%)

Combined treatment

Radiotherapy alone

Time Since Randomization (Years)

Bolla M, et al. *Lancet*. 2002;360:103-106.

Summary-Locally Advanced Tumors: XRT +ADT

- Overall survival

   3 years or longer provides benefit

- Prolonged duration needs to be balanced with side effects

EORTC 22961: Design

Prostate cancer
T1c-T2a-b, N1-2 or pN1-2
or T2c-T4, N0-2
(UICC 1992)
M0
PSA<150 ng/ml
WHO ≤2

→ **Pelvic RT + 6-month CAB** →

30 months LH-RH (LADT)

No further treatment (SADT)

N=1117   **N=970**
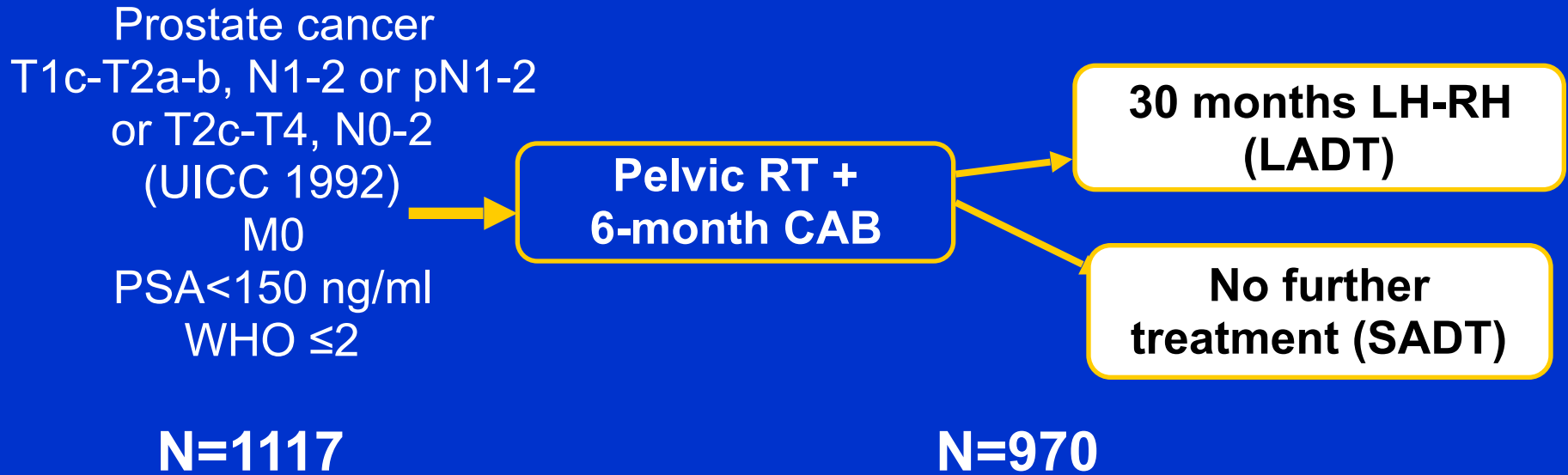
Primary objective: To demonstrate non inferior survival with 6-months adjuvant hormonal treatment compared to 3-years adjuvant ADT treatment
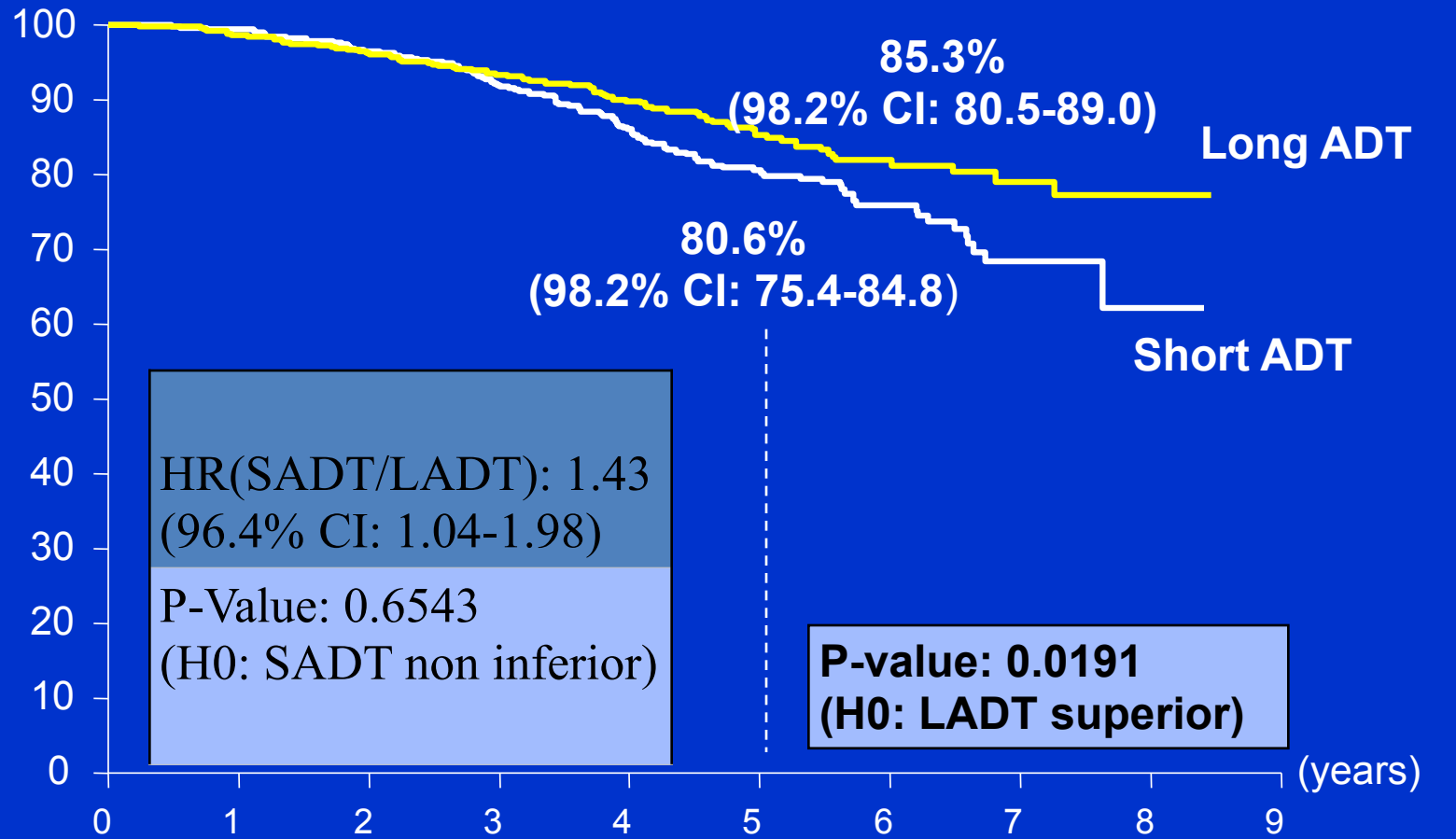
Bolla et al NEJM 2009

Overall survival

Multimodality Therapy:
What about Patients with Intermediate and High Risk but Localized Disease (T1-2)

XRT vs. XRT + ADT for Intermediate and High Risk Patients

- 205 patients with PSA> 10 or Gleason >6
- Randomized to XRT or XRT + 6 months of ADT
- Median follow-up 7.6 years
- Overall survival HR=1.8 (p=0.01)
- PCSM HR=4.1 (p=0.01)

D'Amico et al JAMA 2008

Adjuvant Hormone Ablation
ECOG 3886: Results at 12 Years
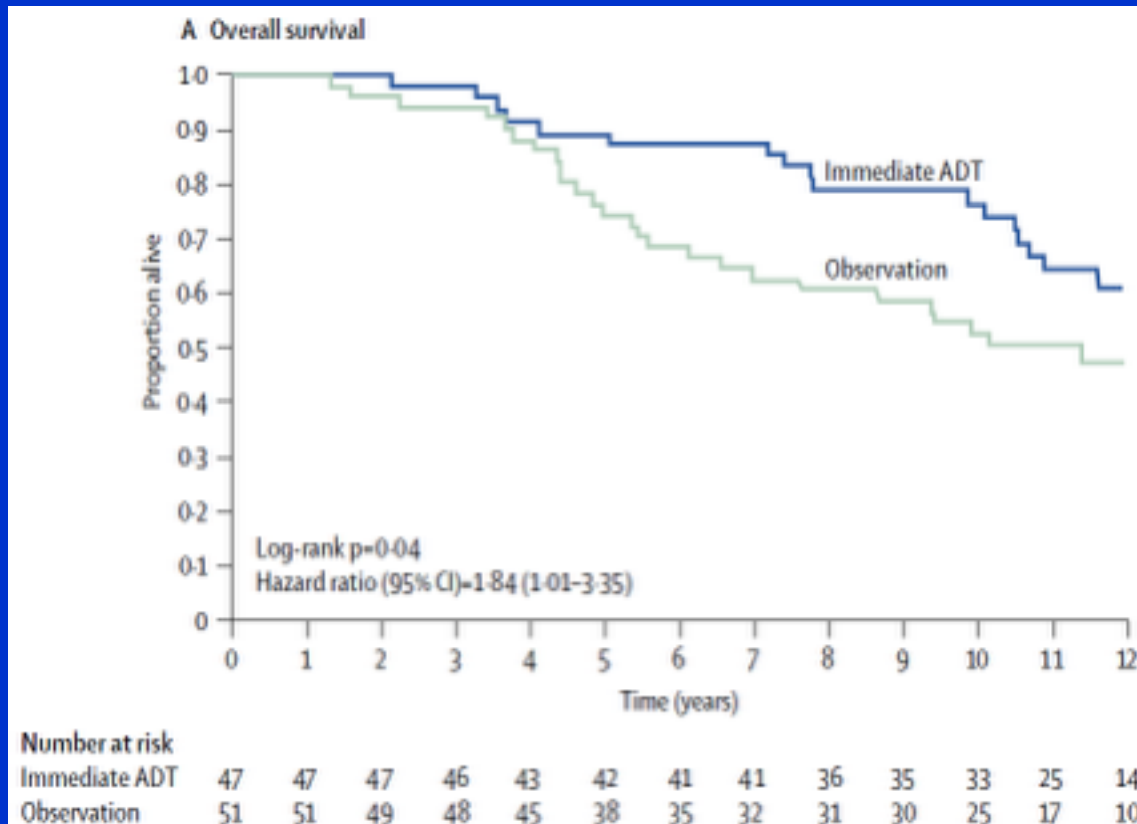
Randomized trial

98 patients

Nodal metastases

Immediate hormonal therapy improves
survival in node positive patients

Messing EM, et al. Lancet Oncol. 2006

Natural History of Prostate Cancer
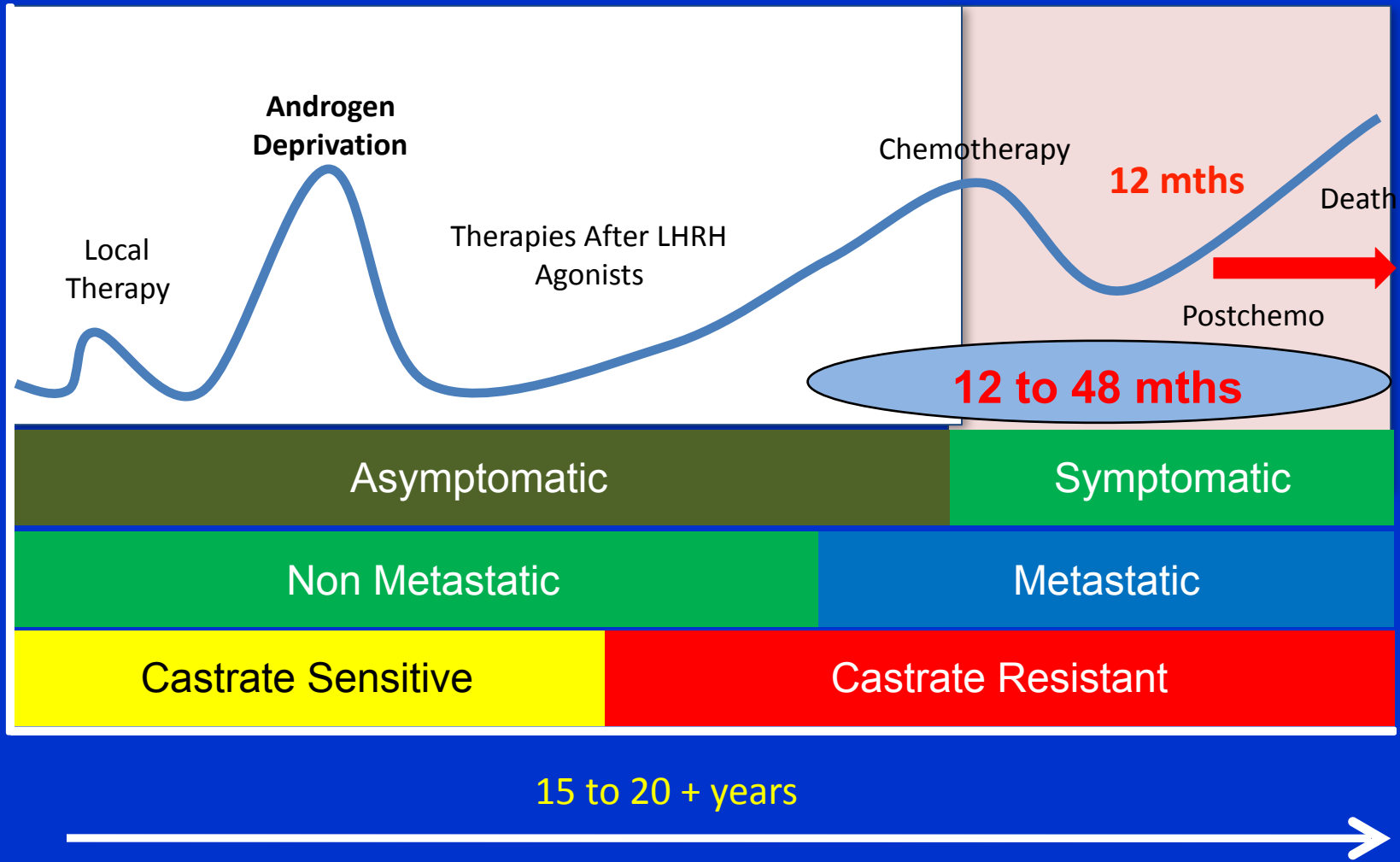
Natural History Of Rising PSA

- 304 men relapsed after surgery
- No hormones until (+) bone scan
- Time to PSA rise, Gleason, PSADT were predictors of survival

RP | First Rise in PSA — 8 yrs — Bone scan (+) — 5 yrs — Death

Pound JAMA 1999

Patients with a Rising PSA-Importance of PSADT
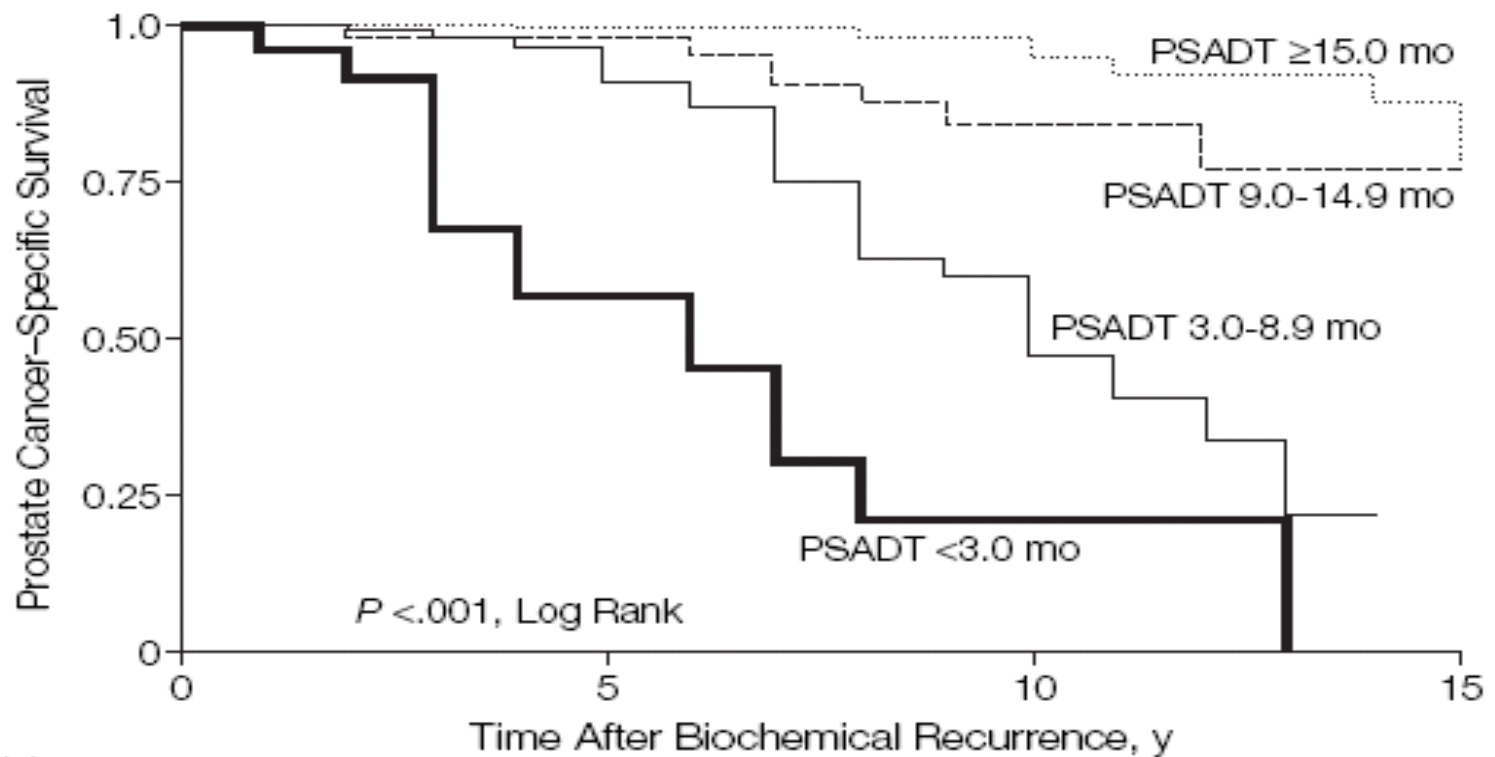
Freedland SJ, et al. *JAMA*. 2005

Does local control matter in locally advanced prostate cancer?

Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer

Malcolm D. Mason, Wendy R. Parulekar, Matthew R. Sydes, Michael Brundage, Peter Kirkbride, Mary Gospodarowicz, Richard Cowan, Edmund C. Kostashuk, John Anderson, Gregory Swanson, Mahesh K.B. Parmar, Charles Hayter, Gordana Jovic, Andrea Hiltz, John Hetherington, Jinka Sathya, James B.P. Barber, Michael McKenzie, Salah El-Sharkawi, Luis Souhami, P.D. John Hardman, Bingshu E. Chen, and Padraig Warde

Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Overall survival

CS survival
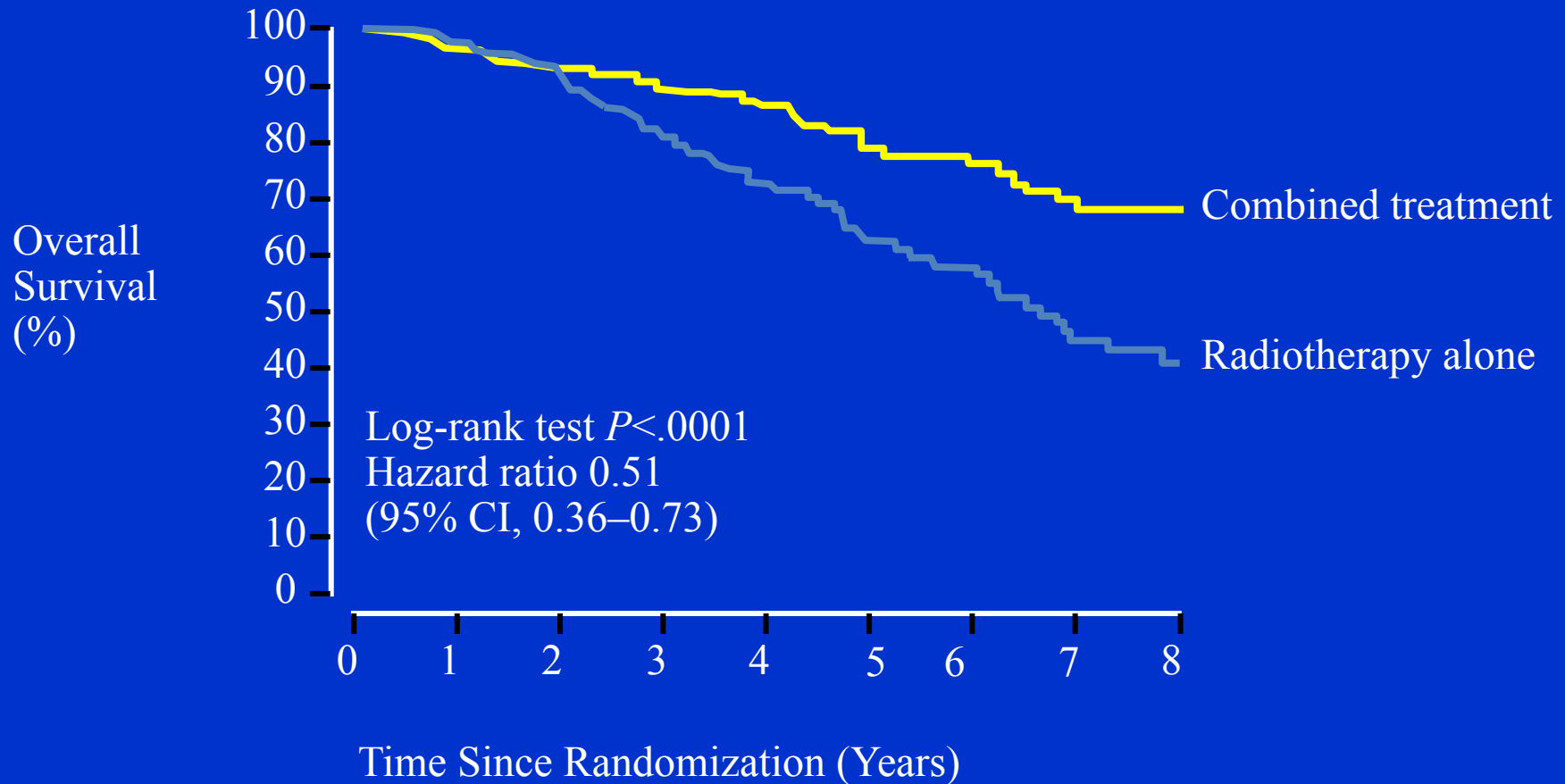

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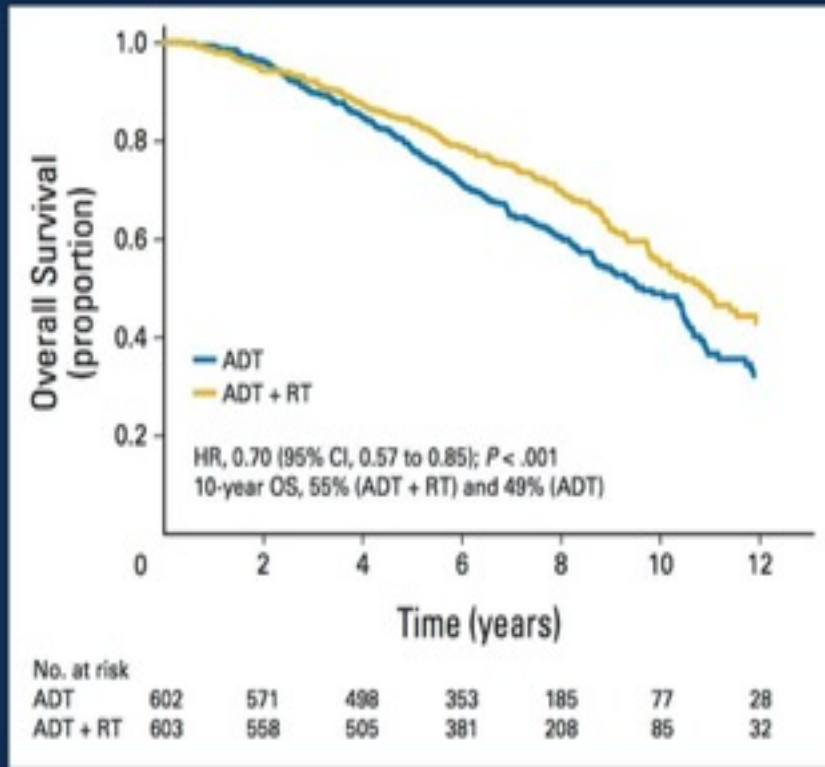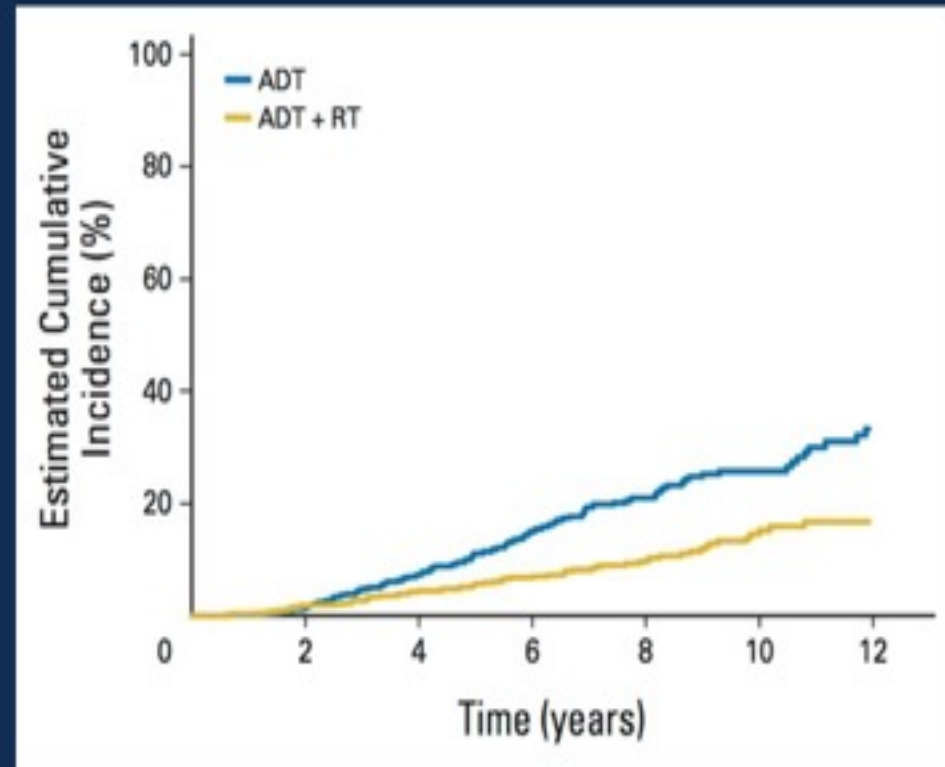
Does local control matter in metastatic patients?

Research

Original Investigation

Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer
Data From Patients in the Control Arm of the STAMPEDE Trial

Nicholas D. James, BSc, MBBS, PhD, FRCP, FRCR; Melissa R. Spears, MSc, BSc; Noel W. Clarke, MBBS, FRCS(Eng), ChM(Manch), FRCS(Urol); David P. Dearnaley, MA, MB, BChir, MD, FRCP, FRC; Malcolm D. Mason, MD, FRCP, FRCR, FSB; Christopher C. Parker, BA, BM, BChir, MD; Alastair W. S. Ritchie, MD, FRCSEd; J. Martin Russell, BSc, MB, ChB, MRCP(UK), FRCR, FRCPSG; Francesca Schiavone, PhD; Gerhardt Attard, MD, PhD; Johann S. de Bono, MBChB, MSc, PhD, FRCP, FMedSci; Alison Birtle, MB, BS, MRCP, FRCR, MD; Daniel S. Engeler, MD; Tony Elliott, BSc, MSc, PhD, MBChB, MRCP, FRCR; David Matheson, BSc, PGCE, DipEd, MEd, PhD, FRSA, FHEA; Joe O'Sullivan, MD, FRCR, FFRRCSI, FRCPI; Delia Pudney, MBChB; Narayanan Srihari, MB, BS; Jan Wallace, MB, ChB, FRCR; Jim Barber, MA, DM, FRCR, MRCP; Isabel Syndikus, MD; Mahesh K. B. Parmar, DPhil, MSc, BSc; Matthew R. Sydes, MSc, CStat; for the STAMPEDE Investigators

Local therapy improves FFS

Figure 2. Failure-Free Survival for Reported Radical Radiotherapy Status, in N0M0 and N+M0 Subcohorts
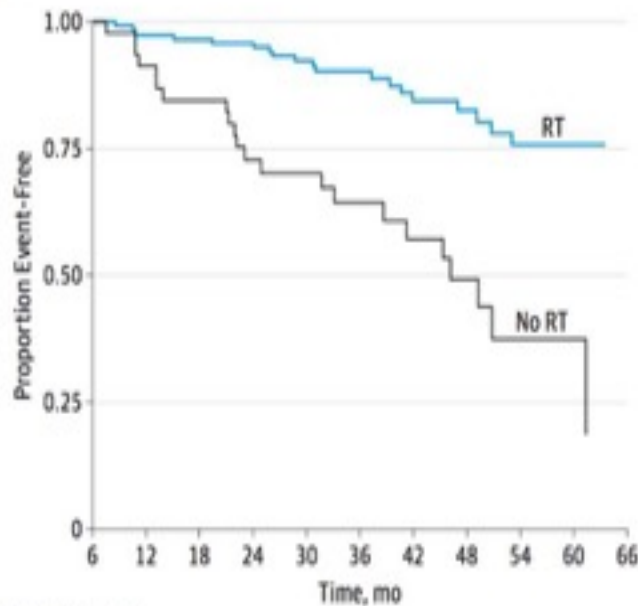
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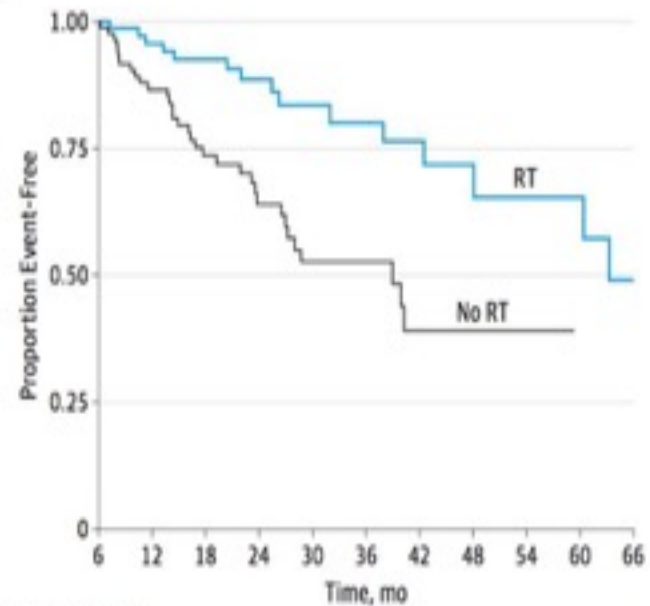
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Conclusion

- Role of radiation therapy clearly established for high risk and locally advanced prostate cancer

- Evidence mounting for metastatic patients

- Mounting evidence for surgery but RCT's not available

Does hormone-therapy improve salvage radiation therapy?

NRG Oncology/RTOG 96-01

A Phase III trial in patients following Radical Prostatectomy (RP) with pT2-3, pN0 prostate cancer and elevated PSA levels: Anti-Androgen Therapy (AAT) with Bicalutamide during and after salvage Radiation Therapy (RT) compared to Placebo + salvage RT

W. U. Shipley[1], W. Seiferheld[2], H. Lukka[3], P. Major[3], N. M. Heney[1], D. Grignon[4], O. Sartor[5], M. Patel[3], J. P. Bahary[6], A. L. Zietman[1], T. M. Pisansky[7], K. L. Zeitzer[8], C. A. F. Lawton[9], F. Y. Feng[10], R. D. Lovett[11], A. Balogh[12], L. Souhami[13], S. A. Rosenthal[14], K. J. Kerlin[15], and H. M. Sandler[16]

Results — Overall Survival
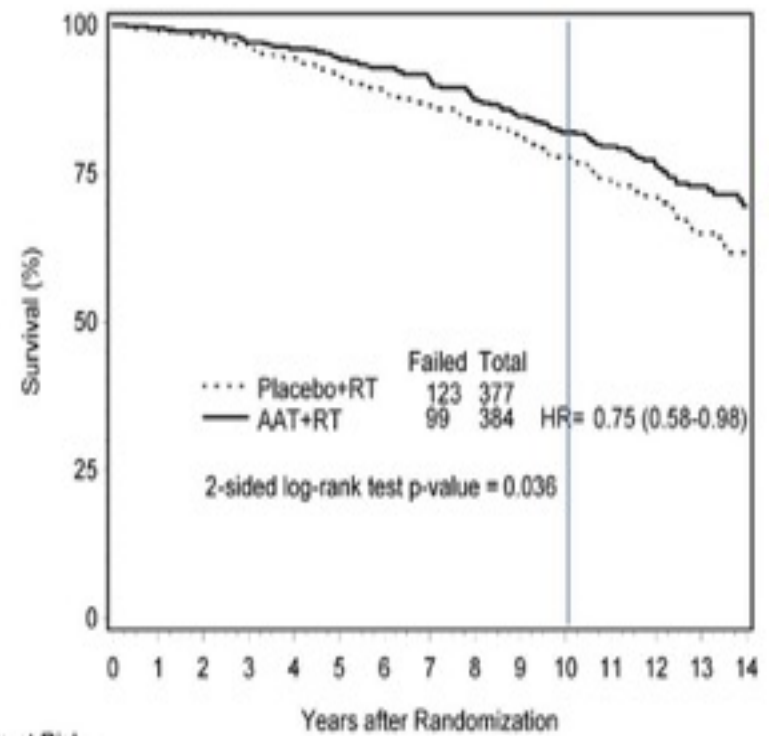
OS at 10 yrs: 82% vs 78%

Conclusions

- With a median F/U of greater than 12 years, the addition of 24 mos. of peripheral androgen blockage (AAT) during and after salvage RT significantly:
  - **Improved Overall Survival (p = 0.036)**
  - **Reduced metastatic PC**
  - **Reduced death from PC – [from 7.5% to 2.3%; NNT = 17]**
  - **Reduced tumor progression and the incidence of local regrowth**
- GI or GU toxicity observed during AAT or placebo treatments were low and similar
- Gynecomastia was extremely common in the bicalutamide arm

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Presented By Fred Saad at Genitourinary Cancers Symposium 2016

More ADT is better for high risk prostate cancer

- Study compared RoRx plus 4 months vs 24 months of ADT
- Improved 5-year BFS (90% *vs* 81%) [HR] 1·88 p=0·01
- Improved 5-year metastasis-free survival (94% *vs* 83% HR 2·31 p=0·01
- Improved 5-year OS (95% *vs* 86% HR 2·48 p=0·009

- The effect of long-term ADT was more evident in patients with high-risk disease than in those with low-risk disease.

- Longer follow-up is needed to determine whether men with intermediate-risk disease benefit from more than 4 months of androgen deprivation.

Endocrine Therapy of Prostate Cancer
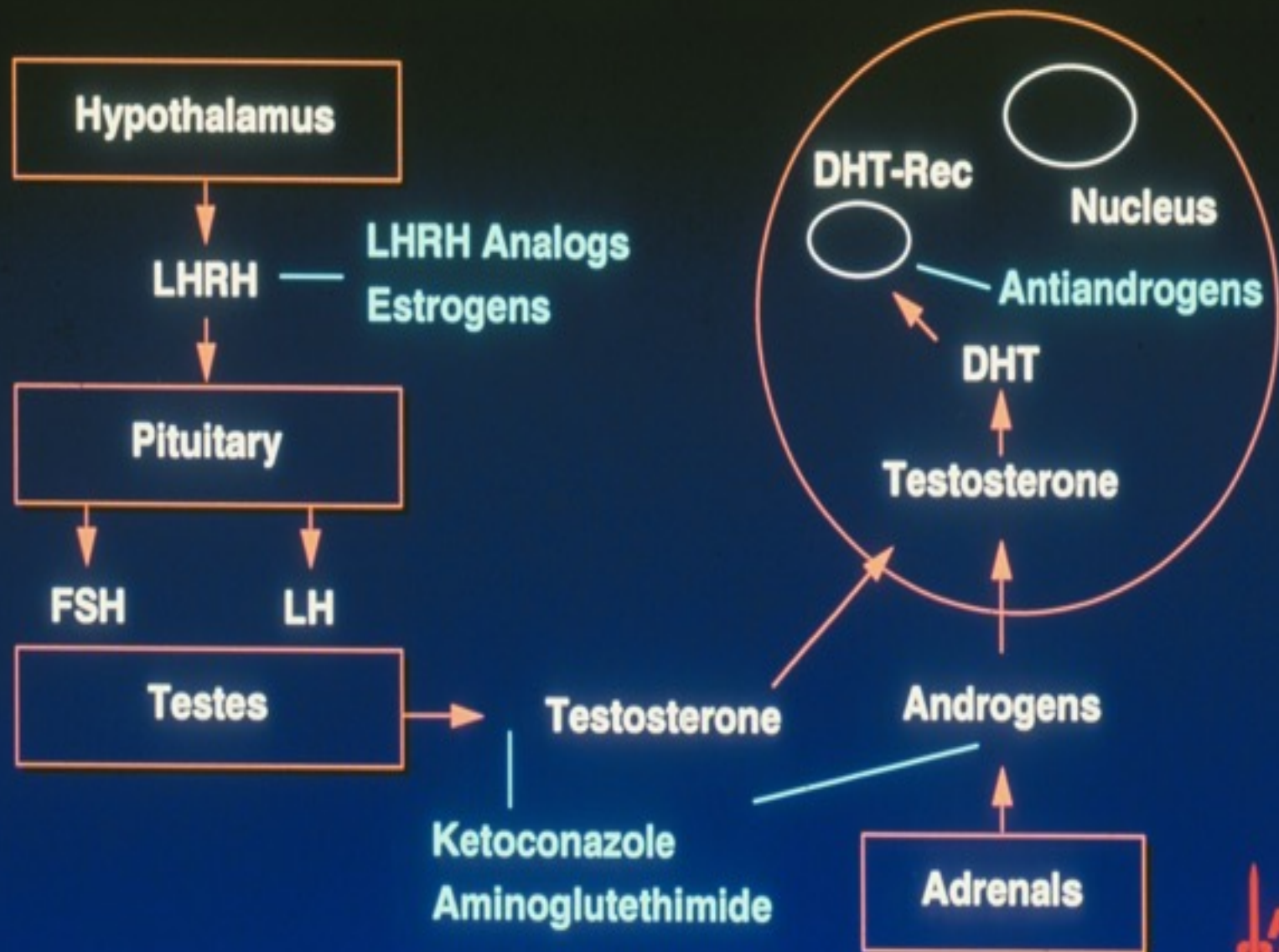
Androgen-Deprivation Therapy: Definition

Androgen-deprivation therapy (ADT) is any treatment that blocks interaction of androgen with the androgen receptor

- Orchiectomy
- LHRH agonists
- LHRH antagonists
- Estrogens
- Combined androgen blockade
- Antiandrogen monotherapy

Existing therapies do not adequately suppress adrenal or intratumoral production of androgen

LHRH = luteinizing hormone-releasing hormone.

ADT: Indications

- Indications
  - Newly diagnosed metastatic disease
  - Adjuvant therapy of node positive disease discovered at prostatectomy
  - Combined with radiotherapy in patients with intermediate/high-risk disease

- Use of ADT in patients with biochemical progression is controversial

What is the Appropriate Timing of Androgen Deprivation Therapy (ADT)?

1,002 randomly allocated	→ 2 centers excluded for quality reasons (17 patients)

985 randomly allocated

492 immediate androgen deprivation → 12 ineligible

13 ineligible ← 493 deferred androgen deprivation

480 eligible

480 eligible

475 treated immediately
17 refused immediate treatment
(including 5 treated upon progression)

245 treated upon progression
8 treated immediately
125 died without needing treatment
8 refused treatment upon progression
9 refused watchful waiting follow-up
15 lost to follow-up
3 ineligible
80 alive without need for treatment

257 died (including 94 of prostate cancer)

284 died (including 99 of prostate cancer)

492 analyzed

493 analyzed

Studer et al. J Clin Onc 2006

Overall survival

Conclusions

- Earlier rather than later therapy is recommended

- The definition of "early" needs greater refinement

- In practice, PSA velocity, patient anxiety, side effects and perception of side effects of therapy guide therapy

- Would not wait for objective evidence of metastasis since progressive disease may increase fatal TE events

- MANY MEN WITH SLOW PSADT WILL NOT DIE OF CaP AND CAN AVOID EARLY ADT

Metastatic Prostate Cancer

M1 Prostate Cancer *Then & NOW*

	At Risk	Death	Median in Months
S9346	1796	1306	49
S8894	791	742	33
S8494	561	523	31
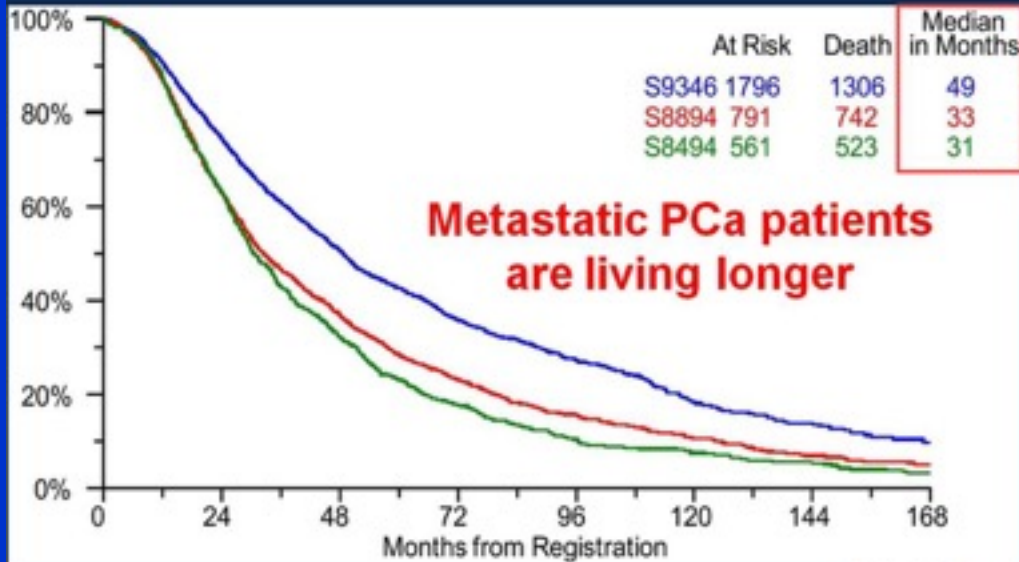
1990s-2000 + (PSA era)
Late 80s-early 1990s
1980

Metastatic PCa patients are living longer

Racial Gap has decreased

	At Risk	Death	Median in Months
S9346, not AA	1480	1069	49
S9346, AA	316	237	48
S8894, not AA	604	563	35
S8494, not AA	454	421	33
S8494, AA	107	102	27
S8894, AA	187	179	27
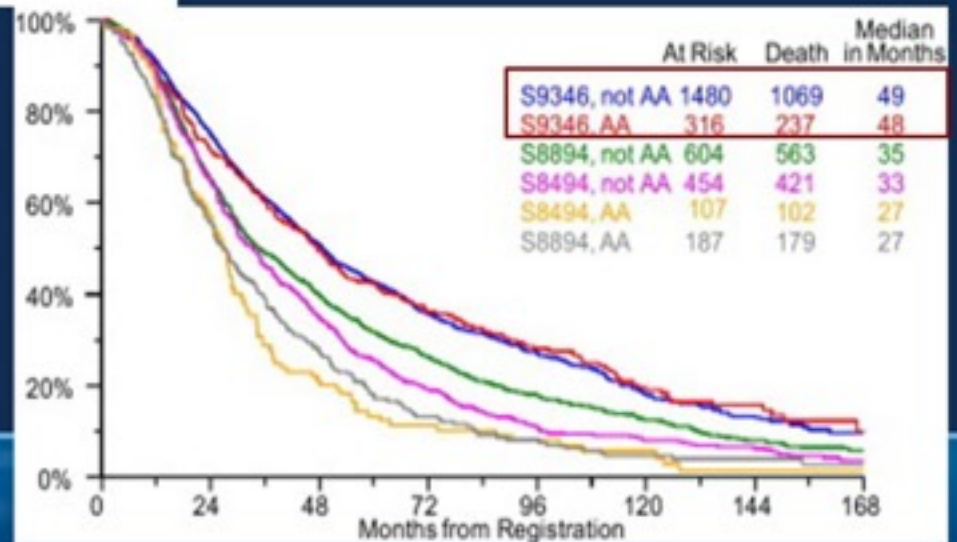
Tangen M, Hussain MH, Higano CS, et al: J Urol 2012

Presented By Maha Hussain at Genitourinary Cancers Symposium 2016

What is a good response to ADT?

- SWOG 9346 Intermittent ADT Trial

- 1345 eligible patients

- Level of PSA after 8 months of ADT

Hussain et al J.Clin Onc 2007

S9346: "A PSA of ≤ 4 and < 0.2 ng/mL after 7 Months of ADT is A Strong Predictor of Overall Survival"

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Hussain et al. J Clin Oncol; 2006

Presented By Maha Hussain at Genitourinary Cancers Symposium 2016
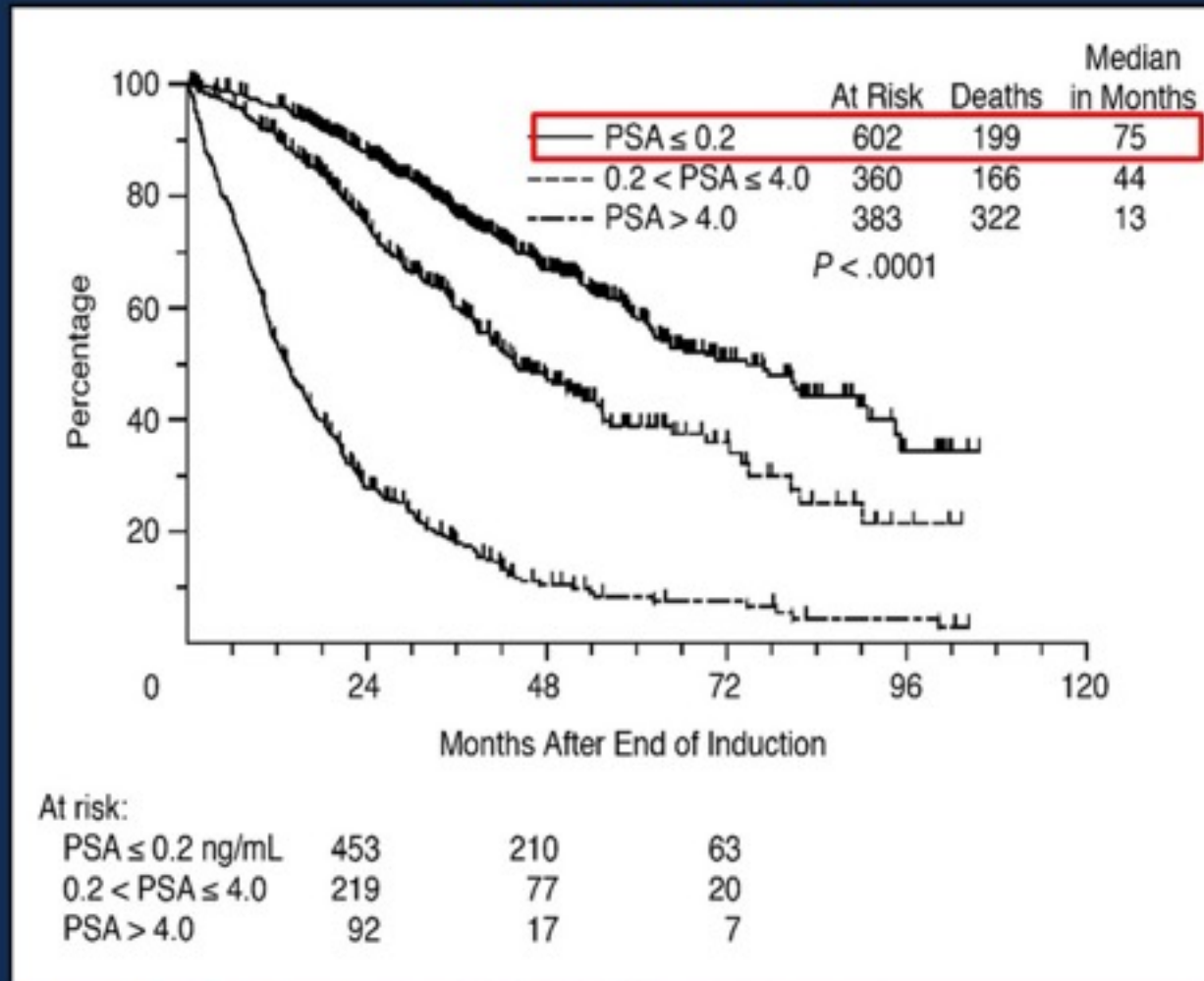
cADT vs iADT Phase III Trials

Trial	Population	No. of pts	Accrual status
NCIC/PR7	**PSA relapse after RT**	1340	closed
EC 507	PSA relapse after RP	201	closed
ICELAND	PSA relapse/locally advanced	700	closed
Japan	Locally advanced	300	closed
SEUG	Advanced disease	766	closed
AP 17/95	Advanced disease and metastatic	325	closed
SWOG 9346	**Metastatic (PSA > 5 ng/mL)**	1500	closed
EC 210	Metastatic (PSA > 20 ng/mL)	387	closed

Rational for Chemo/Hormonal Therapy
Docetaxel Improves Overall Survival in mCRPC

In addition to blocking cell division docetaxel impairs AR signaling in PCa, Zhu et al: Cancer Res, 2010

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E3805:CHAARTED: ChemoHormonal Therapy vs Androgen Ablation Randomized Trial

STRATIFICATION

Extent of Mets
-High vs Low
Age
≥70 vs < 70yo
ECOG PS
- 0-1 vs 2
CAB> 30 days
-Yes vs No
SRE Prevention
-Yes vs No
Prior Adjuvant ADT
≤12 vs > 12 months

- **High volume:** visceral metastases or 4 or more bone mets (at least 1 beyond pelvis and vertebral column)
- **At inception, only pts with high volume disease were to be accrued**

RANDOMIZE

ARM A:
ADT + Docetaxel 75mg/m2 every 21 days for maximum 6 cycles

ARM B:
ADT (androgen deprivation therapy alone)

Evaluate every 3 weeks while receiving docetaxel and at week 24 then every 12 weeks

Evaluate every 12 weeks

Follow for time to progression and overall survival

Chemotherapy at investigator's discretion at progression

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

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Sweeney C, et al ASCO 2014 – NEJM 2015

Presented By Maha Hussain at Genitourinary Cancers Symposium 2016

Therapy Was Feasible:
Majority of Patients Received all 6 Cycles of Docetaxel

# cycles	ADT + Docetaxel (N=390)	
	N	%
1	12	3.1
2	7	1.8
3	7	1.8
4	13	3.3
5	15	3.9
6	335	86.1
Total	390	

Unknown: 1

- 74% with no dose modifications

Presented By Maha Hussain at Genitourinary Cancers Symposium 2016

Overall Survival: All Patients & by Metastatic Disease Extent
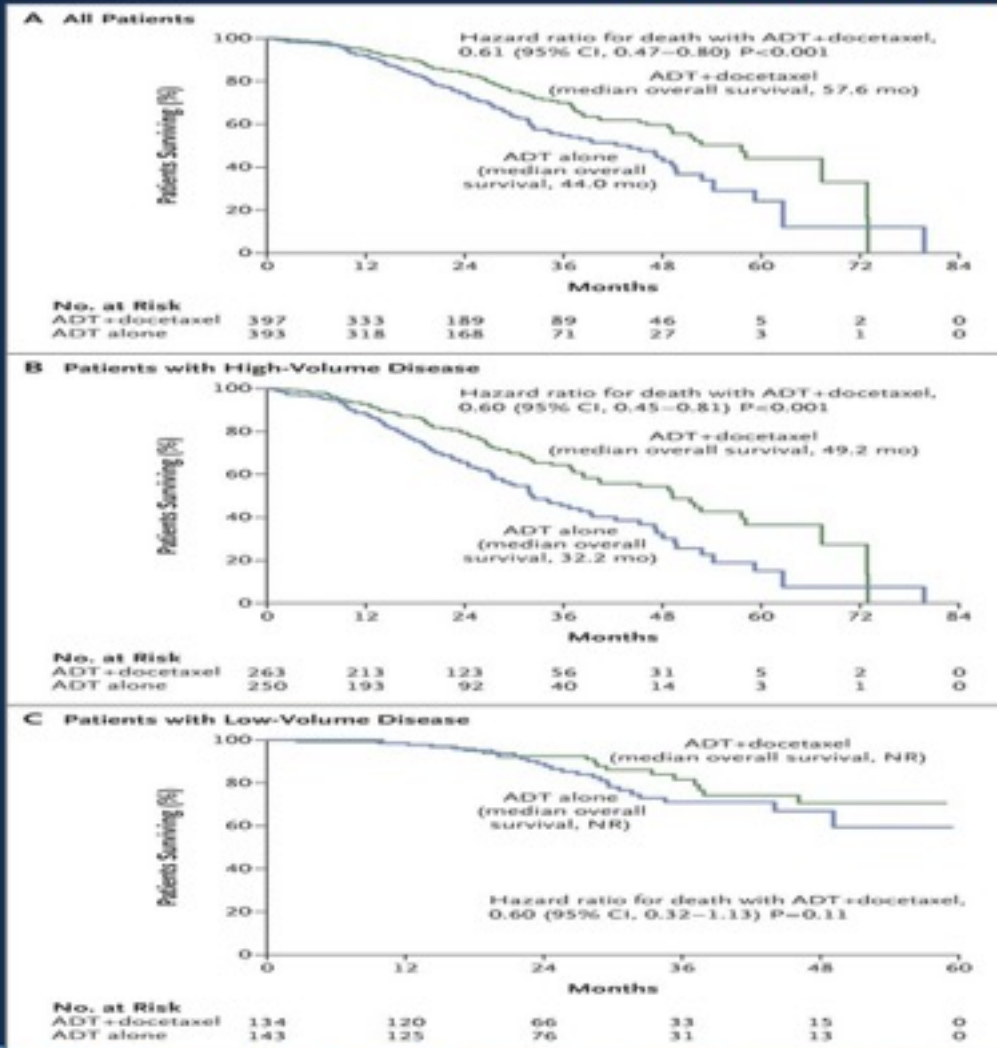
N=790
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months
HR=0.61 (0.47-0.80)
p=0.0003

N=514
Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months

HR=0.60 (0.45-0.81)
p=0.0006

N=276
Median OS:
ADT + D: Not reached
ADT alone: Not reached
HR=0.63 (0.34-1.17)
p=0.1398

Sweeney CJ et al. N Engl J Med 2015

Presented By Maha Hussain at Genitourinary Cancers Symposium 2016

E3805:CHAARTED
Secondary End Points

Table 2. Secondary End Points.

End Point	ADT plus Docetaxel (N=397)	ADT Alone (N=393)	P Value	Hazard Ratio (95% CI)
PSA level <0.2 ng/ml at 6 mo — no. (%)	127 (32.0)	77 (19.6)	<0.001	
PSA level <0.2 ng/ml at 12 mo — no. (%)	110 (27.7)	66 (16.8)	<0.001	
Time to castration-resistant prostate cancer — mo*				
Median	20.2	11.7	<0.001	0.61 (0.51–0.72)
95% CI	17.2–23.6	10.8–14.7		
Time to clinical progression — mo†				
Median	33.0	19.8	<0.001	0.61 (0.50–0.75)
95% CI	27.3–41.2	17.9–22.8		

* The time to castration-resistant prostate cancer was the time until documented clinical or serologic progression with a testosterone level of less than 50 ng per deciliter (or source documentation of medical castration or surgical castration).
† Clinical progression was defined by increasing symptoms of bone metastases; progression according to the Response Evaluation Criteria in Solid Tumors, version 1.0; or clinical deterioration due to cancer according to the investigator's opinion.

Docetaxel and/or Zoledronic Acid for Hormone-Naïve Prostate Cancer: first survival results from STAMPEDE trial: Docetaxel outcomes in M1 patients

Failure-free survival
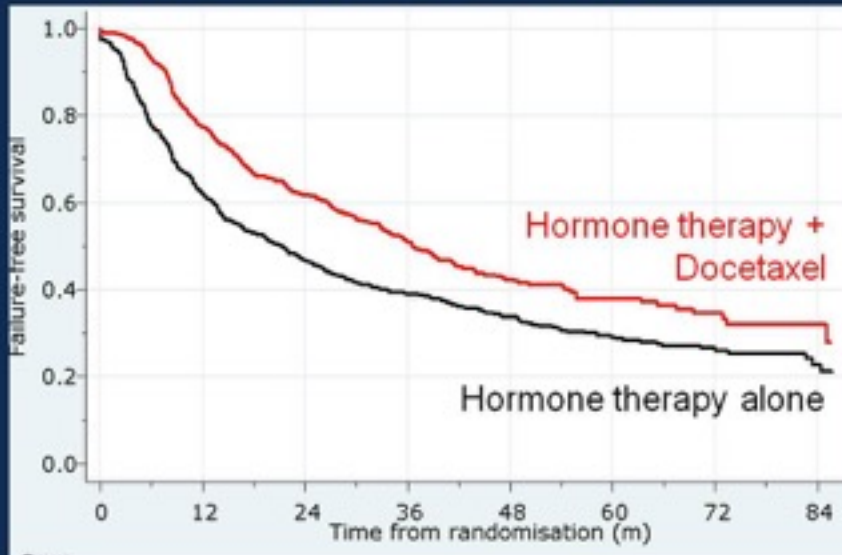
Overall survival
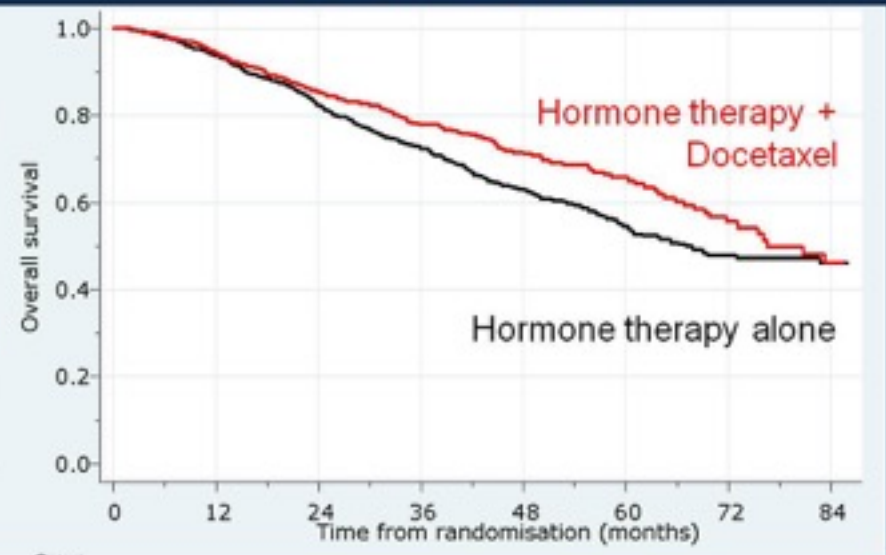
Relative improvement in FFS = 38% (Hazard ratio 0.62)

Relative improvement in survival = 24% (Hazard ratio 0.76)

James N et al., 2015 ASCO

Presented By Maha Hussain at Genitourinary Cancers Symposium 2016

What are the Side Effects of ADT?

Side-Effects of ADT

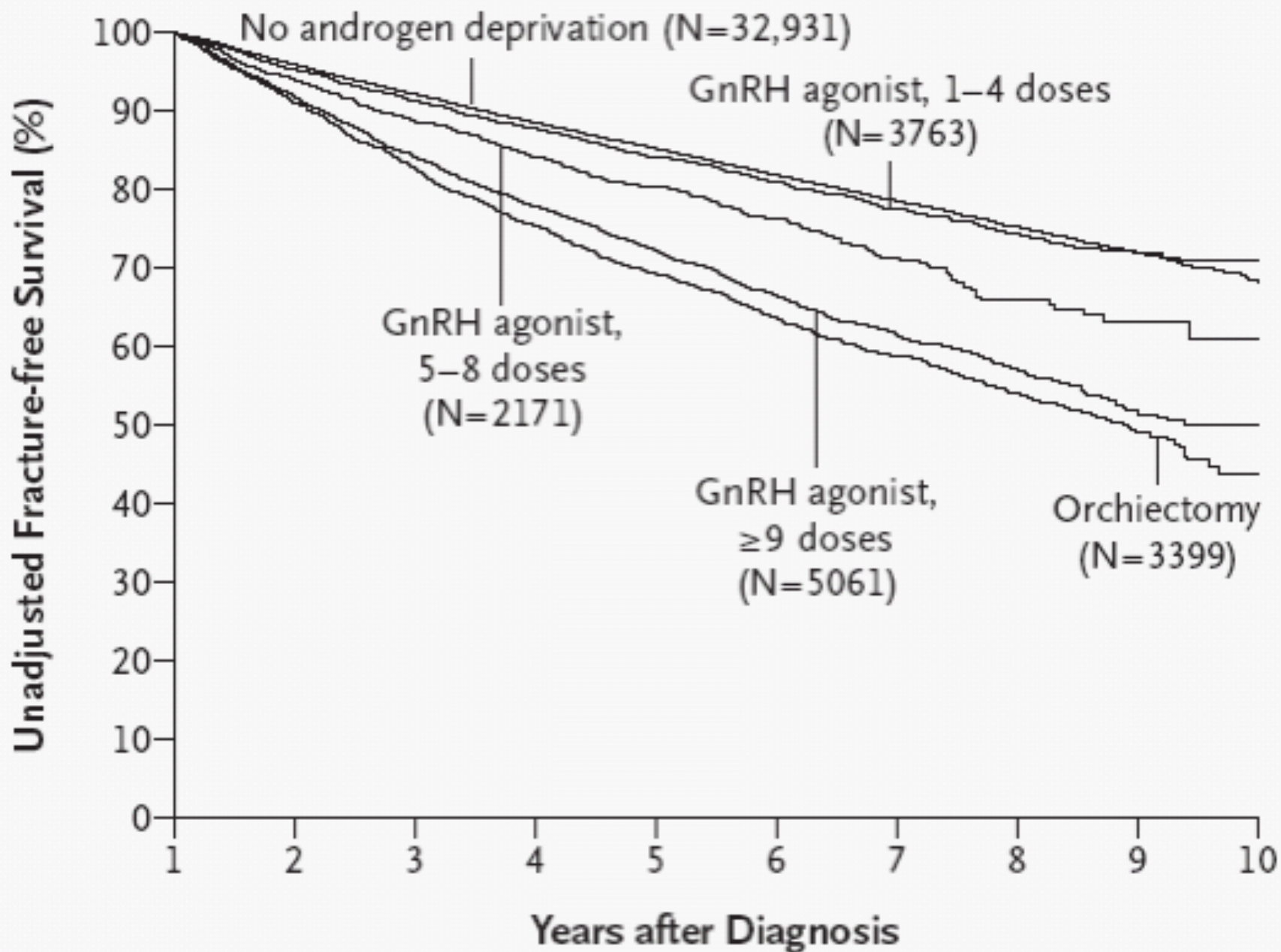| "Big Three"	What you see	What you don't see	What you feel
Loss of libido	Weight gain	Loss of BMD	Fatigue, Lack of energy, Lack of initiative
Erectile dysfunction	Gynecomastia	Anemia	
Hot flashes	Loss muscle mass, strength	Onset/worsening of lipids, HTN, diabetes, CVD	Depression
	Decr size penis and testes		Emotional lability
	Hair changes		Cognitive function

Prevention of Fractures from ADT

- Replete Vitamin D
- Adequate calcium intake
- Risk of fracture assessment based on health profile
- Baseline and yearly BMD

N= 16,888
ADT 2,397 + no ADT 14,491

ADT and alzheimer's

Table 3. Propensity Score–Matched Cox Regression Analysis for the Association of ADT Use With Alzheimer's Disease

Exposure	HR (95% CI)	P
Propensity score–matched analysis		
No ADT use	Ref	Ref
ADT use	1.88 (1.10 to 3.20)	.021
Traditional multivariable-adjusted analysis		
No ADT use	Ref	Ref
ADT use	1.66 (1.05 to 2.64)	.031

Table 4. Propensity Score–Matched Cox Regression Analysis for the Association of ADT Use With Alzheimer's Disease by Therapy Duration

Duration of ADT Use (Months)	HR (95% CI)	P	P for Trend*
No ADT use	Ref	Ref	.016
ADT users			
< 12 months ADT use	1.62 (0.82 to 3.21)	.165	
≥ 12 months ADT use	2.12 (1.11 to 4.03)	.011	
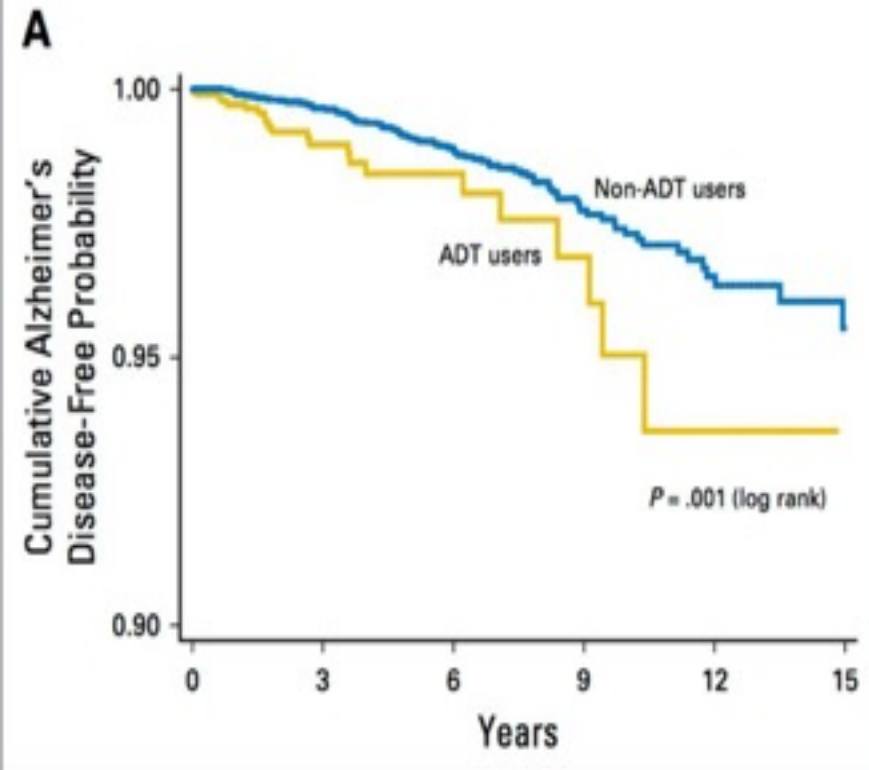
Nead KT, et al. **J Clin Oncol.** 2015 Dec 7

Castrate Resistant Prostate Cancer (CRPC)

- Definition: Rising PSA or objective progression (bone +/- soft tissue) despite castrate testosterone levels
  - Serum Testosterone < 50ng/dl or < 1.7nM/dl

- CRPC will develop in all patients who receive Androgen Deprivation Therapy

- Androgen Receptor (AR) is still present and functional

Castrate Resistant Prostate Cancer

- Increased Androgen Biosynthesis
  - Persistent androgens in primary tumors[1,2]
  - Persistent androgens in metastasis[3]
  - Upregulated enzymes of steroidogenesis[3]

- Persistent Androgen Receptor Signaling
  - AR amplification
  - AR splice variants
  - AR signaling via alternate ligands (steroid receptor superfamily)
  - AR signaling via PI3Kinase/ MAPKinase etc

1. Geller J, 1969.
2. Mohler JL et al. *Clin Cancer Res*. 2004;10:440-448.
3. Montgomery RB et al. *Cancer Res*. 2008; 68:4447-4454.
4. Ryan C et al. 2008 ASCO:5018.
5. Scher HI et al. 2008 ASCO:5006.

Castration Resistant Prostate Cancer-New Clinical Insights

- Most men with CRPC do not yet have radiographic metastases

- Median time to metastasis is 2-3 years

- Determinants of time to onset of metastases are level of PSA and PSADT

Docetaxel Improves Overall Survival in mCRPC

Tannock IF et al. NEJM 2004

Petrylak et al, NEJM 2004

P=0.02
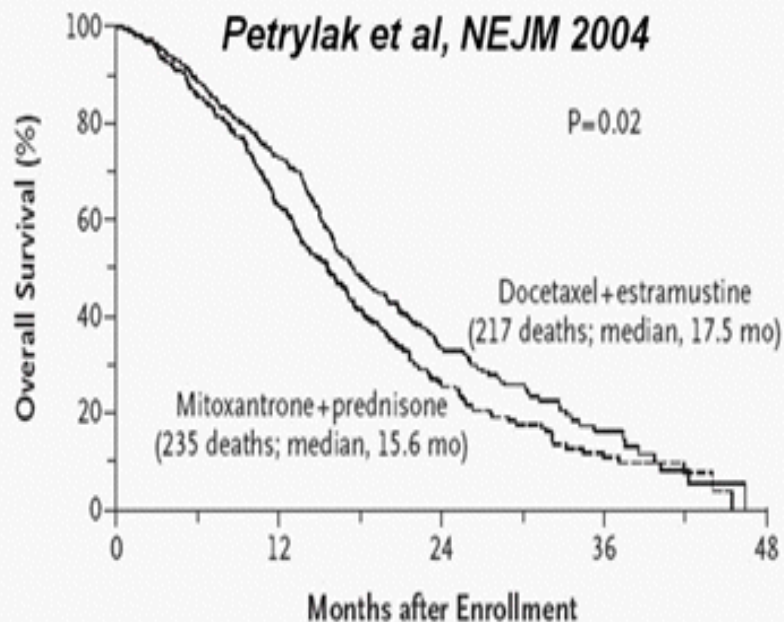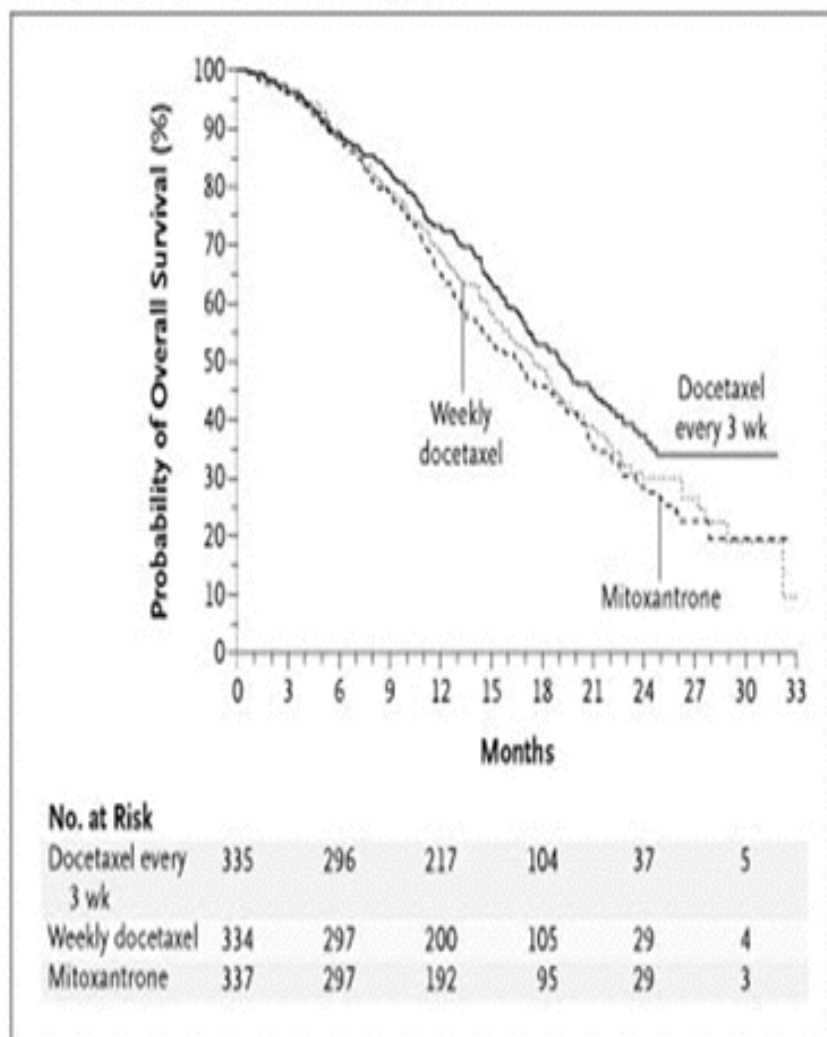
Docetaxel+estramustine
(217 deaths; median, 17.5 mo)

Mitoxantrone+prednisone
(235 deaths; median, 15.6 mo)

Figure 1. Kaplan–Meier Estimates of Overall Survival among Men with Andro-gen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.

Randomized Phase 3 IMPACT Trial

Asymptomatic or minimally symptomatic metastatic CRPC

N=512

2:1

Sipuleucel-T q 2 weeks x 3

Placebo q 2 weeks x 3
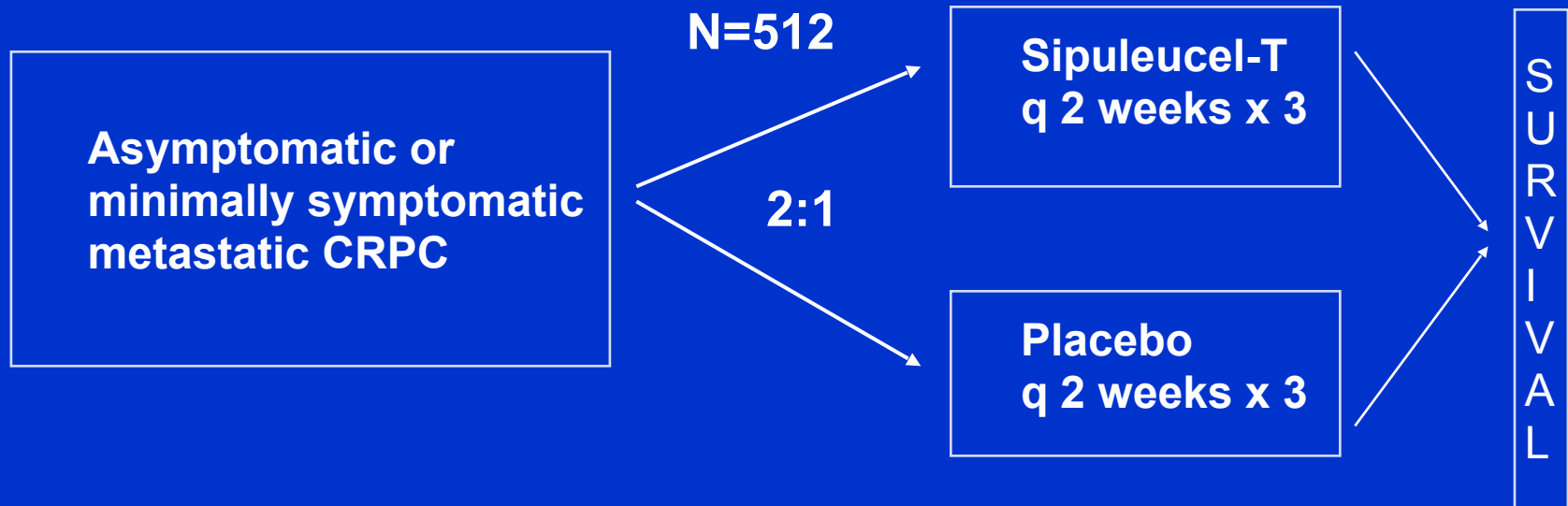
S U R V I V A L

Primary endpoint: Overall survival

Secondary endpoint: Objective disease progression

Kantoff PW, et al, NEJM, July, 2010

Immunotherapy for Prostate Cancer - Provenge
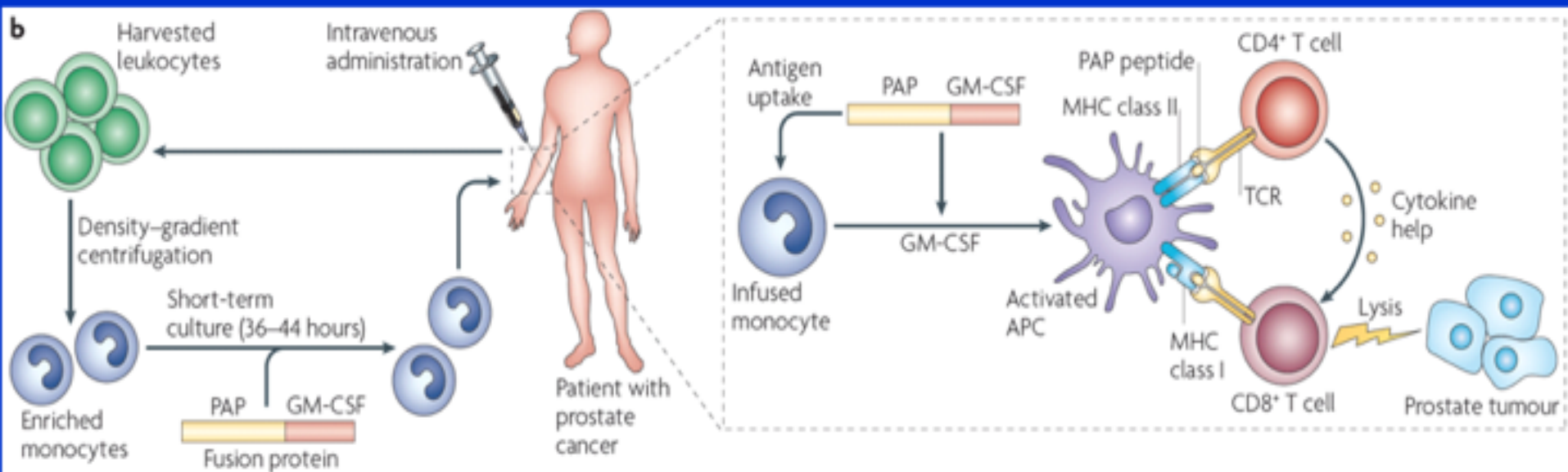
Administering three doses of autologous antigen-presenting cells stimulated by a chimeric protein comprising prostatic acid phosphatase (PAP) and GM-CSF over a 1-month period

Drake CG, Nature Reviews Immunology, Aug. 2010

IMPACT Study

- PROVENGE improved median survival by 4.1 months compared to the control group (25.8 months versus 21.7 months). Overall, PROVENGE reduced the risk of death by 22.5%

- No effect on the time to disease progression was observed

- No evidence of a favorable effect on PSA, tumor regression, or stabilization of soft tissue or bony disease radiographically, or health-related quality of life

Kantoff PW, et al, NEJM July, 2010

Novel Hormonal Agents

- Abiraterone - CYP 17 inhibitors

- Enzalutamide - Antiandrogen

Androgenic Steroidogenesis
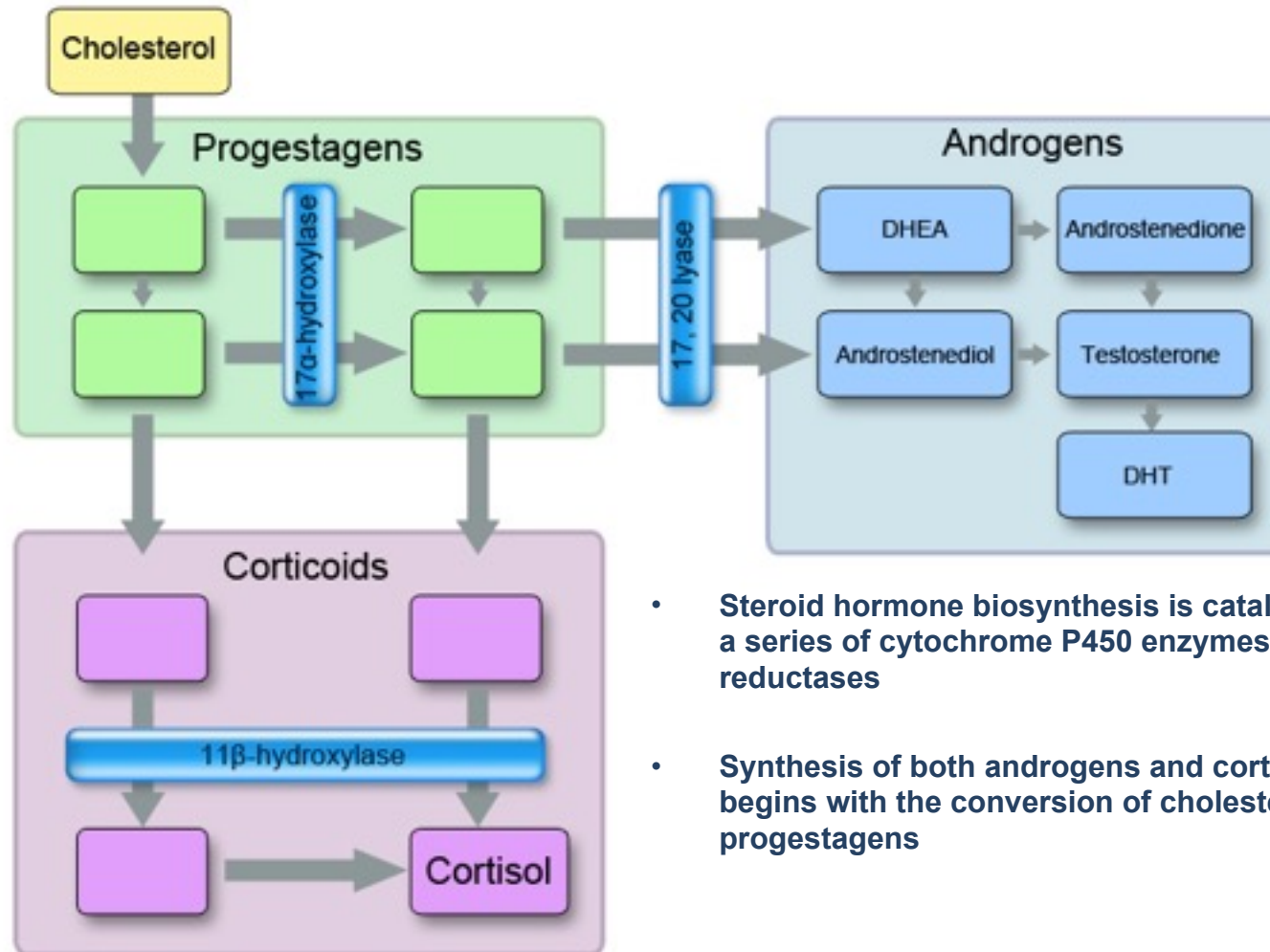
- Steroid hormone biosynthesis is catalyzed by a series of cytochrome P450 enzymes and reductases

- Synthesis of both androgens and corticoids begins with the conversion of cholesterol to progestagens

Abiraterone Acetate
17α hydroxylase, c17-20 lyase inhibitor

Cholesterol → Desmolase

Pregnenolone → 17α OH-pregnenolone → DHEA

Abiraterone

17α hydroxylase   c17-20 lyase

X   X   X   X

Progesterone → 17α OH-progesterone → Androstenedione

11β hydroxylase

21 hydroxylase

Corticosterone   Cortisol   oestrone   testosterone

5αred

18 hydroxylase

Aldosterone   oestradiol   DHT
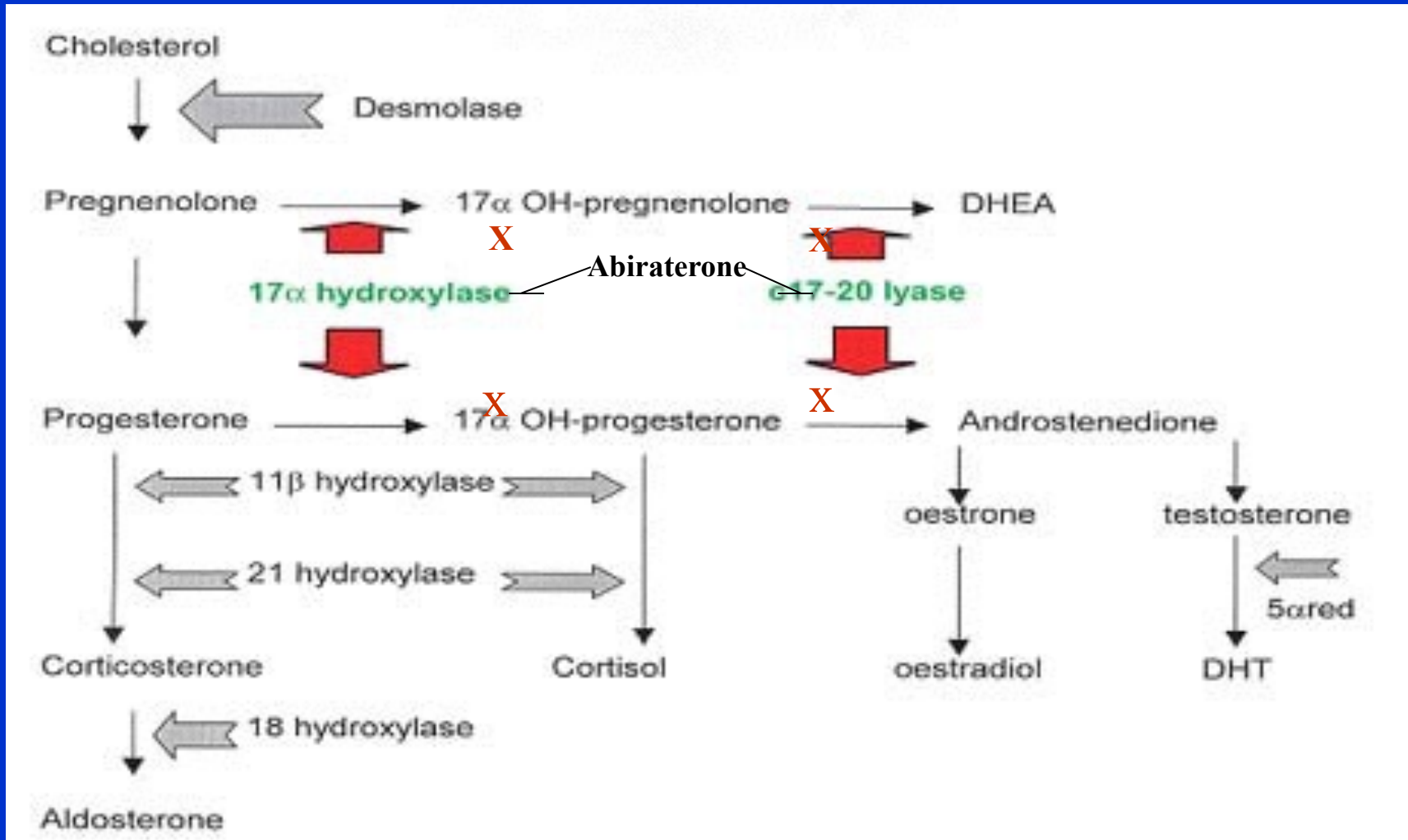
Reid AH, et al. Significant and sustained antitumor activity in post-docetaxel, CRPC with CYP17 inhibitor abiraterone acetate. J Clin Onc 2010;28:1489-95.

AR Activation by Androgen
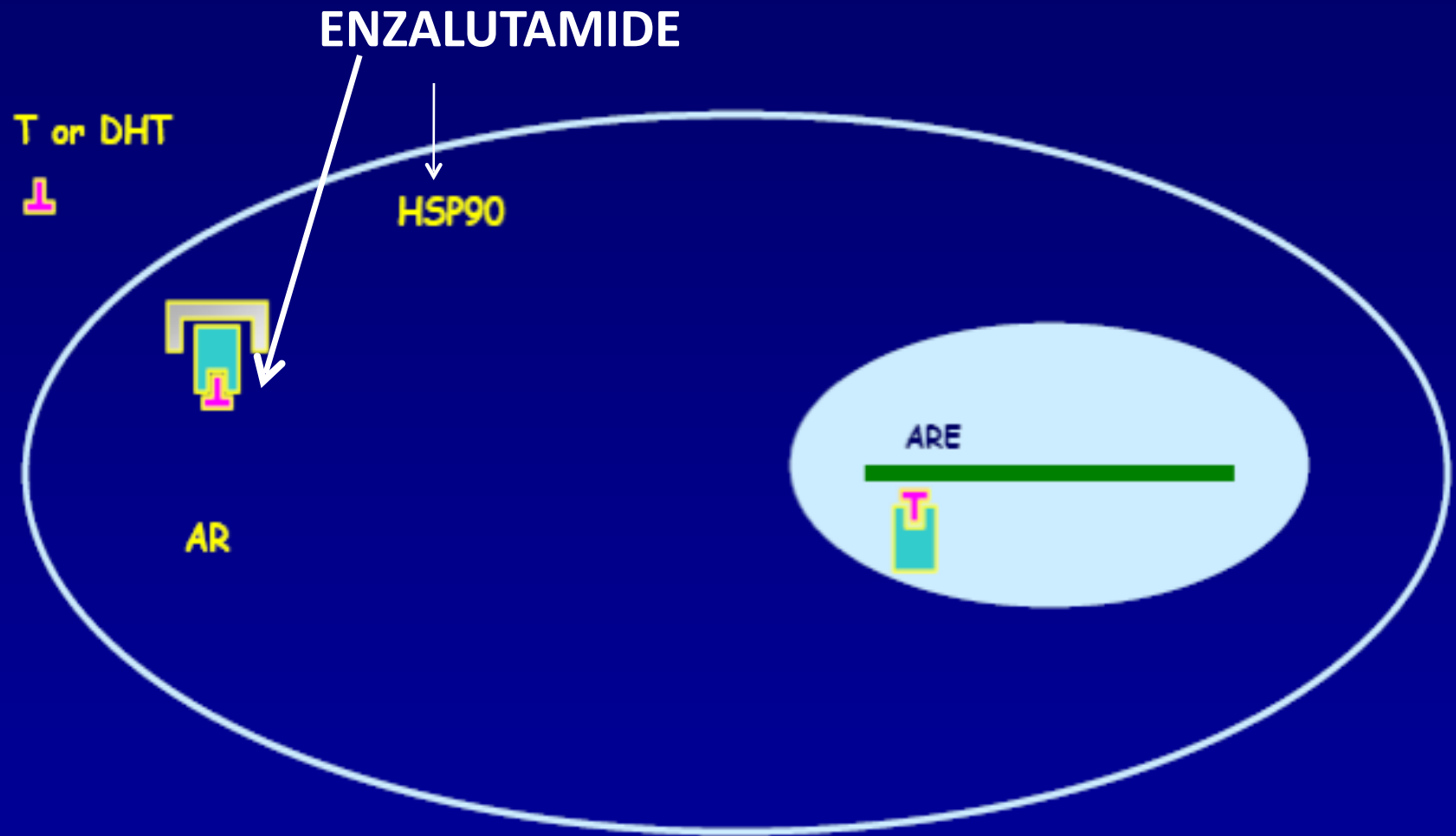
Enzalutamide (MDV3100)

- Oral investigational drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway

- No demonstrated agonist effects in pre-clinical models

T

T/DHT

X Enzalutamide

1 Inhibits Binding of Androgens to AR

AR

Cell cytoplasm

2 Inhibits Nuclear Translocation of AR

X

Cell nucleus

AR

Tumor Death

3 Inhibits Association Of AR with DNA

Tran et al. Science 2009;324:787–90.
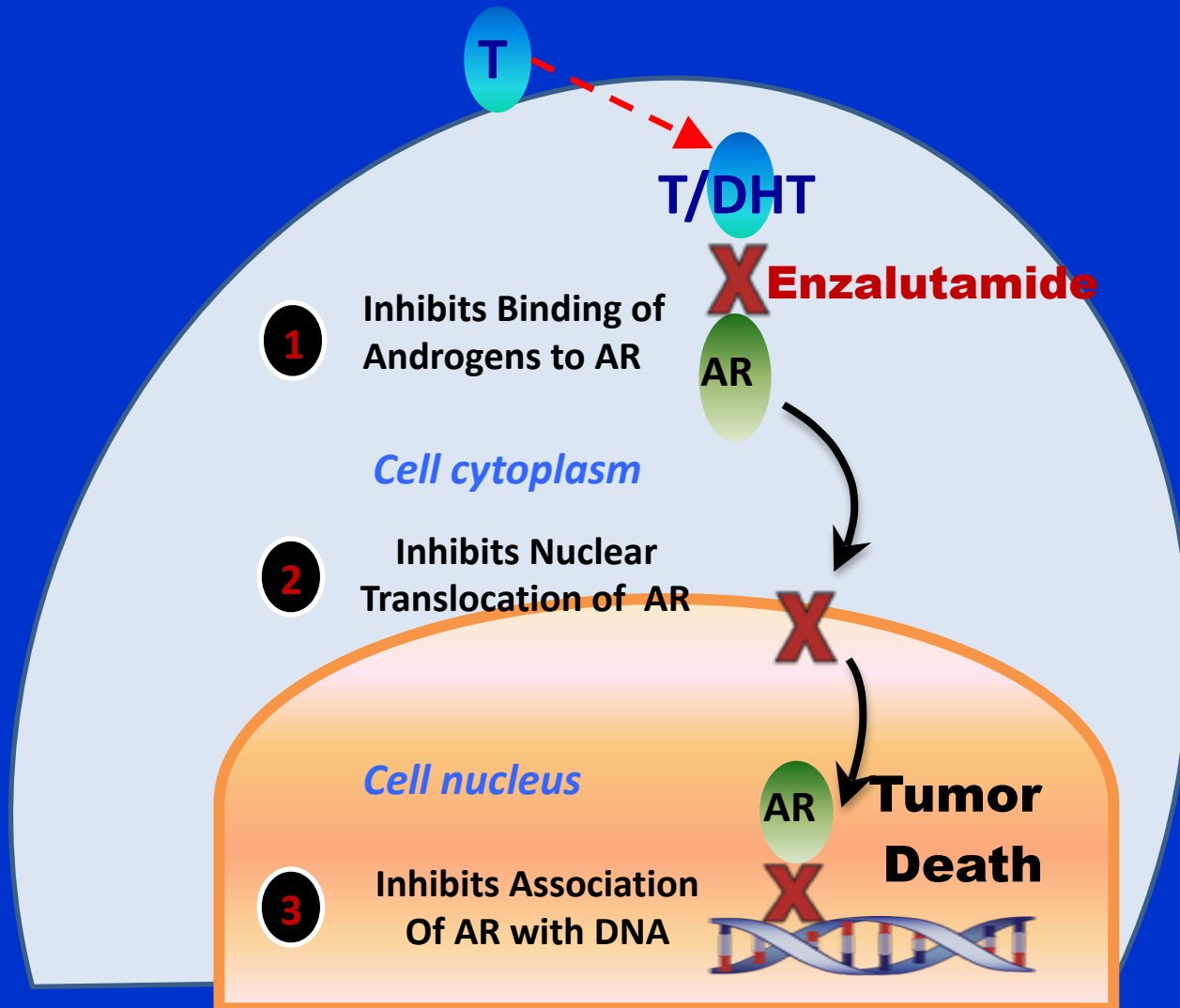
OS Benefit in Recent CRPC Trials

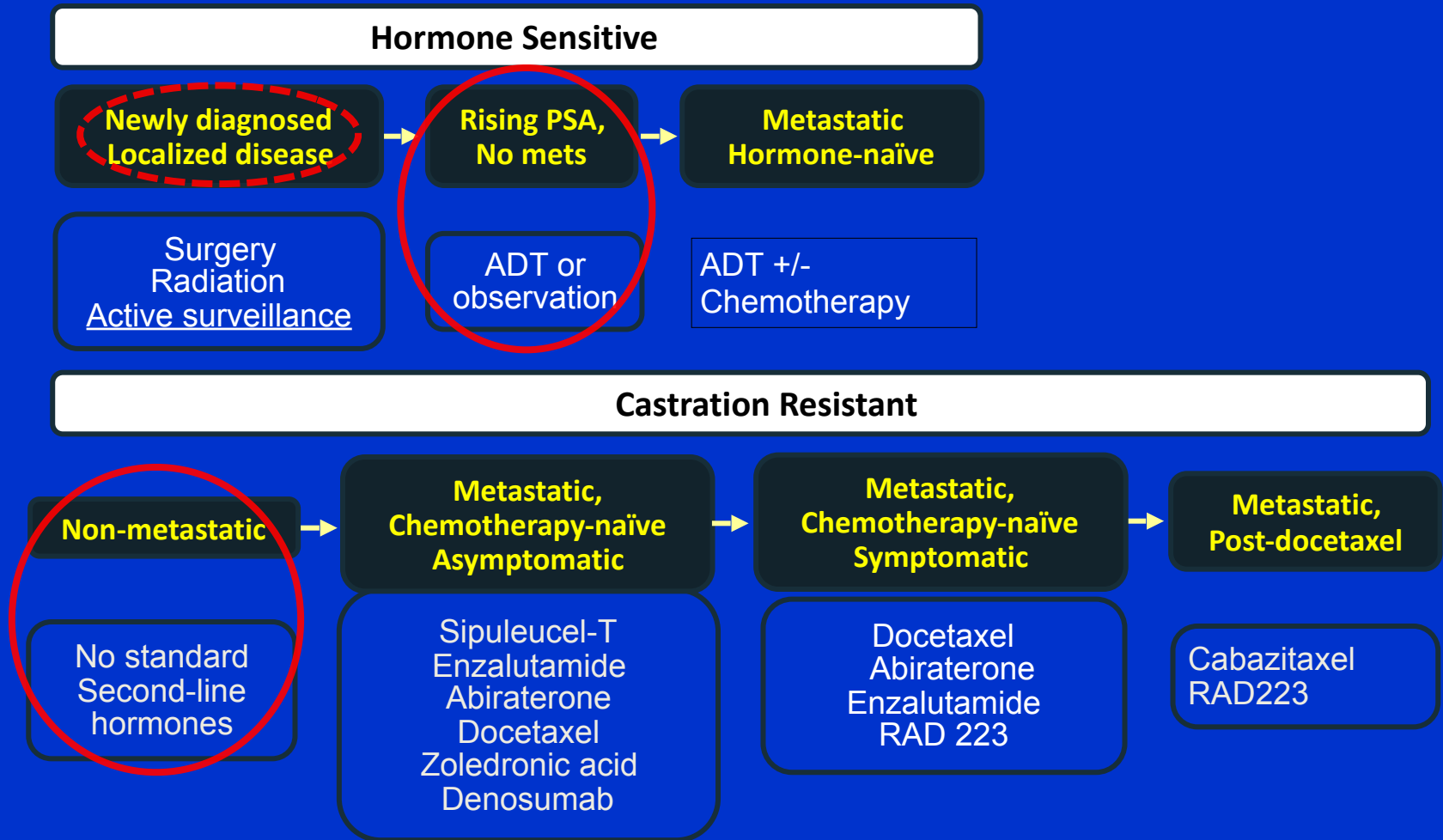| Trial/ Agent	Mechanism	Comparator	Survival (months)	Hazard Ratio	P-value	Reference
AFFIRM Enzalutamide	Androgen Receptor Signaling Inhibitor	Placebo	18.4 vs. 13.6	0.631	<0.0001	de Bono et al, ASCO 2012
COU-AA-301 Abiraterone + prednisone	CYP17 Inhibitor	Placebo + prednisone	14.8 vs. 10.9	0.646	<0.0001	de Bono et al, NEJM 2011
TROPIC Cabazitaxel + prednisone	Cytotoxic	Mitoxantrone + prednisone	15.1 vs. 12.7	0.70	<0.0001	de Bono et al, Lancet 2010
Radium 223*	Alpha-particle emitting radionuclide	Placebo	14.9 vs 11.3	0.69	0.0018	Parker et al, ESMO 2011

Only 60% of these patients were post-docetaxel patients

CRPC therapies that offer a survival benefit

Year approved	Agent	Indication	PFS benefit	OS benefit
2004	Docetaxel	mCRCP	?	√
2010	Sipuleucel-T	a - or minimally symptomatic mCRPC	No	√
2010	Cabazitaxel	Post-docetaxel mCRPC	√	√
2011 and 2012	Abiraterone	mCRPC	√	√
2012 and 2014	Enzalutamide	mCRPC	√	√
2013	Radium-223	Symptomatic bone predominant mCRCP	SSRE	√

Prostate Cancer Landscape: 2016

Hormone Sensitive

Newly diagnosed Localized disease	Rising PSA, No mets	Metastatic Hormone-naïve
Surgery Radiation Active surveillance	ADT or observation	ADT +/- Chemotherapy

Castration Resistant

Non-metastatic	Metastatic, Chemotherapy-naïve Asymptomatic	Metastatic, Chemotherapy-naïve Symptomatic	Metastatic, Post-docetaxel
No standard Second-line hormones	Sipuleucel-T Enzalutamide Abiraterone Docetaxel Zoledronic acid Denosumab	Docetaxel Abiraterone Enzalutamide RAD 223	Cabazitaxel RAD223

Recent Advances

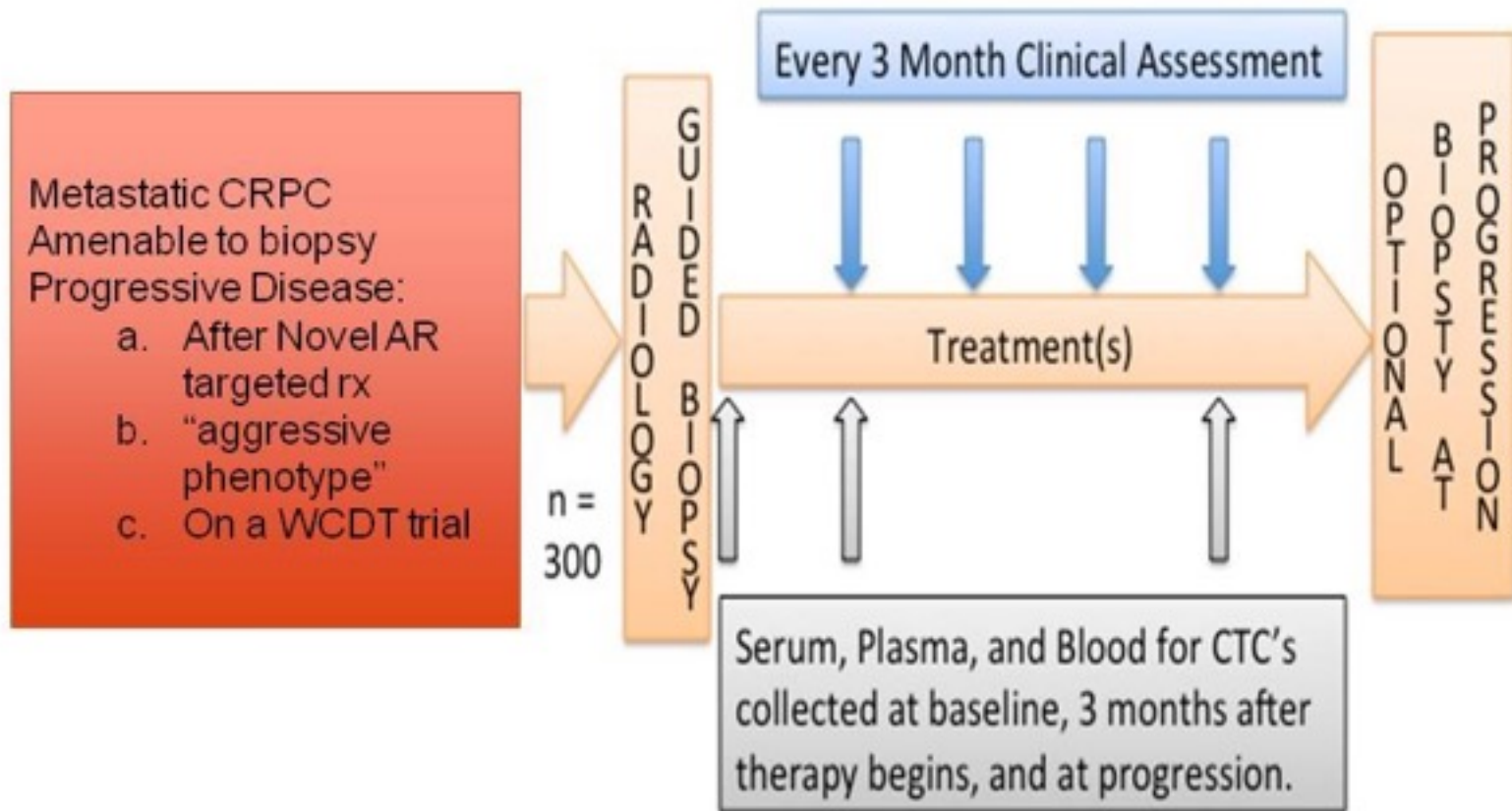# Integrative Clinical Genomics of Advanced Prostate Cancer

Dan Robinson,[1,2,43] Eliezer M. Van Allen,[3,4,43] Yi-Mi Wu,[1,2] Nikolaus Schultz,[5,40] Robert J. Lonigro,[1] Juan-Miguel Mosquera,[6,7,8,38] Bruce Montgomery,[9,10] Mary-Ellen Taplin,[3] Colin C. Pritchard,[26] Gerhardt Attard,[11,12] Himisha Beltran,[7,8,13,38] Wassim Abida,[14,20] Robert K. Bradley,[9] Jake Vinson,[15] Xuhong Cao,[1,42] Pankaj Vats,[1] Lakshmi P. Kunju,[1,2,17] Maha Hussain,[16,17,18] Felix Y. Feng,[1,17,19] Scott A. Tomlins,[1,2,17,18] Kathleen A. Cooney,[16,17,18] David C. Smith,[16,17,18] Christine Brennan,[1] Javed Siddiqui,[1] Rohit Mehra,[1,2] Yu Chen,[13,14,20] Dana E. Rathkopf,[13,20] Michael J. Morris,[13,20] Stephen B. Solomon,[21] Jeremy C. Durack,[21] Victor E. Reuter,[22] Anuradha Gopalan,[22] Jianjiong Gao,[40] Massimo Loda,[3,4,23,39] Rosina T. Lis,[3,23] Michaela Bowden,[3,23,39] Stephen P. Balk,[24] Glenn Gaviola,[25] Carrie Sougnez,[4] Manaswi Gupta,[4] Evan Y. Yu,[10] Elahe A. Mostaghel,[9,10] Heather H. Cheng,[9,10] Hyojeong Mulcahy,[27] Lawrence D. True,[28] Stephen R. Plymate,[10] Heidi Dvinge,[9] Roberta Ferraldeschi,[11,12] Penny Flohr,[11,12] Susana Miranda,[11,12] Zafeiris Zafeiriou,[11,12] Nina Tunariu,[11,12] Joaquin Mateo,[11,12] Raquel Perez-Lopez,[11,12] Francesca Demichelis,[7,29] Brian D. Robinson,[6,7,8,38] Marc Schiffman,[7,31,38] David M. Nanus,[7,8,13,38] Scott T. Tagawa,[7,8,13,38] Alexandros Sigaras,[7,30,32] Kenneth W. Eng,[7,30,32] Olivier Elemento,[30] Andrea Sboner,[6,7,30,38] Elisabeth I. Heath,[33,34] Howard I. Scher,[13,20] Kenneth J. Pienta,[35] Philip Kantoff,[3,44] Johann S. de Bono,[11,12,44] Mark A. Rubin,[6,7,8,38,44] Peter S. Nelson,[10,36,37,38,44] Levi A. Garraway,[3,4,44] Charles L. Sawyers,[14,41,44,*] and Arul M. Chinnaiyan[1,2,17,18,42,44,*]

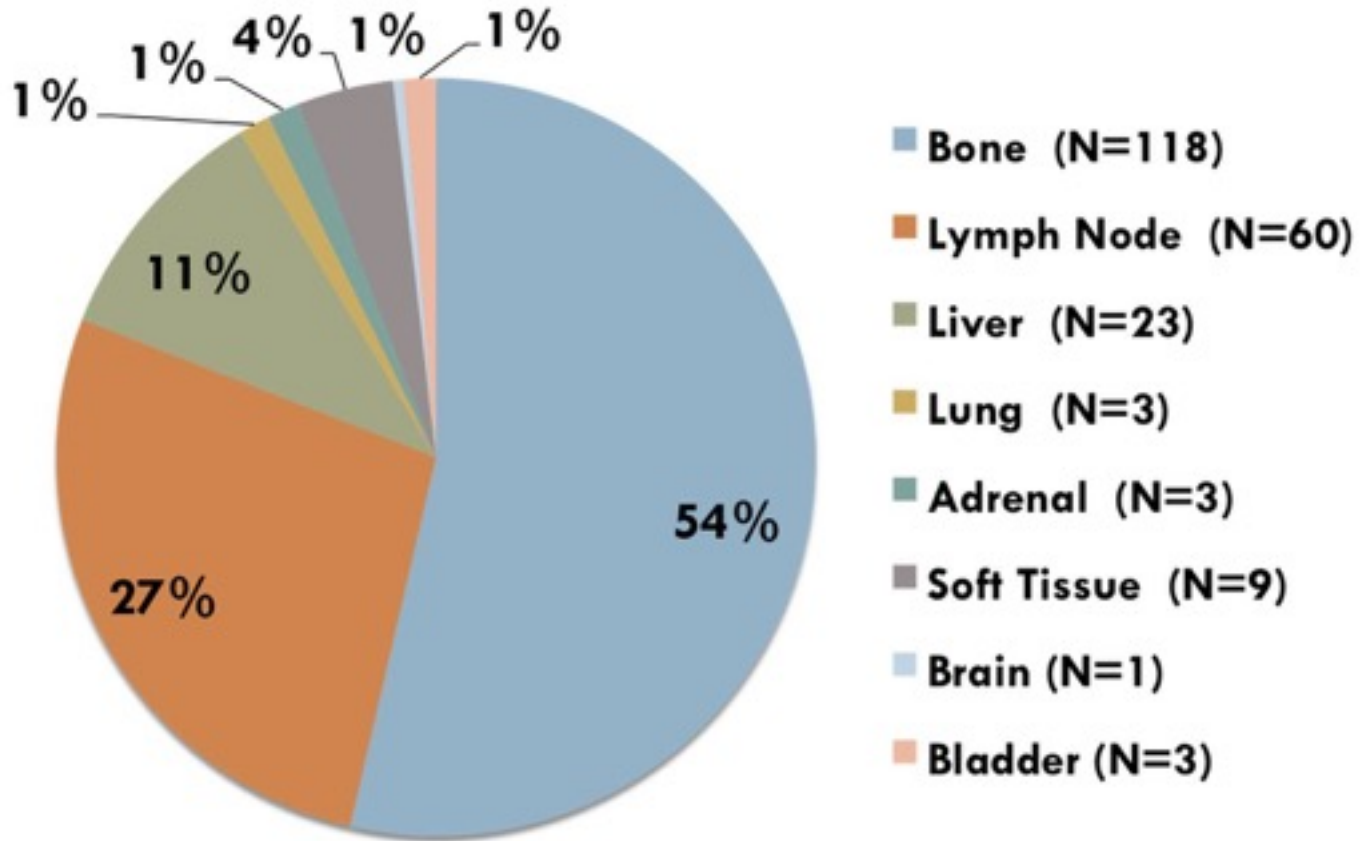KNIGHT CANCER INSTITUTE
OHSU Oregon Health & Science University

Presented By Tomasz Beer at Genitourinary Cancers Symposium 2016

Dream Team Biopsy Trial

Metastatic CRPC
Amenable to biopsy
Progressive Disease:
a. After Novel AR targeted rx
b. "aggressive phenotype"
c. On a WCDT trial

n = 300

RADIOLOGY GUIDED BIOPSY

Every 3 Month Clinical Assessment

Treatment(s)

OPTIONAL BIOPSTY AT PROGRESSION

Serum, Plasma, and Blood for CTC's collected at baseline, 3 months after therapy begins, and at progression.

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Robert Dreicer at 2015 ASCO Annual Meeting

Sites of Biopsy Acquisition
(as of 12/1/15; n = 220)

- Bone (N=118)
- Lymph Node (N=60)
- Liver (N=23)
- Lung (N=3)
- Adrenal (N=3)
- Soft Tissue (N=9)
- Brain (N=1)
- Bladder (N=3)

54%
27%
11%
1%
1%
4%
1%
1%

KNIGHT CANCER INSTITUTE
Oregon Health & Science University
OHSU

Histology of 124 Evaluable Biopsies

- 13% classic small cell/neuroendocrine cancer (SCNC)

- 26% of biopsies are an Intermediate Atypical Carcinoma (IAC) distinct from AdenoCa and SCNC

- 26% of biopsies had distinct, but mixed populations

PRESENTED AT: ASCO Annual '15 Meeting

Intermediate Atypical Carcinoma is a new, highly reproducible pathologic subclass

J Huang (UCLA), G Thomas (OHSU), L True (U Wash), B Robinson, M Rubin (Cornell)

Huang Criteria

"cytologically bland"

	AdenoCa	Intermediate Atypical Carcinoma	SCNC
Cytoplasm	Abundant	Moderate to abundant	Scant
Nuclear chromatin	Clumpy, vacuolated, open chromatin pattern	Fine homogeneous chromatin pattern	Fine homogeneous chromatin pattern
Nuclear staining	Light	Dark	Dark
Nuclear shape	Some degree of irregularity	Round and regular	Irregular
Nuclear molding	No	No	Yes
Nucleoli	Prominent macronucleoli	Absent or central small nucleolus	No nucleoli
Crush artifact	No	No	Yes
Mitotic figures	Rare	Rare	Common
Glandular formation	Obvious	Vague	No

Overall survival as function of biopsy pathology Grouping IAC and SCNC
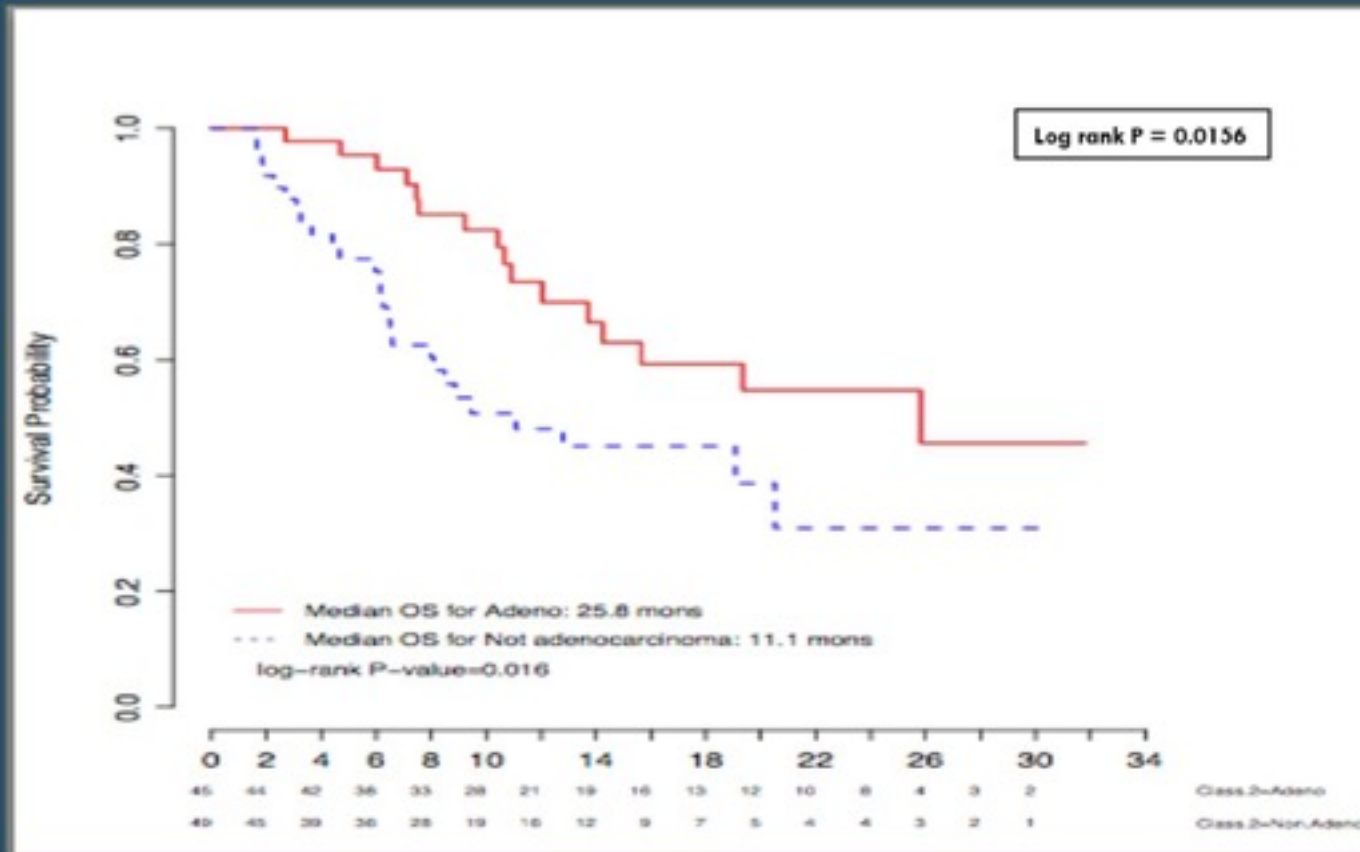
Conclusions

A new histologic subset of metastatic CRPC has been identified which appears to be intermediate to adenocarcinoma and small cell/neuroendocrine cancer (SCNC).

Despite being histologically bland, this is an aggressive cancer with survival similar to that seen with SCNC.

More that a third of biopsies revealed a non-adenocarcinoma histology, representing an important – and potentially growing – group of patients.

Is this a true effect of greater use of highly potent AR targeted therapy or ascertainment bias, or both?
- More biopsies of metastases
- FFPE increases discrimination

Eligibility: Recognition That the *Optimal Sequence* *To Utilize* the Currently Approved Life Prolonging Therapies is Unknown and that the *Histology* Can Change Over Time

Non-castrate

Castration Resistant

Clinically Localized Disease → Rising PSA → Clinical Metastases: Noncastrate

Rising PSA → Non-Metastatic CRPC

Clinical Metastases: Noncastrate / Non-Metastatic CRPC →

| Castration Resistant Metastatic Pre-	Castration Resistant Metastatic 1st-Line	Castration Resistant Metastatic Post-
Abiraterone Enzalutamide Sipuleucel-T Radium-223	Docetaxel	Abiraterone Enzalutamide Cabazitaxel Radium-223

Eligibility: A Revised Clinical States Model to Account for the Effect of Prior Therapy(ies) on Disease Biology

Clinically Localized Disease → Rising PSA → Clinical Metastases: Noncastrate / Non-Metastatic CRPC → Castration Resistant Metastatic 1st Line → Castration Resistant Metastatic 2nd Line → Castration Resistant Metastatic 3rd Line → Castration Resistant Metastatic 4th Line
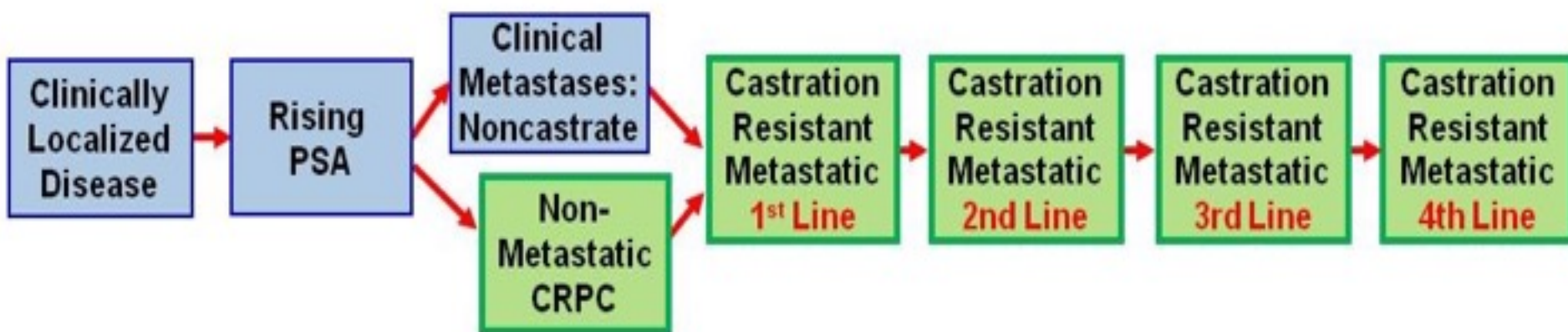
Action: Detail prior therapies **in the order administered**: including start and stop dates, and response if applicable

Blood based diagnostics: testosterone (ultrasensitive), CTC, cf DNA, immune

Rebiopsy: **Histology**: adenocarcinoma, small cell, intermediate phenotypes **Biologic characterization**

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Controlling for Flare with 2+2, per PCWG3

Baseline	Week 9 POSTERIOR	Week 17 POST WB	Week 25 POSTERIOR	Week 37 POSTERIOR	Week 49 POSTERIOR
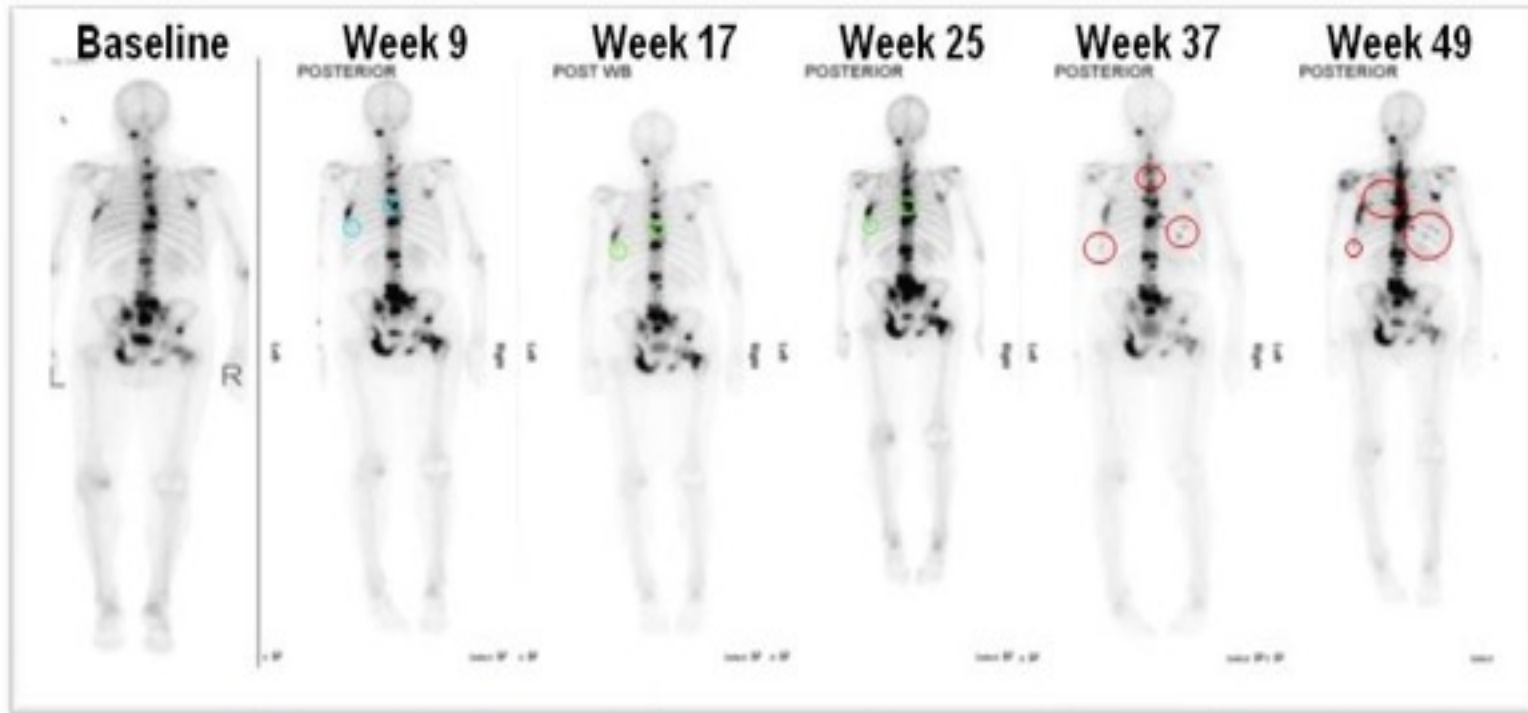
Two new lesions at week 9 (new baseline)

No progression at week 17 (2+2 not met)

Progression at week 37 (two new lesions relative to week 9 at week 37 confirmed at week 49)

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Identifying Molecular Alterations in CRPC

Robinson et. al. Cell 161, 1215-1228 (2015)

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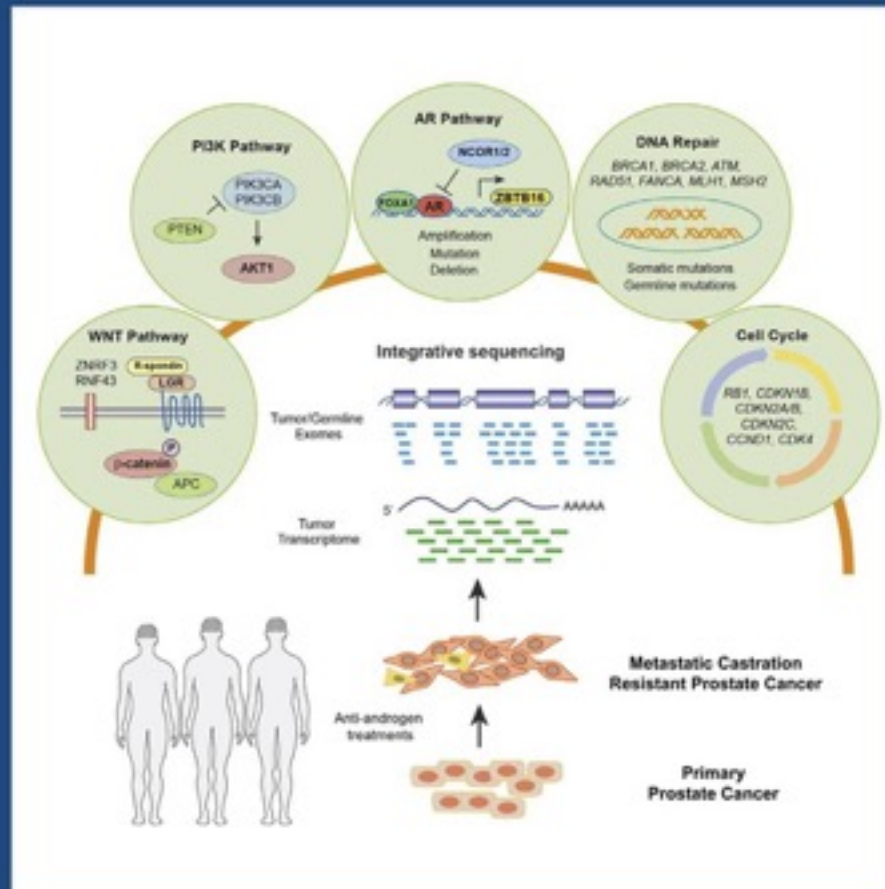
Clinical Utility

- Nothing in routine clinical use yet
- Allocation to investigational trials
  - DNA repair defects
  - PI3K pathway
  - Raf kinases
  - MMR - Immunotherapy
  - AR defects
    - Amplification
    - Resistance mutations
    - Splice variants
      - AR-V7

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Presented By Tomasz Beer at Genitourinary Cancers Symposium 2016

Biomarker based treatment


PRESENTED AT: **2016 Genitourinary Cancers Symposium**

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Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Presented By Peter Nelson, MD at 2014 Genitourinary Cancers Symposium

Prognosis in mCRPC

VOLUME 33 · NUMBER 12 · APRIL 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Circulating Tumor Cell Biomarker Panel As an Individual-Level Surrogate for Survival in Metastatic Castration-Resistant Prostate Cancer

Howard I. Scher, Glenn Heller, Arturo Molina, Gerhardt Attard, Daniel C. Danila, Xiaoyu Jia, Weimin Peng, Shahneen K. Sandhu, David Olmos, Ruth Riisnaes, Robert McCormack, Tomasz Burzykowski, Thian Kheoh, Martin Fleisher, Marc Buyse, and Johann S. de Bono

Survival
Based on CTC and LDH at 12 weeks
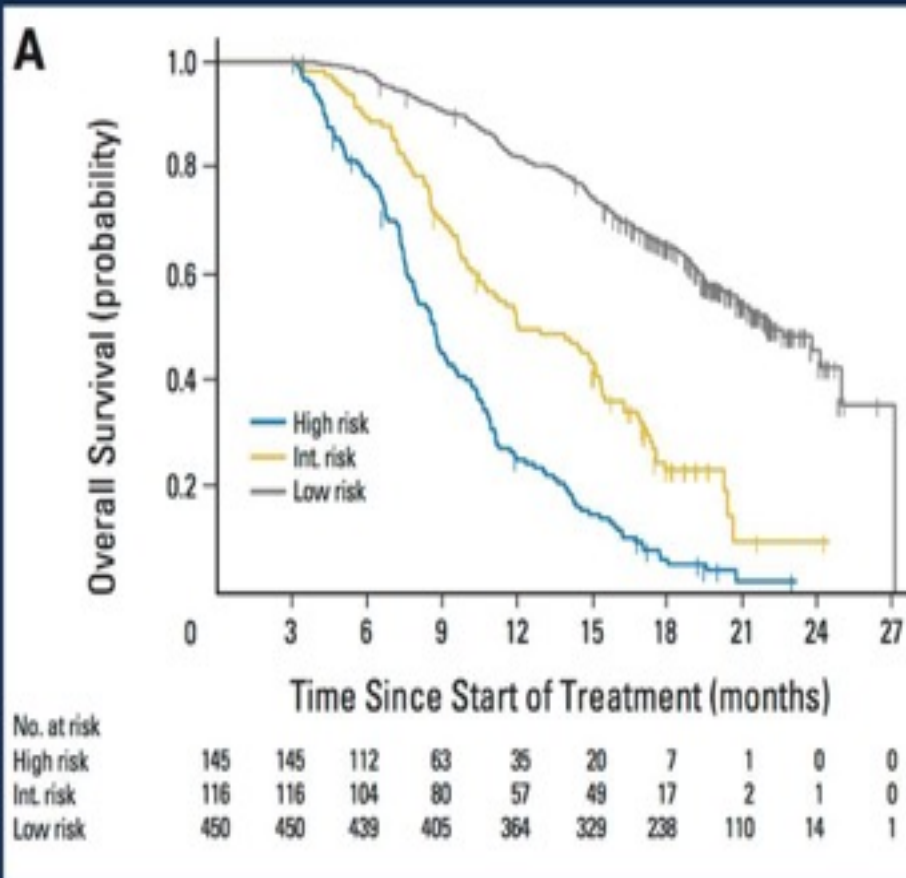
- 2-year survival
  - CTCs ☐☐ < 5 (low risk) 46%

  - CTCs ☐☐ > 5 cells and LDH ☐☐ > 250 U/L (high risk) 2%

AR-V7: predictor of treatment response?
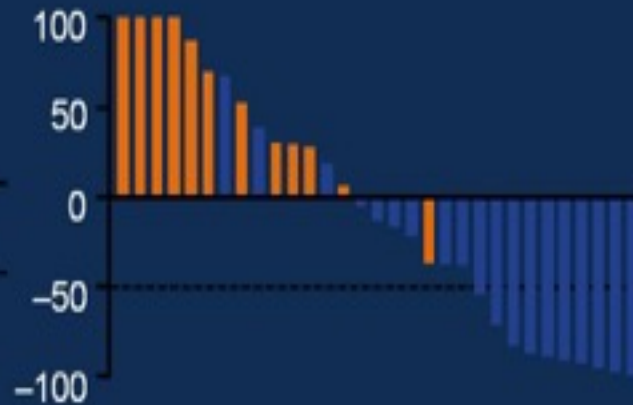
Abiraterone

PSA change, %
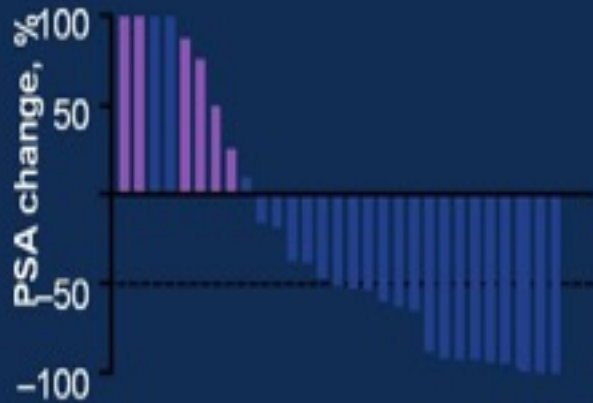
PSA response rate
AR-V7 positive: **0%** (95% CI: 0-46%)
AR-V7 negative: **68.0%** (95% CI: 46-85%)
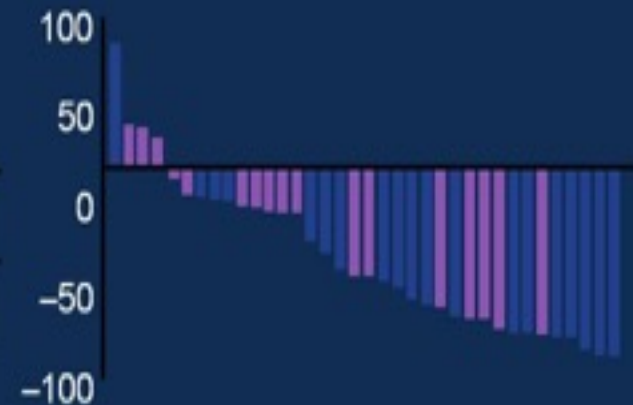*P*=0.004

Enzalutamide

PSA response rate:
AR-V7 positive: **0%** (95% CI: 0-26%)
AR-V7 negative: **52.6%** (95%CI: 29-76%)
P=0.004

Taxane

PSA response rate:
AR-V7 positive: **41%** (95% CI: 18-67%)
AR-V7 negative: **65%** (95%CI: 41-85%)
P=0.19

Antonarakis ES et al. NEJM 2014, JAMA Oncology August 2015 Volume 1, Number 5

Presented By Fred Saad at Genitourinary Cancers Symposium 2016

Final Conclusions

- Widespread screening is out and Intelligent screening is in

- Active surveillance is safe and dissociates screening from treatment

- Local therapy for prostate cancer in all non-metastatic patients
    - May be beneficial in metastatic

- Chemotherapy in metastatic prostate is here to stay (for now)
    - For high risk non-metastatic?

- Abiraterone and enzalutamide 1st line for most mCRPC
    - Earlier may be better

- Personalization and new targeted therapies are on their way
    - Good for research and patients

Presented By Fred Saad at Genitourinary Cancers Symposium 2016