Prostate cancer 101, 2007

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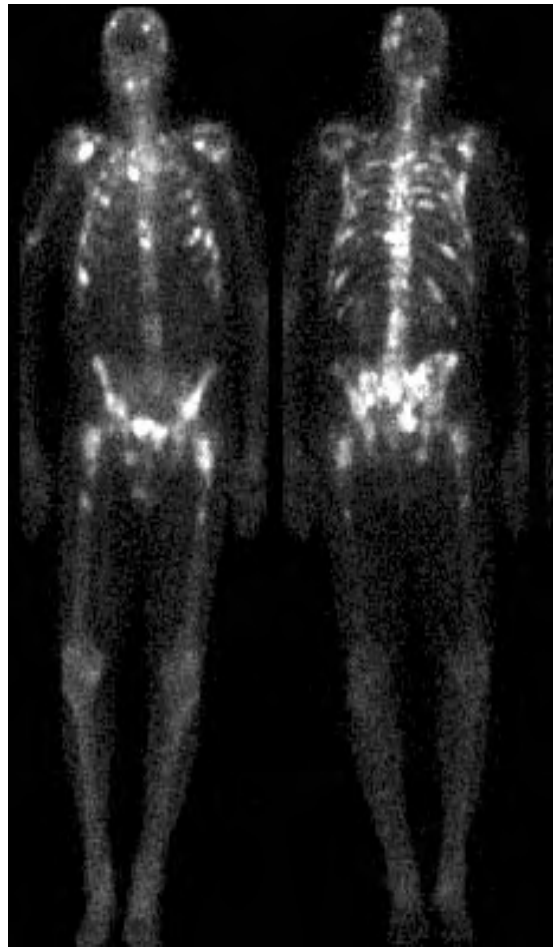


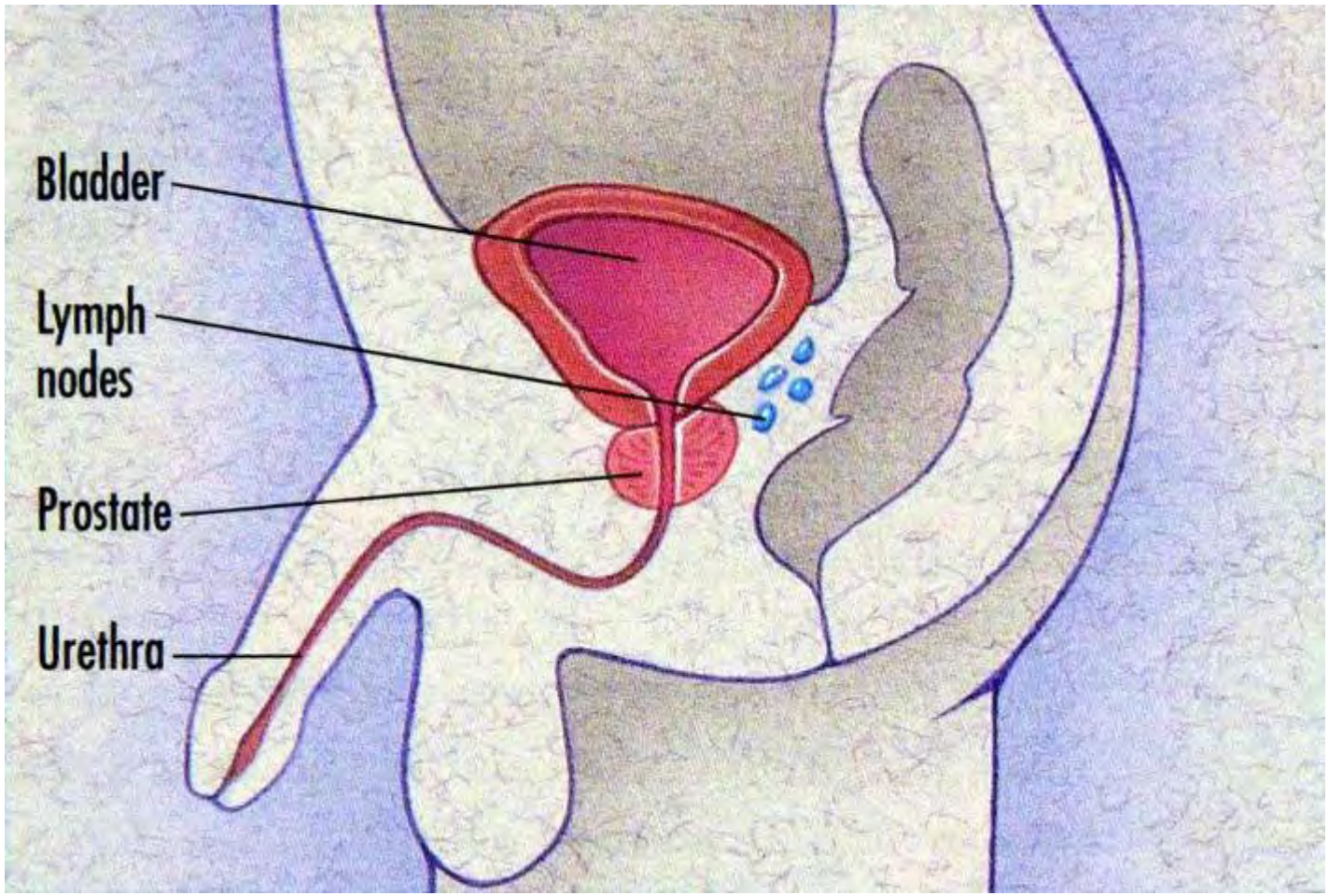
http://gamma.wustl.edu/bs045te143.html

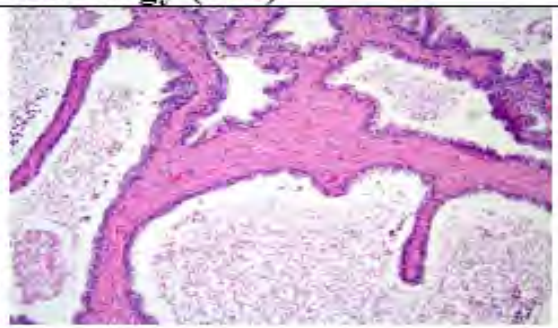
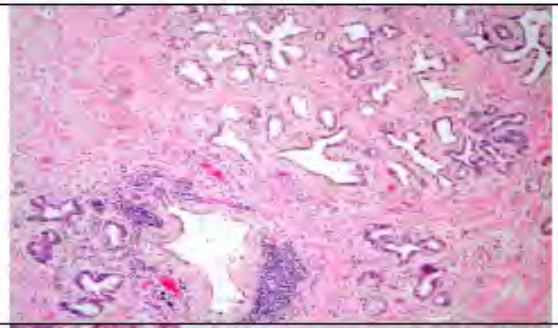
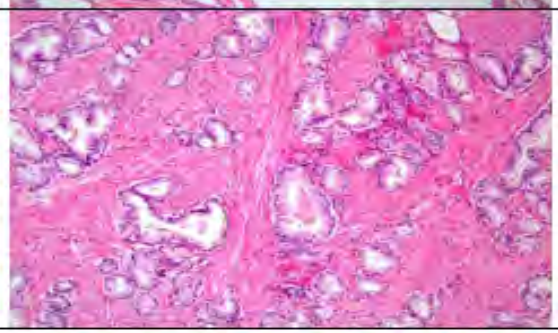
Five-year Relative Survival (%)* during Three Time Periods By Cancer Site

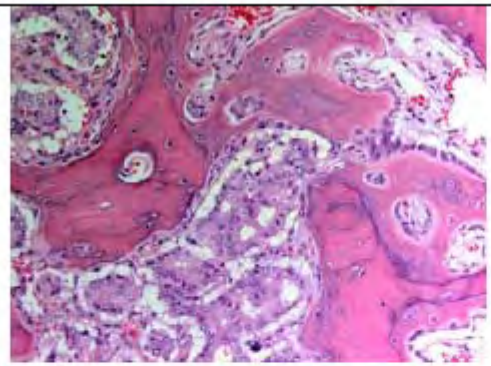
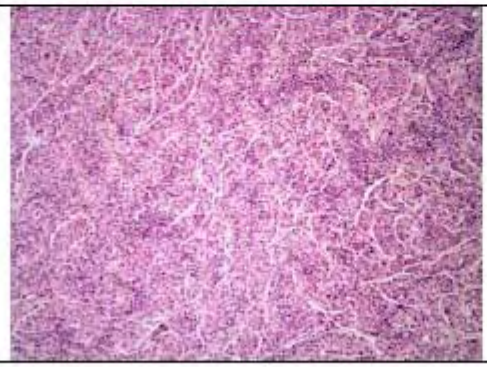
Site	1974-1976	1983-1985	1995-2001
• All sites	50	53	65
• Breast (female)	75	78	88
• Colon	50	58	64
• Leukemia	34	41	48
• Lung and bronchus	12	14	15
• Melanoma	80	85	92
• Non-Hodgkin lymphoma	47	54	60
• Ovary	37	41	45
• Pancreas	3	3	5
• Prostate	67	75	100
• Rectum	49	55	65
• Urinary bladder	73	78	82

***5-year relative survival rates based on follow up of patients through 2002.**
Source: Surveillance, Epidemiology, and End Results Program, 1975-2002, Division of Cancer Control and Population Sciences, National Cancer Institute, 2005.

PROSTATE ANATOMY



Disease State	Histology (10x)	Description
Normal prostate		Large glands with papillary in-foldings that are lined with a 2-cell layer consisting of basal cells and columnar secretory epithelial cells with pale cytoplasm and uniform nuclei **Susceptibility genes or events:** *HPC1/RNASEL, HPC2, HPC20, HPCX, MSR1, PCAP, CAPB*
Proliferative inflammatory atrophy (PIA)		Atrophic glands have scant cytoplasm and hyperchromatic nuclei and occasional nucleoli **Susceptibility genes or events:** Loss of *NKX3.1, PTEN, CDKN1B*
Prostatic intraepithelial neoplasia (PIN)		Intermediate to large size glands with proliferative changes contained within the gland **Susceptibility genes or events:** *GSTP1* hypermethylation; Increased hepsin, *AMACR*, *TMPRSS2:ETS* Loss of *p27*,
Prostate cancer		Small glands with abnormal nuclei and nucleoli; 2-cell layer architecture as well as glandular architecture; glands fuse as grade increases **Susceptibility genes or events:** Loss of, *Rb*

Metastatic prostate cancer		Nests of cancer cells within the bone **Susceptibility genes or events:** mutation of *TP53*; Decreases in *E-cadherin*, *nm23*, *KAI1*, *CD44*; Increase in *EZH2*
Androgen independent prostate cancer		**Susceptibility genes or events:** AR amplification, AR promiscuity, phosphorylation of AR by non-androgen growth factors, up-regulation of bcl-2, stem cell repopulation

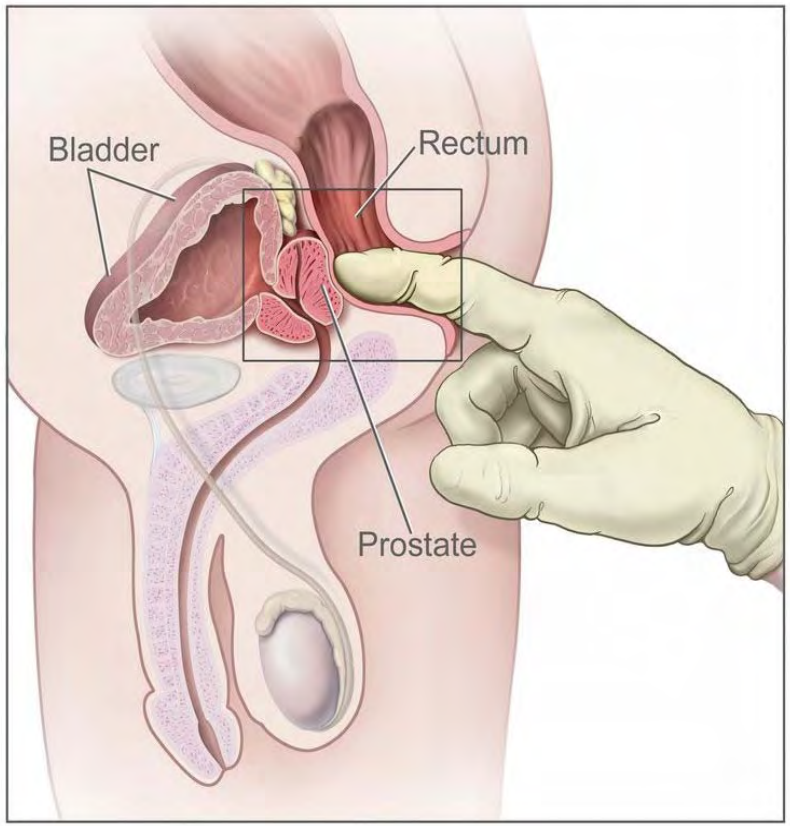
HOW COMMON IS PROSTATE CANCER?

Fill up UM Stadium with just men, then fill it up again, then fill up the Palace and THEN you have the number of men diagnosed with prostate cancer every year

PROSTATE CANCER

- INCIDENCE: 230,000 men diagnosed/year
    - # 1 cancer in men
    - One every 3 minutes
- DEATHS: 30,000 men die each year
    - # 2 cancer in men
    - One every 16 minutes

Prostate Cancer Detection



1. Digital rectal exam (dreaded DRE)
2. PSA (Prostate Specific Antigen)

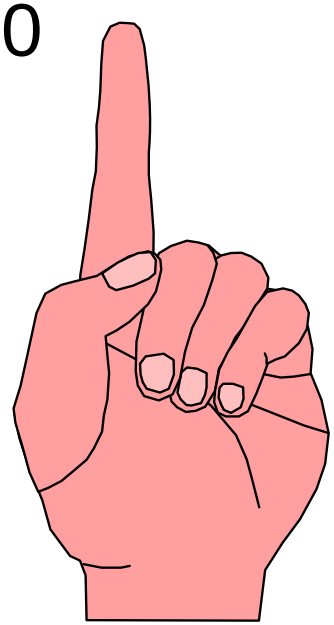
Prostate Cancer Screening: Old guidelines

DRE and PSA every year starting at age 50
Until patient is deemed to have < 10 yrs to live

If African American or + FH start at age 40

PSA > 4.0 or + DRE = Biopsy
(0.75ng/ml per yr rise)

* Endorsed by the AUA and the ACS, not the AMA or NCI



Prostate Specific Antigen

A serine protease

In the blood, binds to proteins (70-95%)

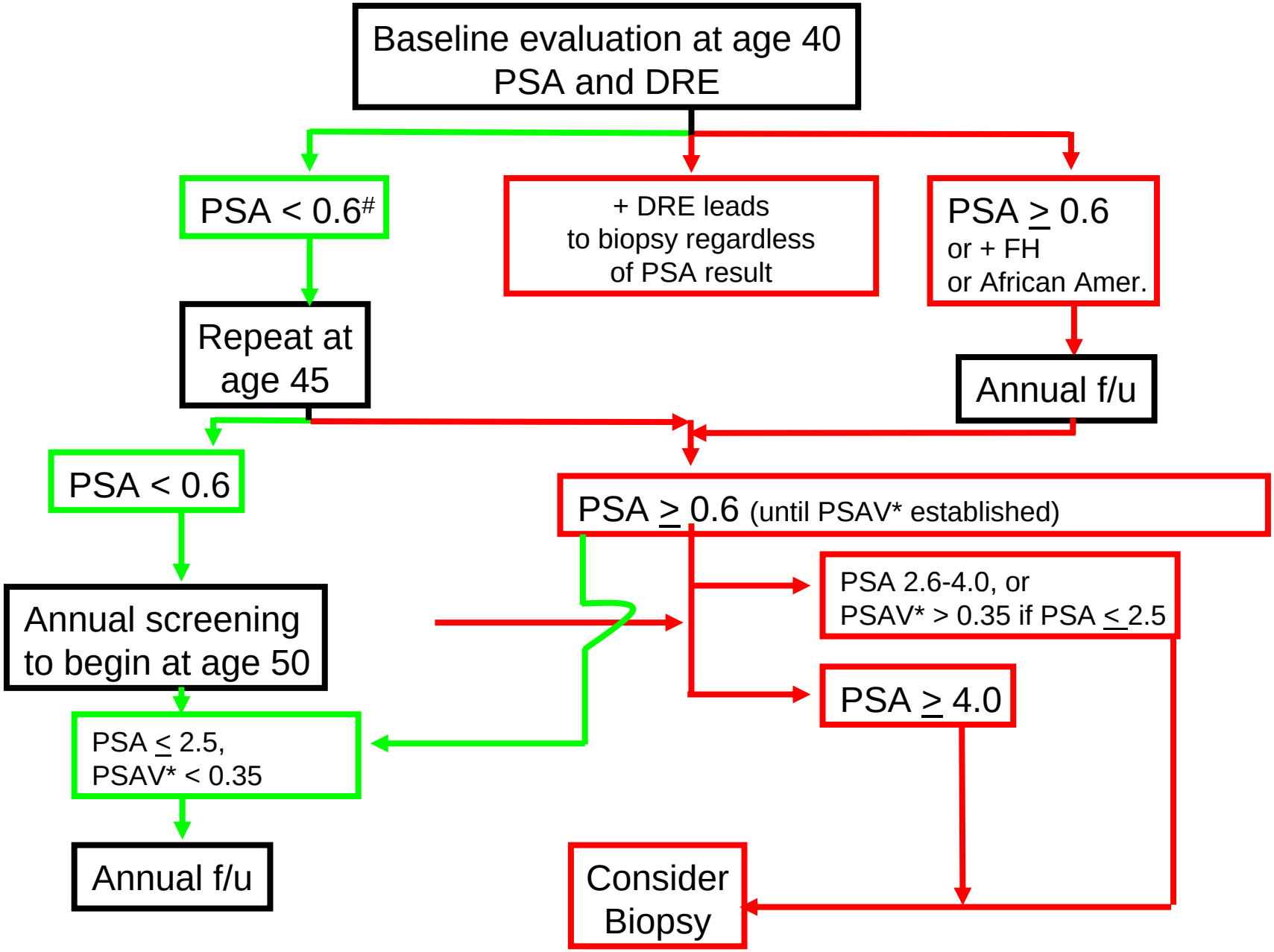
In the range of 2.5-15 ng/ml, the free/total PSA improves cancer detection

The higher the ratio, the less likely the patient has cancer

Cancer risk = 55% if <10% % fPSA
Cancer risk = 5% if >25% % fPSA

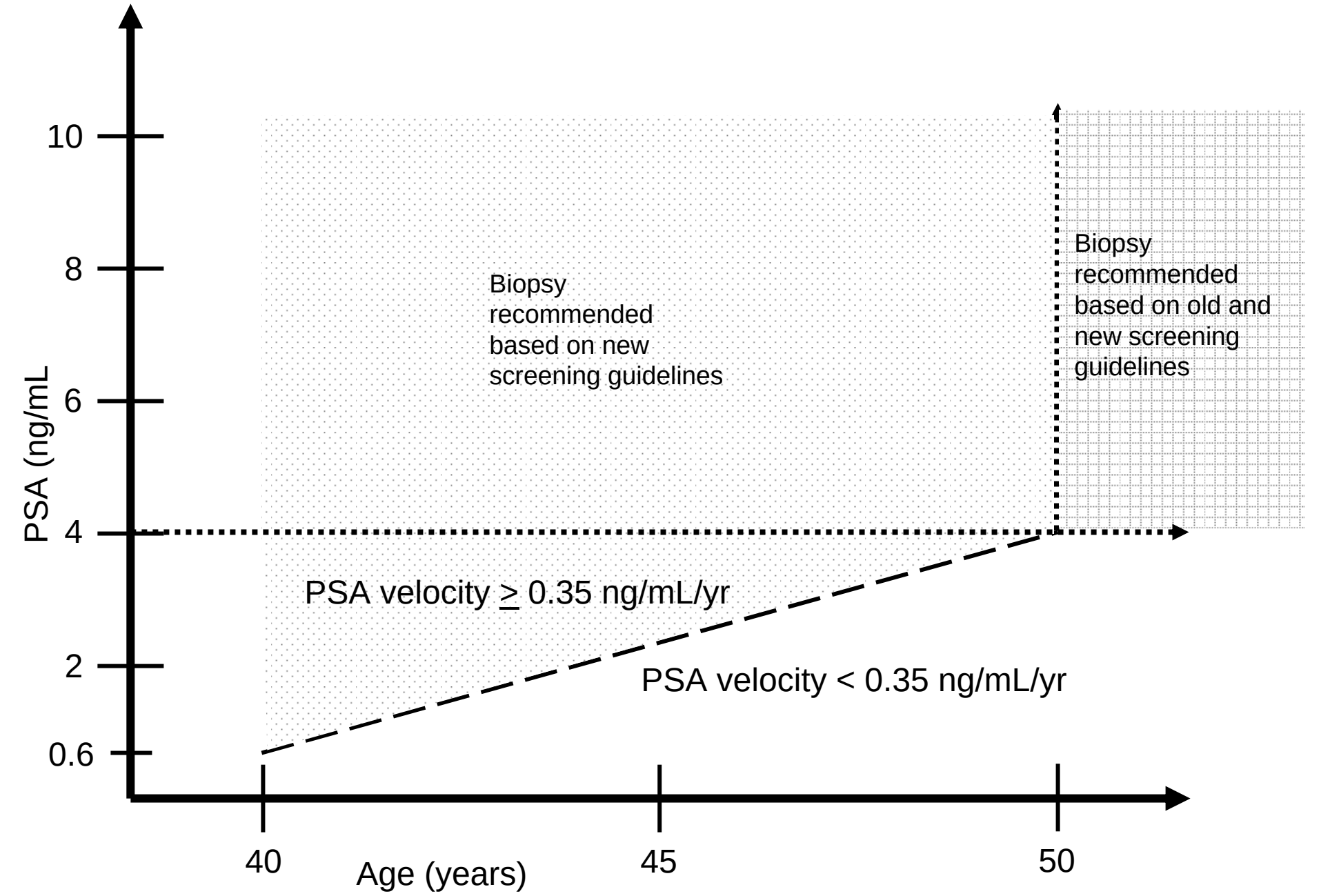
Primary Prostate Cancer Work-up

- PSA = 4-10: Ultrasound + sextant biopsies
  - NO bone scan, CT scan necessary
  - If Gleason Score 8-10, add bone scan and CT scan
- DRE +: Ultrasound + biopsies
- PSA > 10: US + biopsies + bone scan and CT scan of abdomen and pelvis



#PSA value in ng/mL

*PSAV = PSA velocity measurement in ng/mL/year. Measurements should be made on at least 3 consecutive specimens drawn over at least an 18-24 month period.


10
8
6
4
2
0.6
PSA (ng/mL
Biopsy recommended based on new screening guidelines
Biopsy recommended based on old and new screening guidelines
PSA velocity ≥ 0.35 ng/mL/yr
PSA velocity < 0.35 ng/mL/yr
40
45
50
Age (years)

- *We are on the verge of accusing 1 in 5 men of having prostate cancer.*

  –H. Ballentine Carter, MD

  –Prouts Neck, ME

  –November 2, 2006

FABLE FOR PROSTATE CANCER

There once was a pen with a turtle, a bird, and a rabbit in it.

FABLE FOR PROSTATE CANCER

- The turtle is like slow growing PCa—it will just stay there

  The problem is that these often get diagnosed with screening and treated aggressively (or even non aggressively) when they don't need treatment

FABLE FOR PROSTATE CANCER

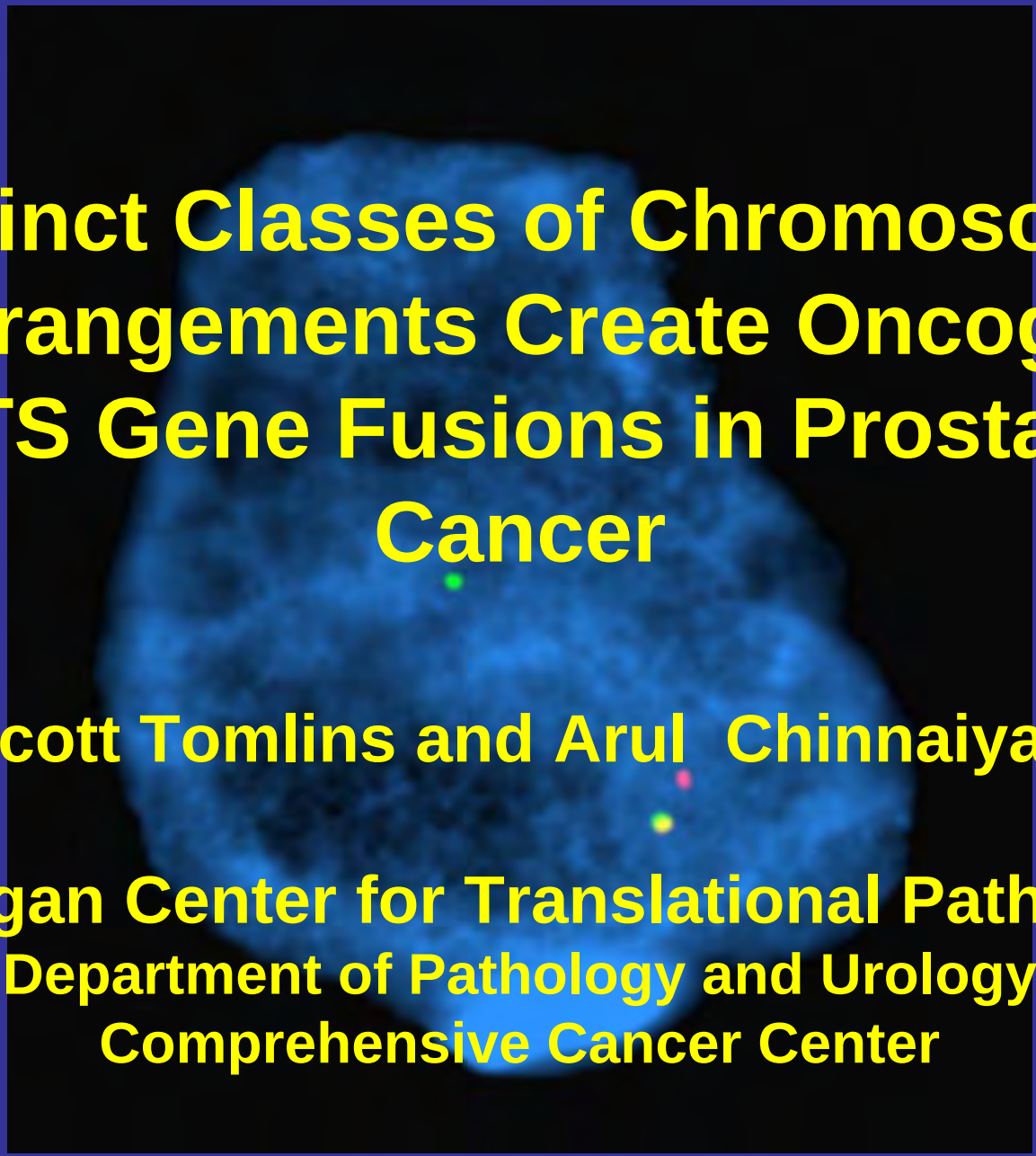
- The bird is like fast growing PCa—it flies out of the pen (spreads very quickly)

  The problem is these PCa are less likely to be detected with screening and are locally advanced or metastatic even at diagnosis and current treatments may not be aggressive or effective enough

FABLE FOR PROSTATE CANCER

- The rabbit is like moderate risk PCa which stays in the prostate for a while but eventually will jump out the prostate

  The problem with these is that even though screening and treatment may work, the side effects of the treatment are substantial and need to be diminished



Distinct Classes of Chromosomal Rearrangements Create Oncogenic ETS Gene Fusions in Prostate Cancer

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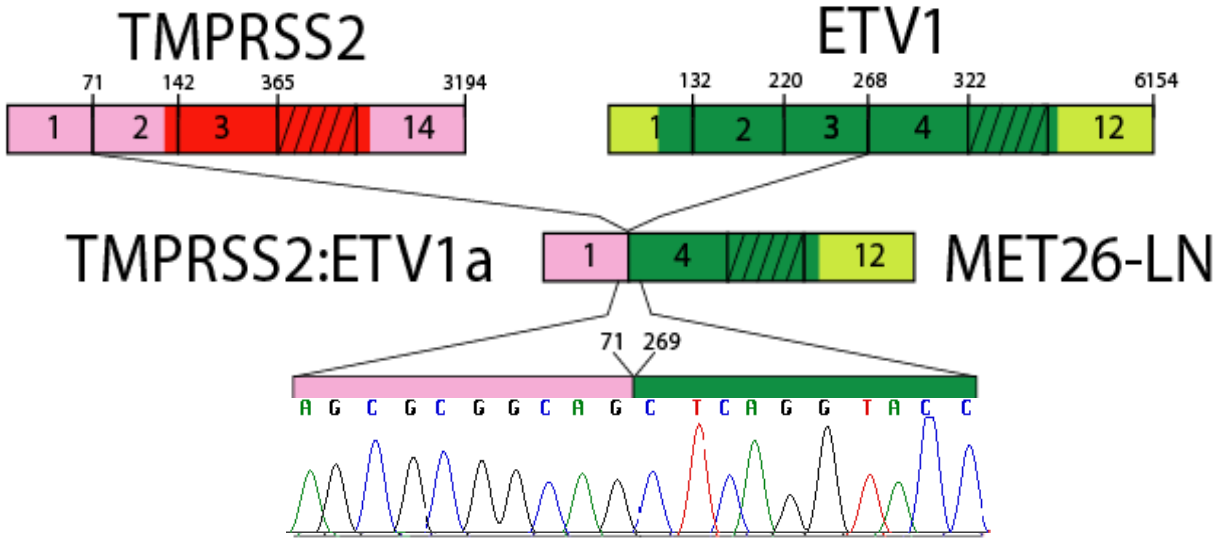
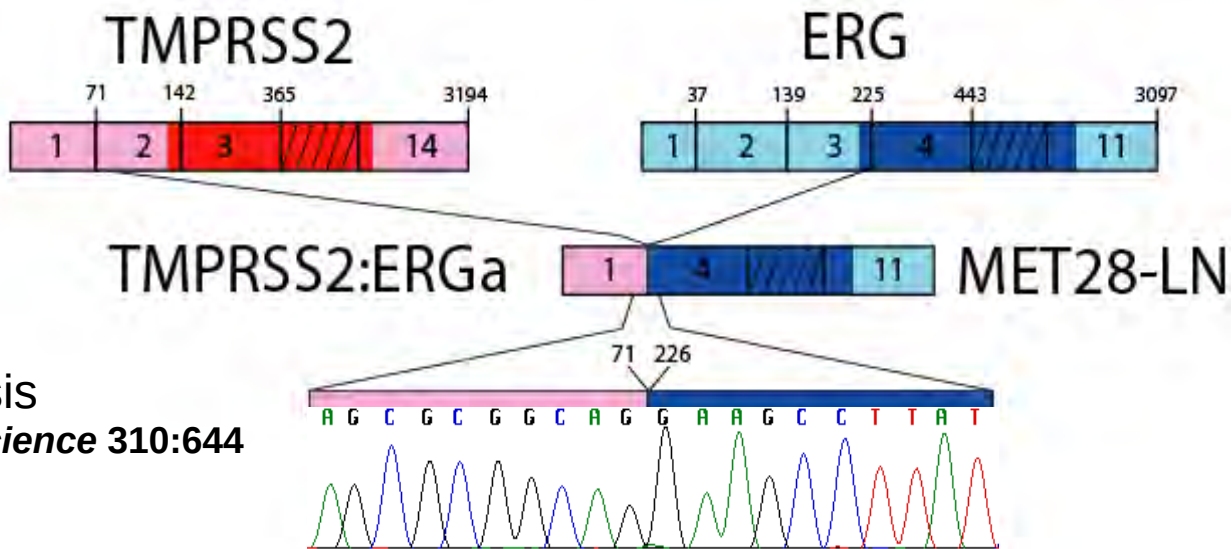
Department of Pathology and Urology
Comprehensive Cancer Center

University of Michigan
Medical School

Fusions of TMPRSS2 to the ETS Family of Transcription Factors





COPA analysis

Tomlins et al *Science* 310:644

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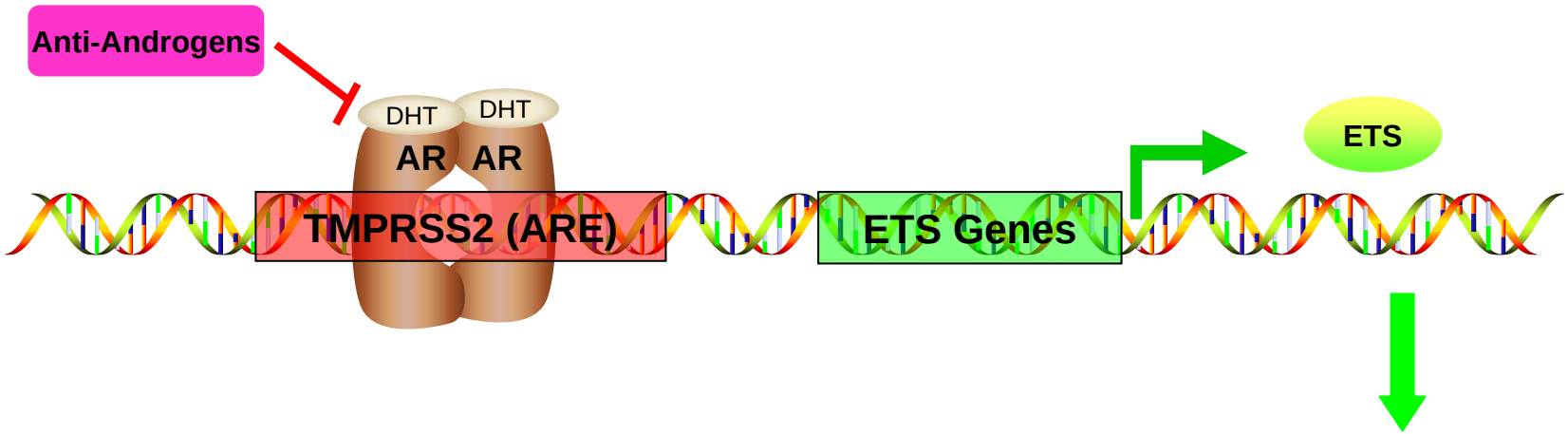
ETS Family Members

- Nuclear transcription factors
- Implicated in Ewing's sarcoma and AML as recurrent gene fusions

  (TEL, Fli-1, ERG, ETV1, PEA3)
- Have been shown to be oncogenic when over-expressed
- Bind to ETS consensus sequence

A Molecular Basis for Prostate Cancer



ETS Target Genes

- Cell growth
- Invasion/Metastasis
- Cell Survival

AR= androgen receptor
ARE= androgen response element
DHT= dihydrotestosterone
ETS= ETS family of transcription factors (ERG/ETV1)

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Molecular Subtypes of Prostate Cancer

- **~ 70% of North American prostate cancers have TMPRSS2 gene fusions**

50-70%	TMPRSS2-ERG
	TMPRSS2-ERG with deletion (50-60%)
	TMPRSS2-ERG without deletion (40-50%)
	About 15 variant fusion transcripts
~5%	TMPRSS2-ETV1
~1%	TMPRSS2-ETV4
~1%	Other ETS family members?

- **~30% Negative for TMPRSS2 fusions**

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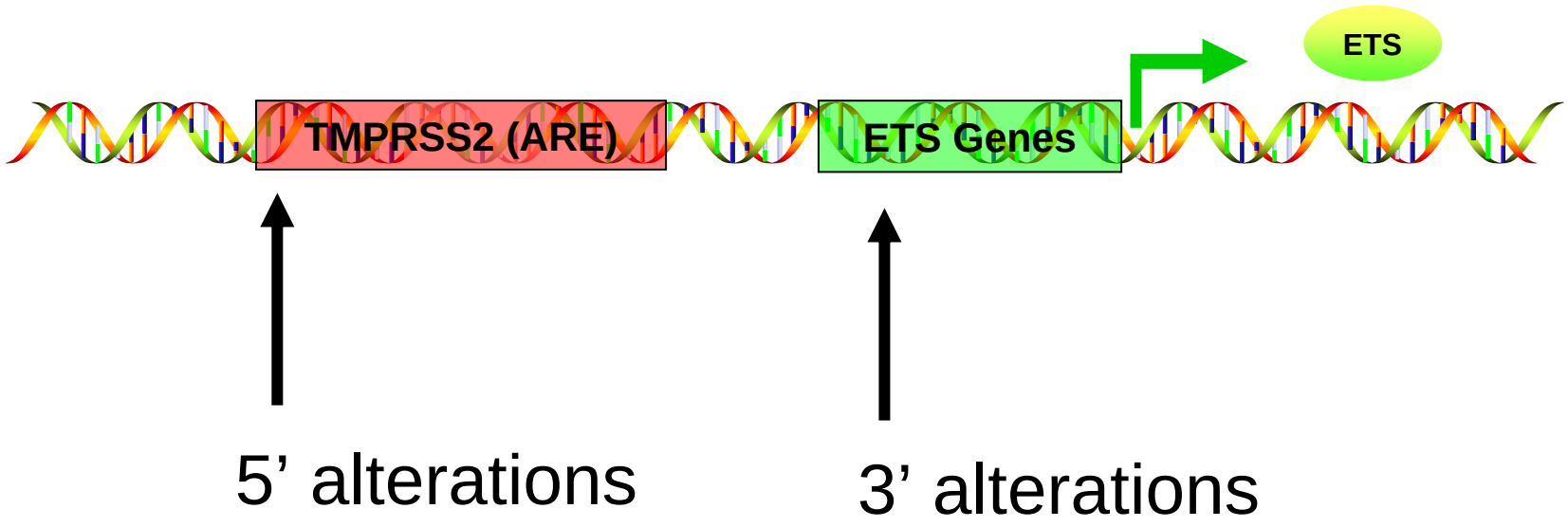
TMPRSS2-ETS:
Prototype Gene Fusion in Prostate Cancer



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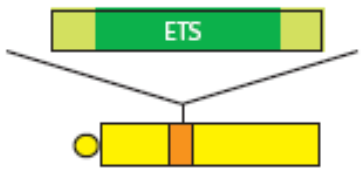
Distinct Classes of Chromosomal Rearrangements Create Oncogenic ETS Gene Fusions in Prostate Cancer

Class	Prototypes	Prostate specific	Androgen regulation	Fusion transcript	Element type
I	 TMPRSS2:ETV1 TMPRSS2:ERG TMPRSS2:ETV4	+	Induced	+	Proximal promoter
IIa	 SLC45A3:ETV1	+	Induced	+	Proximal promoter
IIb	 HERV-K:ETV1	+	Induced	+	Retroviral element
III	 C15ORF21:ETV1	+	Repressed	+	Proximal promoter
IV	 HNRPA2B1:ETV1	-	Unchanged	+	Proximal promoter
V	 ins(7;14)(p21;q21) (LNCaP) t(7;14)(p21;q21) (MDA-PCa 2B)	+	Induced	-	Enhancer

Molecular Subtypes of Prostate Cancer

5’ Fusion Partners

TMPRSS2
SLC45A3
HERV-K
C15ORF21
HNRP2AB1
MIPOL1
Others???

3’ Fusion Partners

ERG
ETV1
ETV4
ETS Family
Others???

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Prostate Cancer Risk Assessment: 2007

- Age, race and family history are most important recognized risk factors for PC:

  THEY CANNOT BE MODIFIED

- Modifiable risk factors (e.g. diet) for PC:

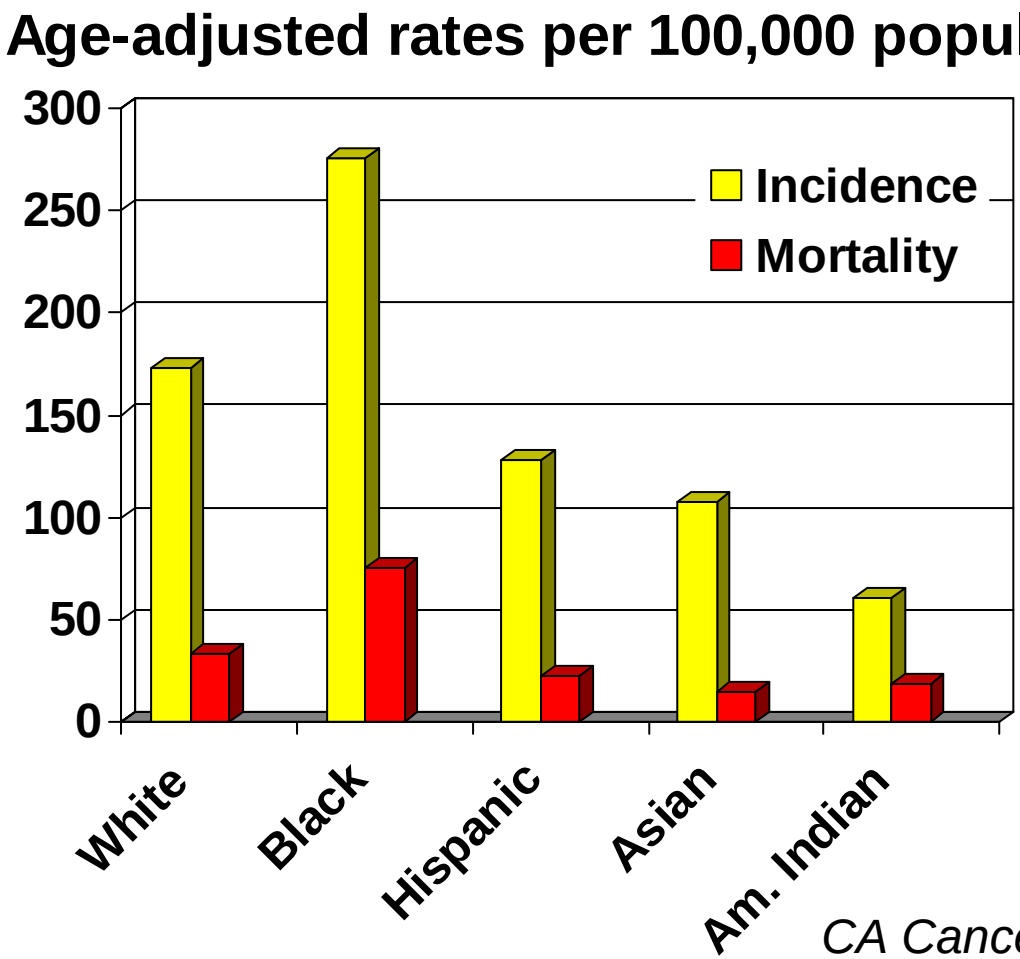
  RISK ATTRIBUTED TO THESE FACTORS IS NOT HIGH

Probability of Developing Prostate Cancer by Age

	< 40 years	40-59 years	60-69 years	Lifetime
% of population	0.005	2.22	13.70	16.67
Probability	Less than 1 in 19,299	1 in 45	1 in 7	1 in 6

CA Cancer J Clin 2003;53(1)

RACE AS A RISK FACTOR: US Prostate Cancer Incidence and Mortality: 1992-99



CA Cancer J Clin 2003;53(1)

Cancer Sites in Which African American Death Rates* Exceed White Death Rates* for Men, US, 1998-2002

Site	African American	White	Ratio of African American/White
•All sites	339.4	242.5	1.4
•Prostate	68.1	27.7	2.5
•Larynx	5.2	2.3	2.3
•Stomach	12.8	5.6	2.3
•Myeloma	8.8	4.4	2.0
•Oral cavity and pharynx	7.1	3.9	1.8
•Esophagus	11.2	7.5	1.5
•Liver and intrahepatic bile duct	9.5	6.2	1.5
•Small intestine	0.7	0.5	1.4
•Colon and rectum	34.0	24.3	1.4
•Lung and bronchus	101.3	75.2	1.3
•Pancreas	15.8	12.0	1.3

***Per 100,000, age-adjusted to the 2000 US standard population.**
Source: Surveillance, Epidemiology, and End Results Program, 1975-2002, Division of Cancer Control and Population Sciences, National Cancer Institute, 2005.

FAMILY HISTORY: Relative Risk of Prostate Cancer for First Degree Relatives of Probands

Age of Onset	1 Affected Relative	> 1 Affected Relative
50	1.9 (1.2-2.8)	7.1 (3.7-13.6)
60	1.4 (1.1-1.7)	5.2 (3.1-6.7)
70	1	3.8 (2.4–6.0)

Carter et al. *J Urol* 1993

Risk of PC influenced by:

- *No. of affected relatives*
- *Early age of prostate cancer dx within family*

Minor risk factors: hormones

- **Androgens required for prostate growth**
- **Some epidemiologic studies show association between increased T and PC and low estradiol and PC**
- **Variants in genes that encode proteins involved in androgen biosynthesis**

Other Minor Risk Factors

- Diet
  - Fat/meat consumption +
  - Vitamin E –
  - Soy (phytoestrogens) –
  - Lycopene –
  - Vitamin D –
- Environment
  - Pesticides +
  - Agent Orange +
- Other
  - Smoking +
  - Alcohol +/-
  - Vasectomy +

“Charred meat”

- The prostate has been identified as a target for 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced carcinogenesis.
- Humans are exposed to PhIP through ingestion of well-done cooked meats.
- The alpha and pi class isoforms of glutathione S-transferases (GSTs) have been shown to inhibit adduction of activated PhIP metabolites to DNA.
- Silencing of GST pi(GSTP1) through CpG island hypermethylation is found in nearly all prostate carcinomas and is believed to be an early event in prostate carcinogenesis.

Cancer Res. 2001 Jan 1;61(1):103-9

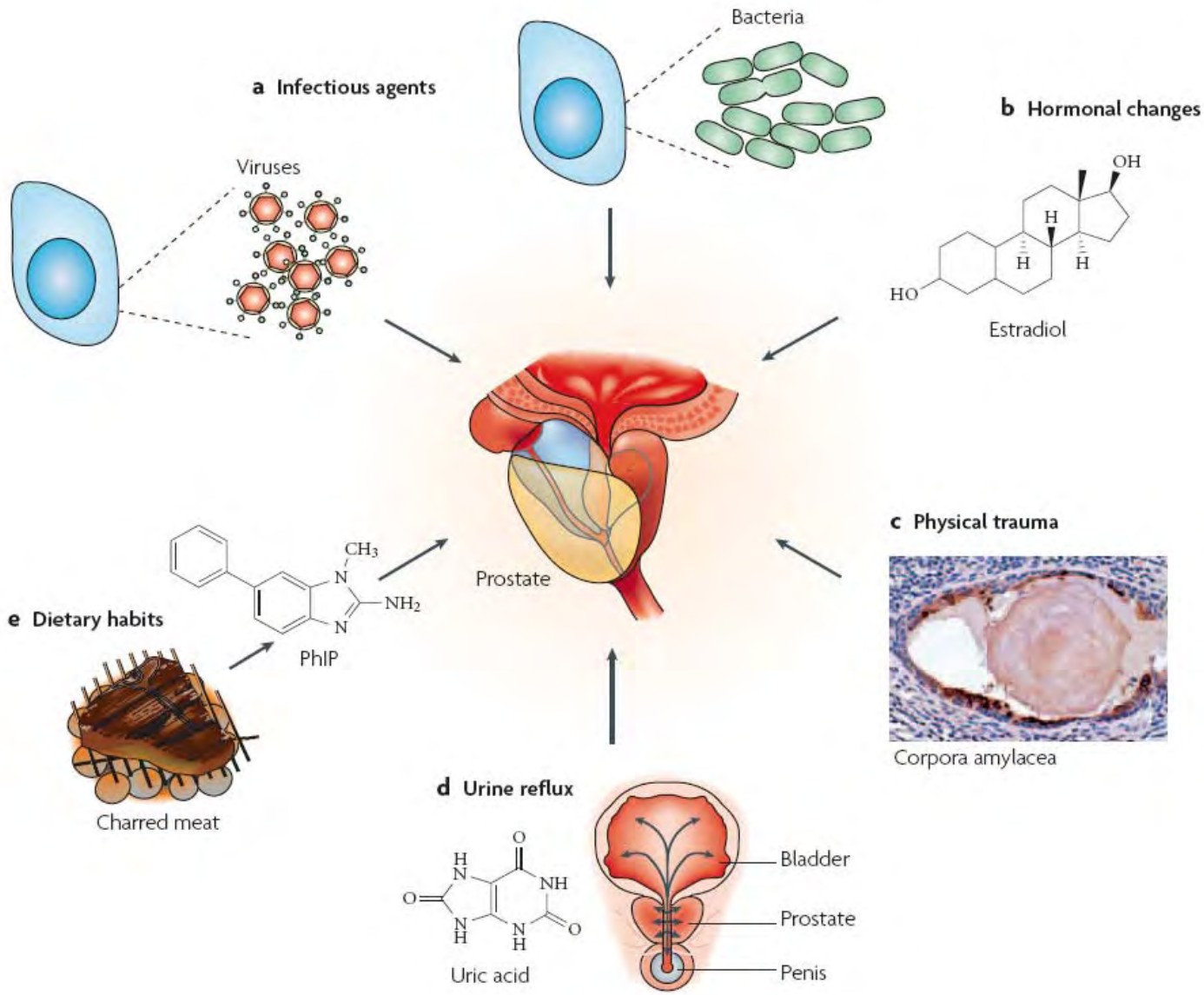
Cancer Res. 2007 Feb 1;67(3):1378-84.

“Viruses”

- A retrovirus has been found in prostate cancer tissue [xenotropic murine leukemia virus-related virus (XMRV)].
- Patients homozygous for a reduced activity variant of the antiviral enzyme RNase L appear to be a higher risk for developing prostate cancer.

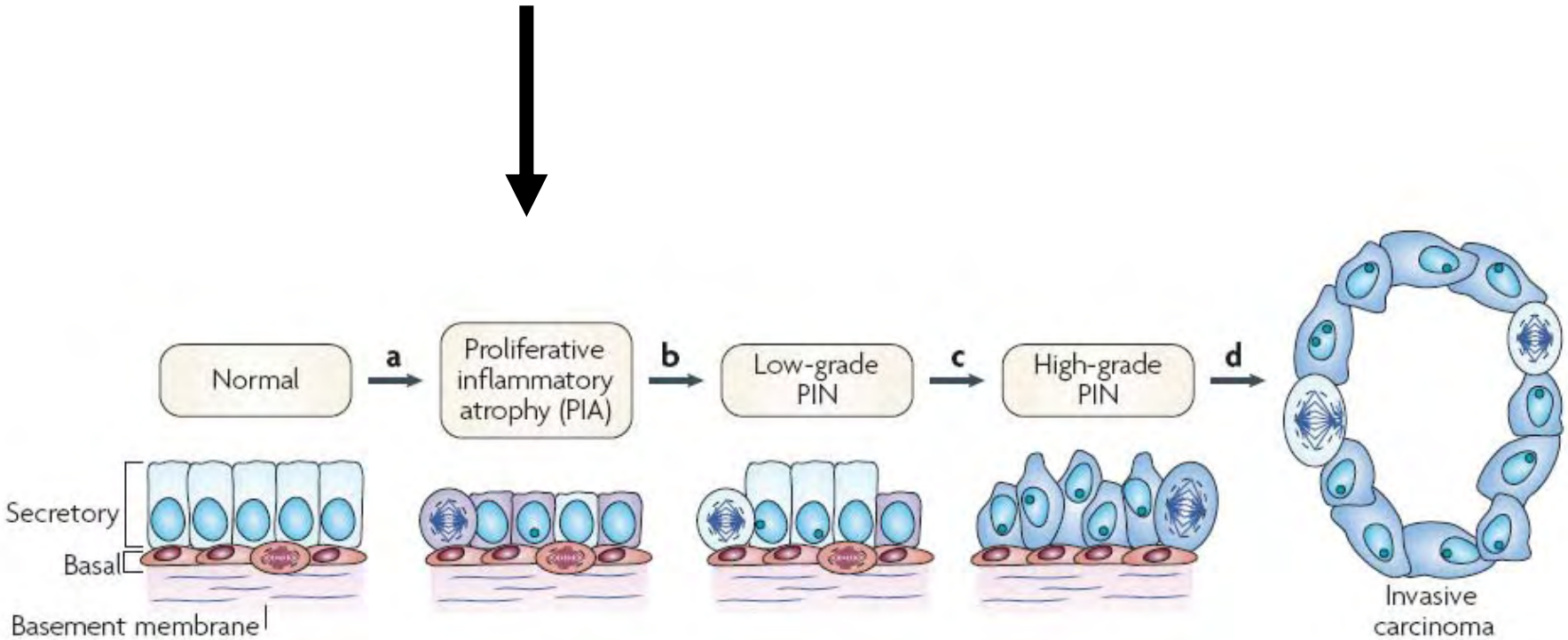
Proc Natl Acad Sci U S A. 2007 Jan 30;104(5):1655-60.

“Inflammation”



DeMarzo et al, Nat Rev Cancer. 2007 Apr;7(4):256-69.

PIA as a common endpoint of inflammation



Current thoughts on lowering Prostate cancer risk

- Chemoprevention versus *chemosuppression*
  - soy
  - Vitamin E
  - selenium
  - green tea
  - lycopene
  - low fat diet
  - Vitamin D
  - no: saw grass palmetto, vitamin A, vitamin C, coQ10

Finasteride Chemoprevention Study

- 18,000 men randomized to finasteride 5 mg per day versus placebo
- 25% risk reduction in men who took agent
- Controversial because men who did develop PCa on finasteride had higher Gleason grade – this is being more closely looked at

Prognostic factors for localized prostate cancer

- PSA (How much cancer is present)
  - 4-10 ng/ml
  - 10-20 ng/ml
  - >20 ng/ml Cancer has escaped
- Gleason score (How bad the cancer looks)
  - 1-3
  - 4-6 moderately differentiated
  - 7
  - 8-10 poorly differentiated

Localized Prostate Cancer Treatment Options

Active Surveillance

Radical Prostatectomy

- Radical retropubic prostatectomy
- Perineal prostatectomy
- Laparoscopic “robotic” prostatectomy

Radiation Therapy

- external beam
- seed implants (PSA < 7, <40 gram prostate)
- Seed implants + external beam (poor risk factors)

Local Prostate Cancer Therapies – The future?

- Focal Therapy
  - IMRT
  - Cryosurgery
  - Photodynamic therapy
  - More to come, i.e. cavitational ultrasound

Treatment of “Localized” prostate cancer is dependent on it’s stage and prognostic factors

- Tumor present only in the gland (T1-T2) can be treated by surgery or radiation
  - implant therapy should only be used in prostates less than 40 grams in size and Gleason score <7
- Tumor outside the gland (T3) is usually treated with external beam radiation

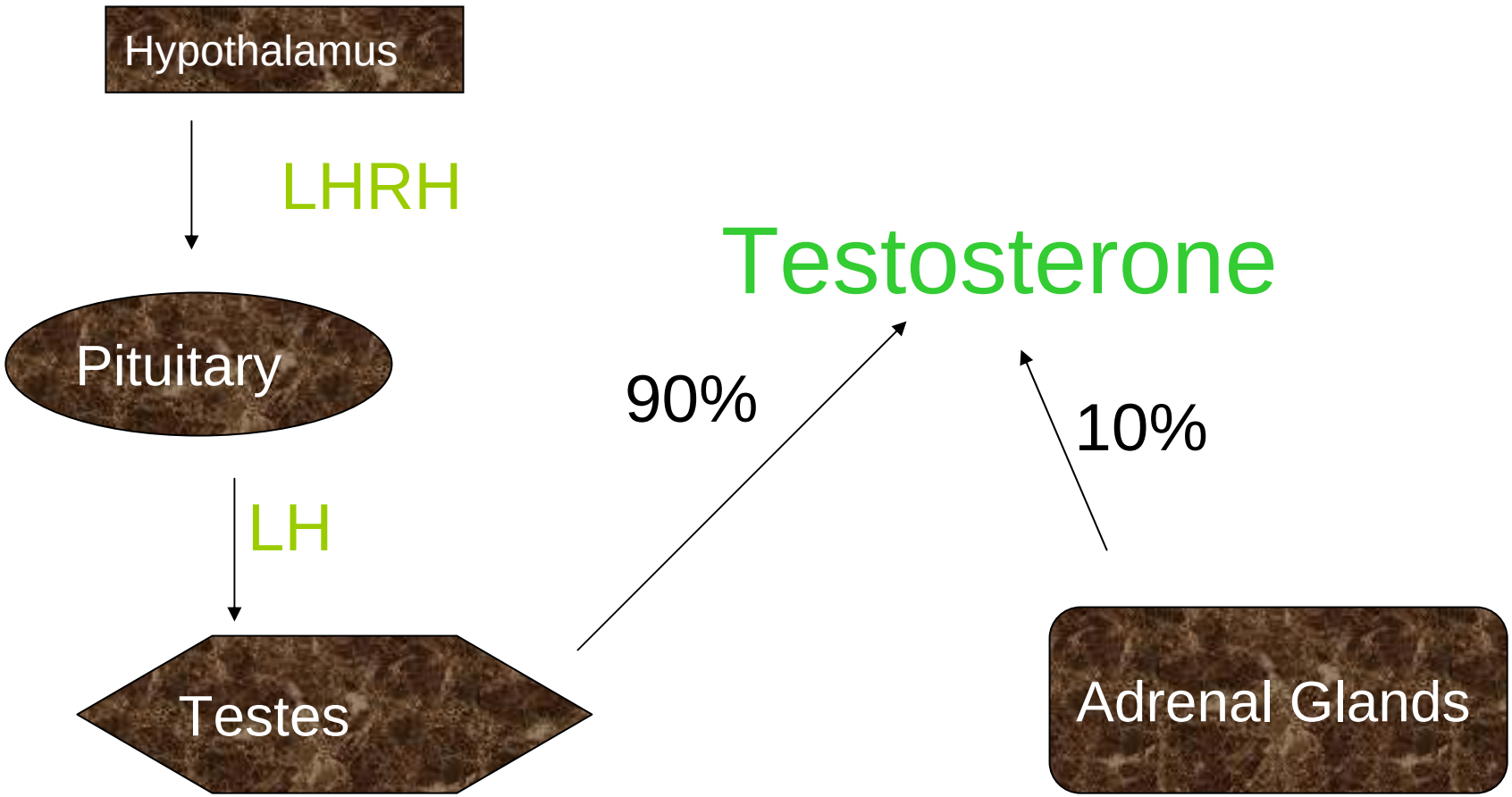
Side effects of primary therapy

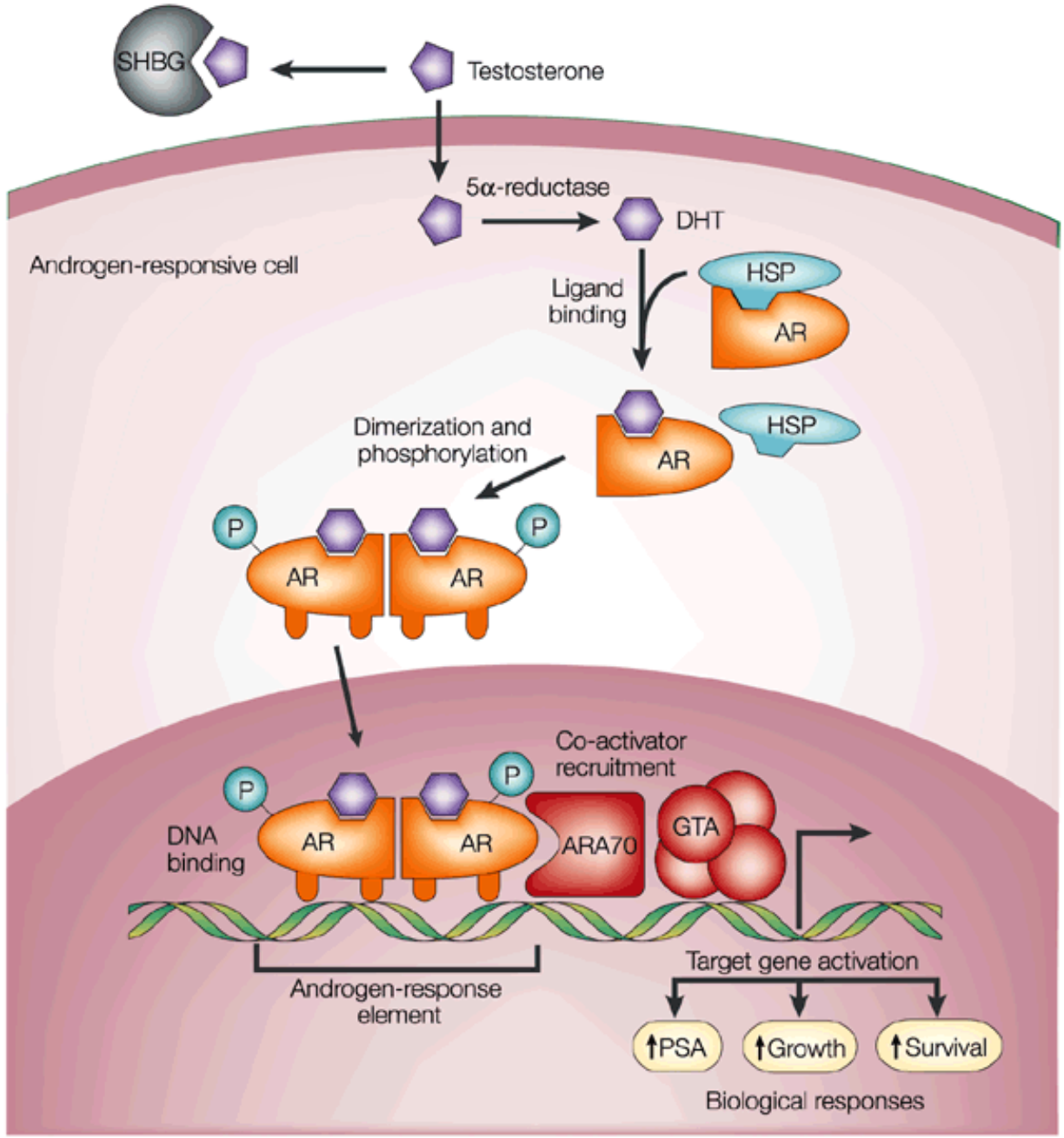
- Surgery:
  - 5-10% incontinence
  - 50-80% impotence
  - <1% death
- Radiation
  - 1-5% incontinence
  - 1-5% rectal injury / bleeding
  - 40-70% impotence
  - <1% death

Rising PSA after primary therapy

- After prostatectomy:
  - PSA <1.0, radiation to primary bed
  - prognosis better if rise after 1 year
- After radiation or RRP + radiation:
  - vaccine studies
  - hormone studies
  - chemotherapy studies
  - castration therapy - ? timing

Testosterone Production




SHBG
Testosterone
5α-reductase
DHT
Androgen-responsive cell
Ligand binding
HSP
AR
Dimerization and phosphorylation
AR
HSP
P
AR
AR
P
Co-activator recruitment
P
DNA binding
AR
AR
P
ARA70
GTA
Androgen-response element
Target gene activation
↑PSA
↑Growth
↑Survival
Biological responses

Androgen ablation for advanced prostate cancer - primary therapy

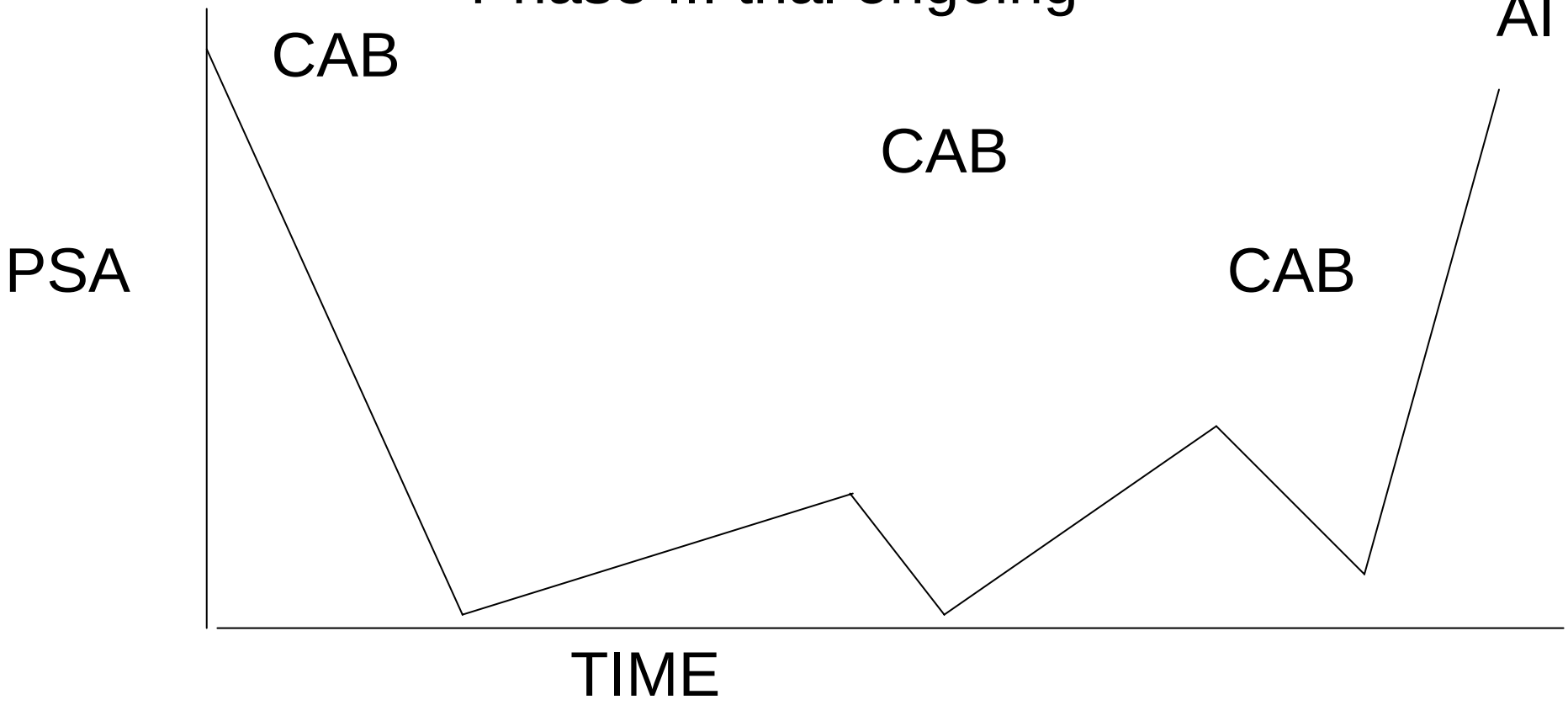
- Surgical castration
- LHRH analogs (lupron, zoladex)
  - nonsteroidal antiandrogens (flutamide, bicalutamide) = competitive antagonists for the androgen receptor
- Complete androgen blockade = LHRH + antiandrogen

Intermittent androgen blockade:

May slow the growth of androgen insensitive cells

Improves quality of life in phase II trials

Phase III trial ongoing

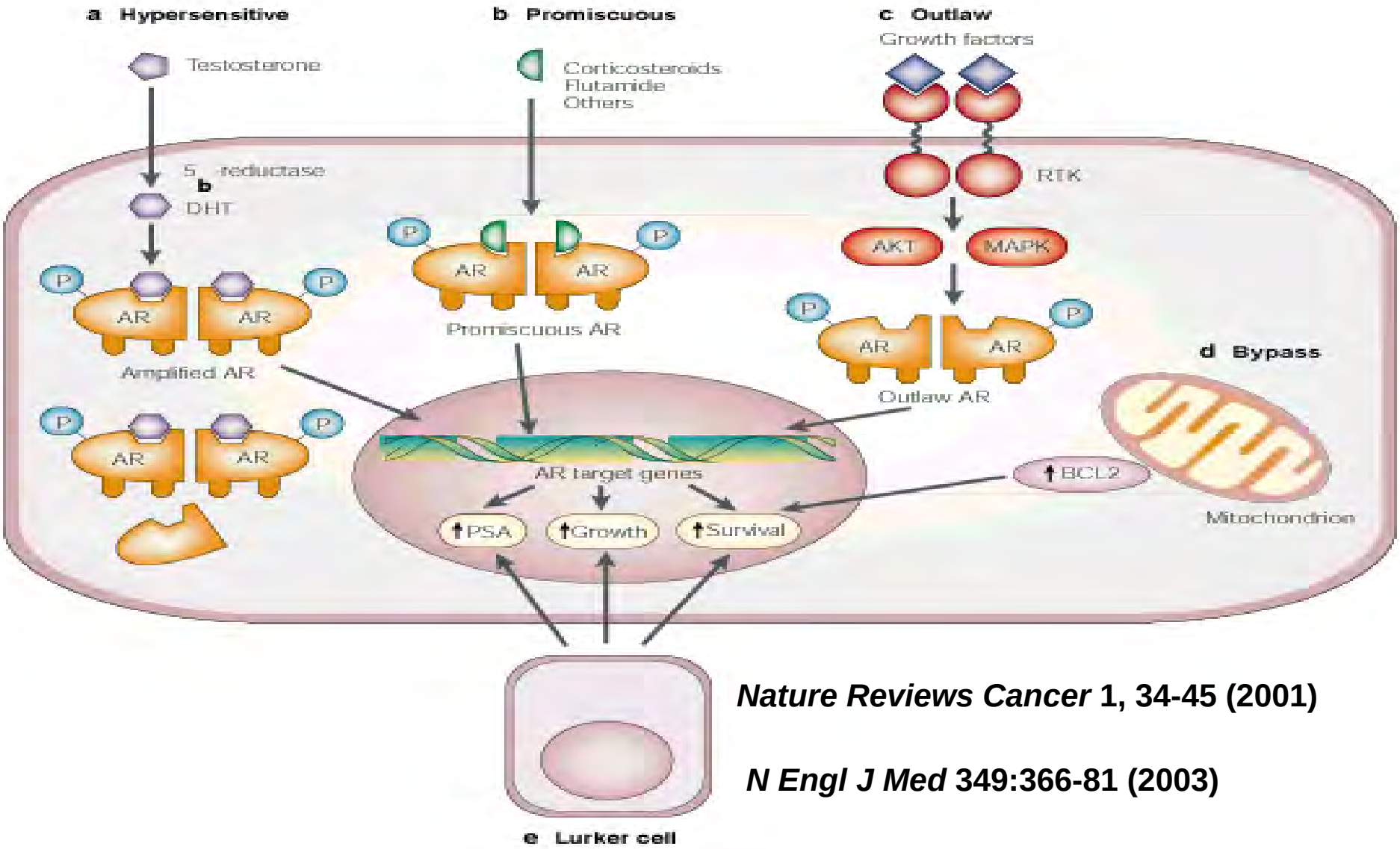


Total peripheral blockade

- 150 mg bicalutamide (Casodex) daily

- As first line therapy, may be as good as LHRH analogs
  - Boccardo et al:JCO;17,1999.

Why does androgen blockade fail?



***Nature Reviews Cancer* 1, 34-45 (2001)**

***N Engl J Med* 349:366-81 (2003)**

Treatment after Androgen blockade failure: Second Line Hormone Therapy

DES 1 mg po q day

40% of patients decreased PSA by > 50% for an average of 8 months

ESTROGEN 1.25 mg po q day

KETOCONAZOLE + PREDNISONE

10-15%- 50% response rate

PREDNISONE 10% response rate

HIGH DOSE BICALUTAMIDE (150 mg)

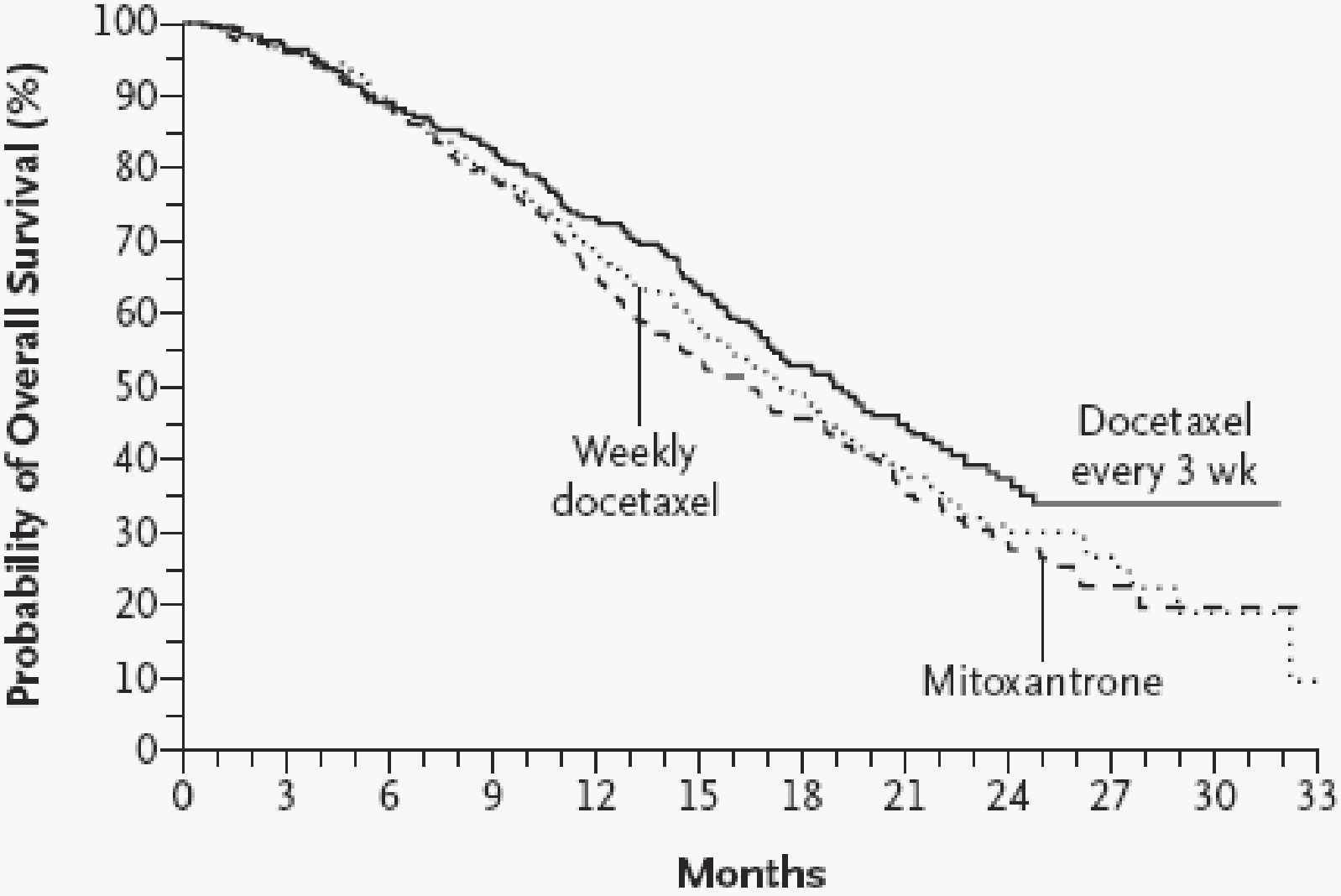
approximately 20% RR

CHEMOTHERAPY FOR HORMONE REFRACTORY PROSTATE CANCER

2007 Chemotherapy

- 1st line: docetaxel 75 mg/m^2 every 3 wks + prednisone 5 mg bid

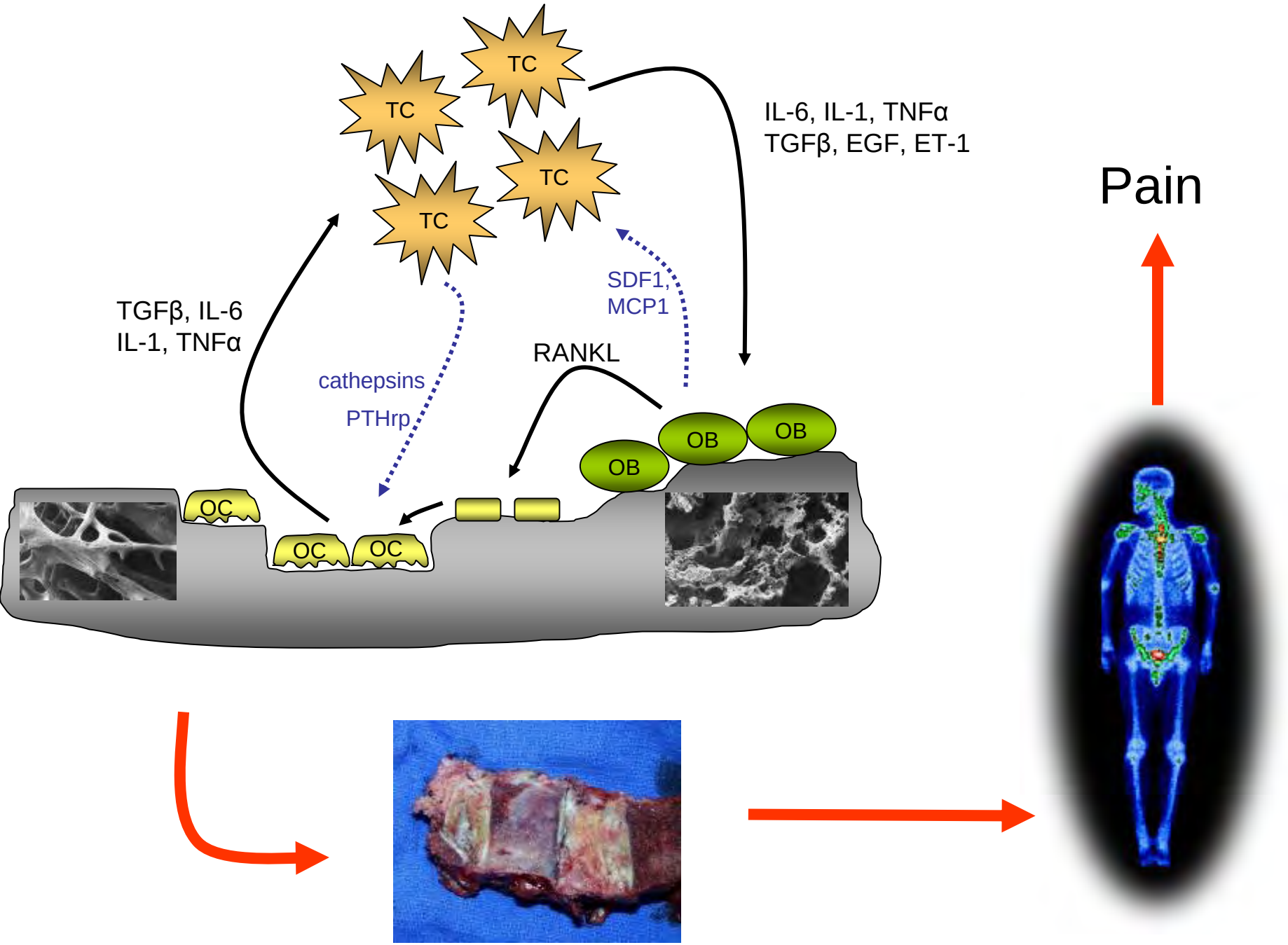
- 2nd line: mitoxantrone 12 mg/m^2 every 3 wks + prednisone 5 mg bid

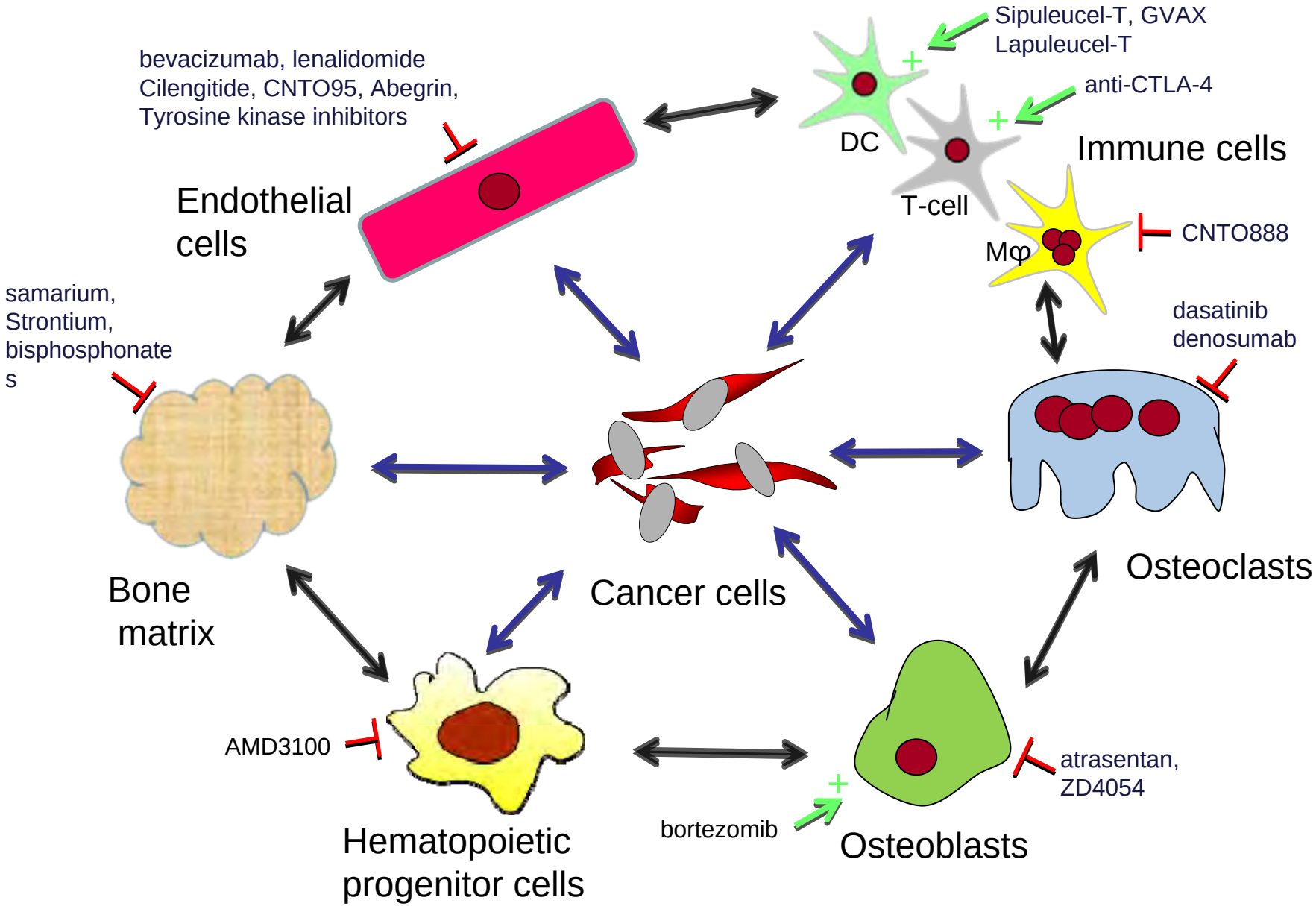


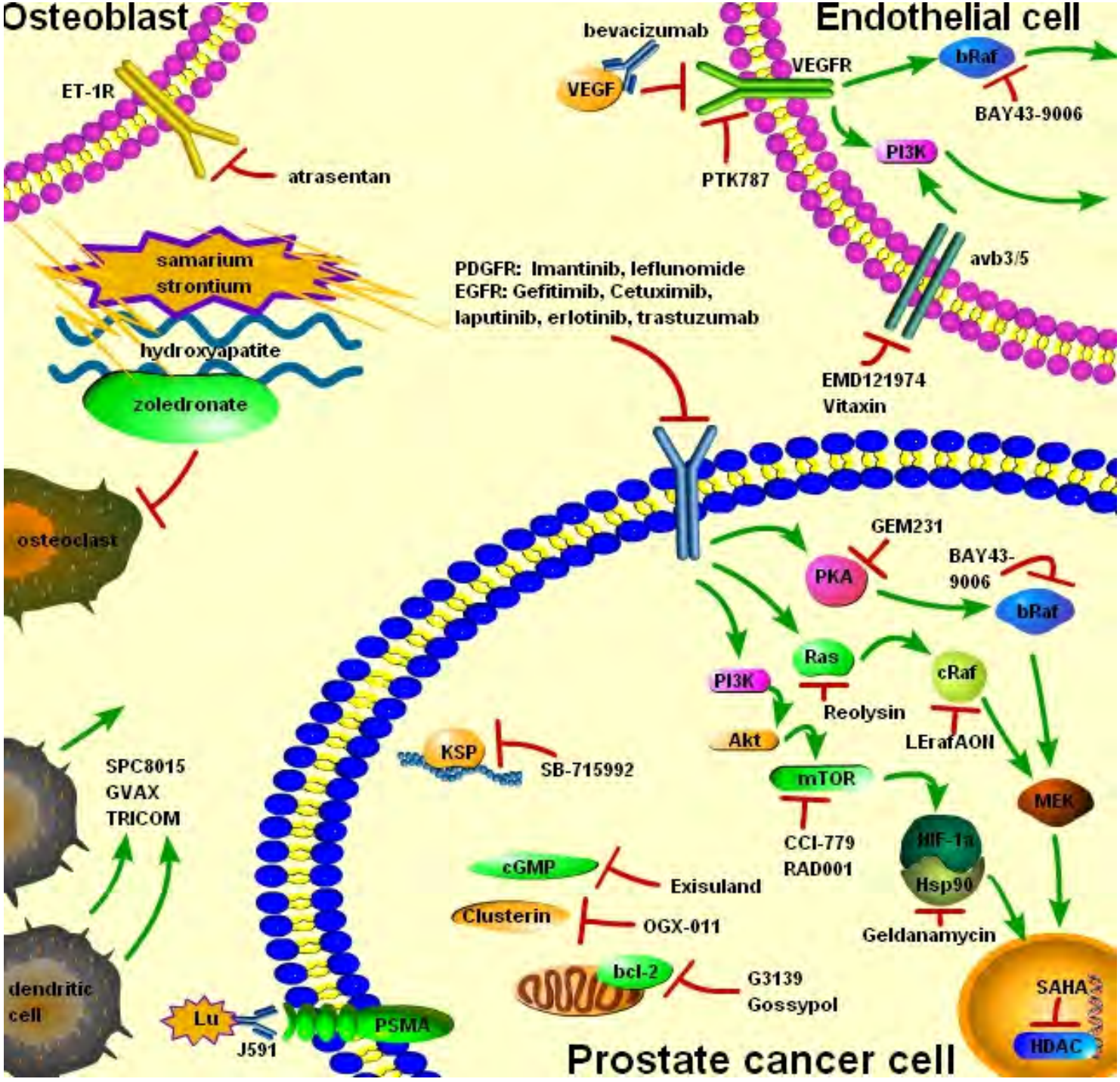
No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Adjuncts to chemotherapy

- The bisphosphonate zometa to prevent skeletal related events
- Radioisotopes to treat bone pain


TC
TC
TC
TC
IL-6, IL-1, TNFα
TGFβ, EGF, ET-1
Pain
TGFβ, IL-6
IL-1, TNFα
SDF1,
MCP1
RANKL
cathepsins
PTHrp
OB
OB
OB
OC
OC
OC


Sipuleucel-T, GVAX
Lapuleucel-T
anti-CTLA-4
bevacizumab, lenalidomide
Cilengitide, CNTO95, Abegrin,
Tyrosine kinase inhibitors
DC
Immune cells
T-cell
Endothelial cells
CNTO888
Mφ
samarium,
Strontium,
bisphosphonate
s
dasatinib
denosumab
Bone matrix
Cancer cells
Osteoclasts
AMD3100
atrasentan,
ZD4054
bortezomib
Hematopoietic progenitor cells
Osteoblasts


Osteoblast
ET-1R
atrasentan
samarium
strontium
hydroxyapatite
zoledronate
osteoclast
bevacizumab
VEGF
Endothelial cell
VEGFR
bRaf
BAY43-9006
PTK787
PI3K
avb3/5
EMD121974
Vitaxin
PDGFR: Imantinib, leflunomide
EGFR: Gefitimib, Cetuximib,
laputinib, erlotinib, trastuzumab
GEM231
PKA
BAY43-
9006
bRaf
Ras
cRaf
PI3K
Reolysin
LErafAON
Akt
KSP
SB-715992
mTOR
MEK
CCI-779
RAD001
HIF-1a
Hsp90
Geldanamycin
cGMP
Exisuland
Clusterin
OGX-011
bcl-2
G3139
Gossypol
SAHA
HDAC
SPC8015
GVAX
TRICOM
dendritic
cell
Lu
J591
PSMA
Prostate cancer cell