

Patients Living Longer: The Promise of Newer Therapies

David M. Nanus, MD

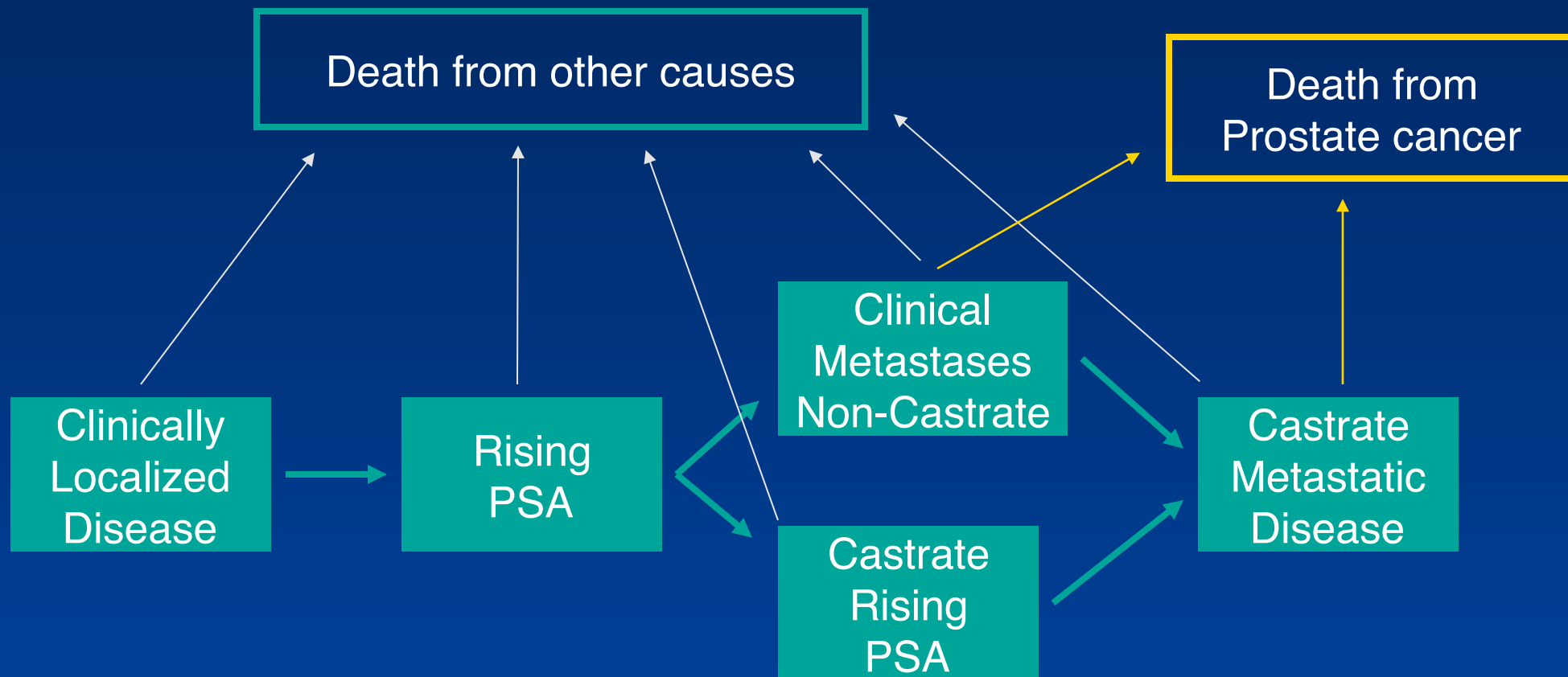
Chief, Division of Hematology and Medical Oncology

Weill Cornell Medicine

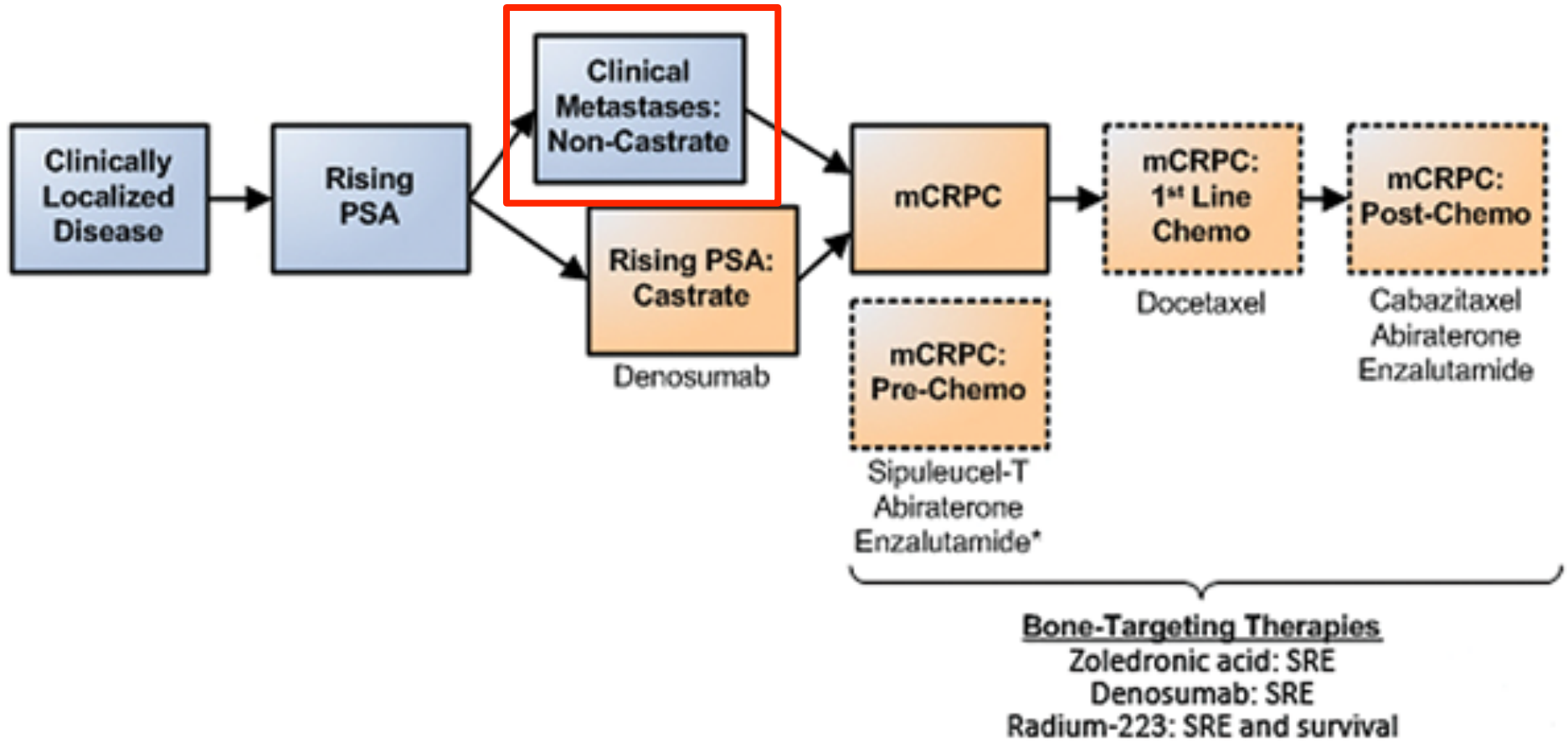
New York Presbyterian Hospital

Demographics

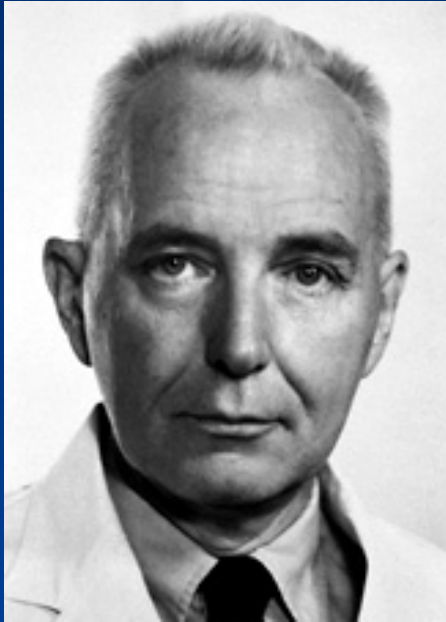
- 180,890 estimated new cases in 2016
 - 21.5% of all cancers in males
 - most common cancer in men
 - Lifetime risk: 16% (1 in 6)
- 26,120 estimated deaths
 - 8.3% of cancer deaths in males
 - second to lung cancer in men
 - decreased by 3.5% per year 2003 to 2012



Prostate Cancer Clinical States Model



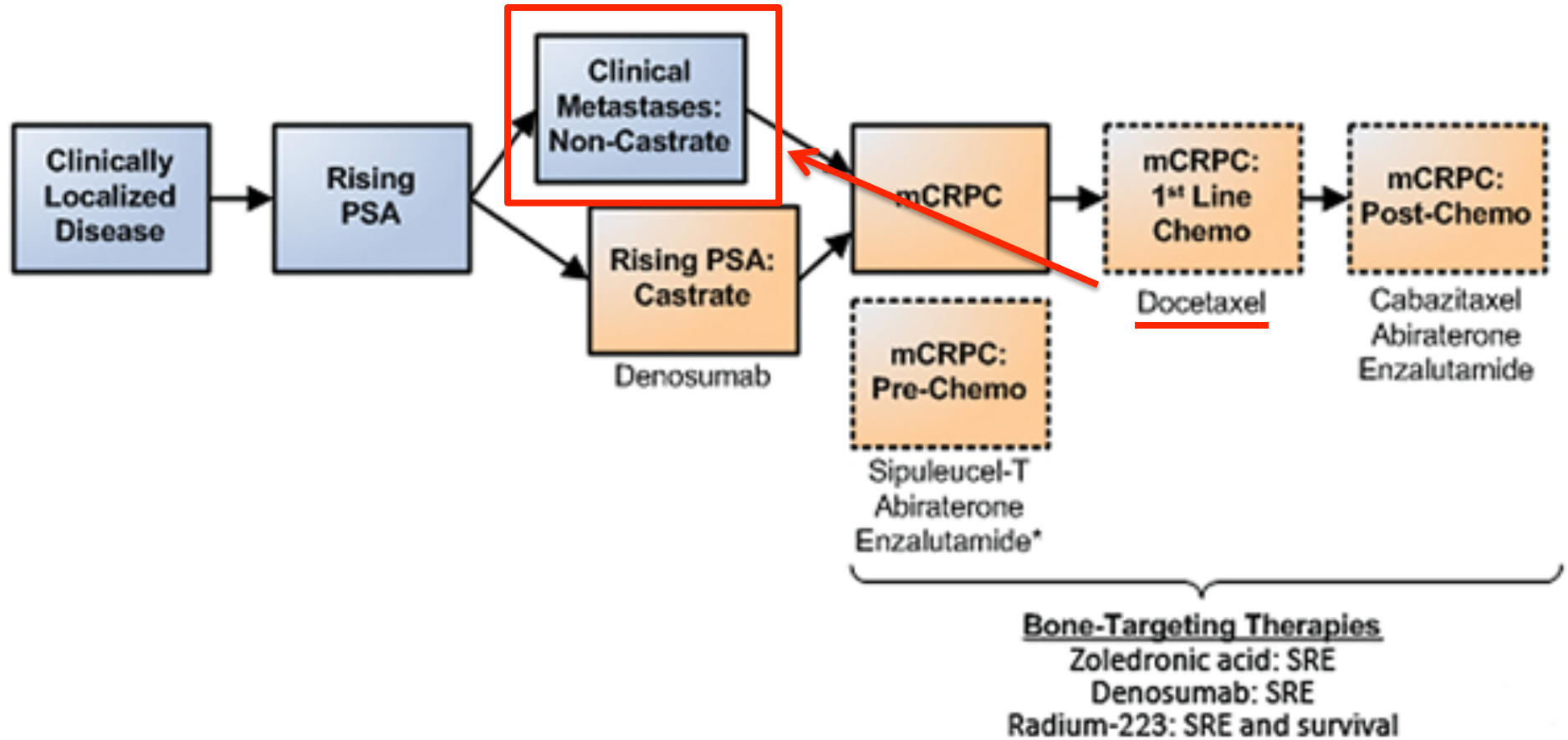
Androgen Deprivation Therapy (ADT) = Testosterone Lowering Therapy = Hormonal Therapy



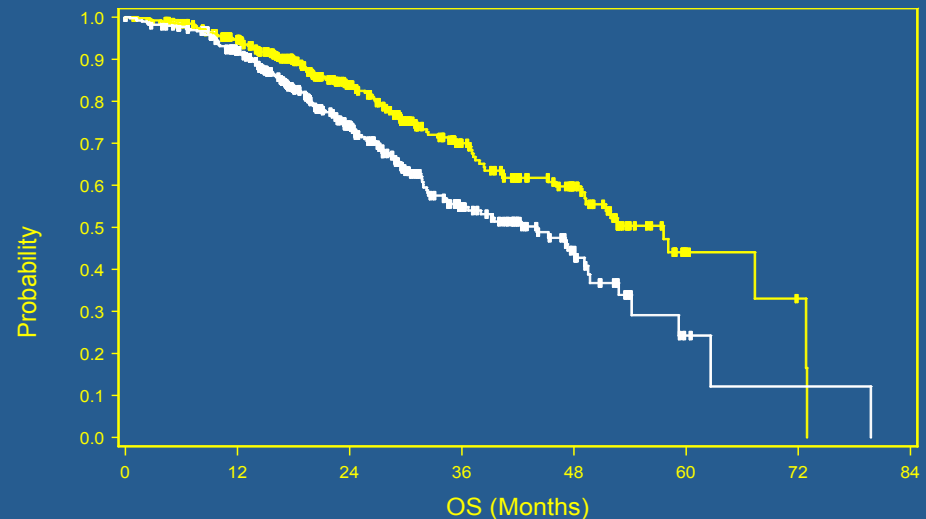
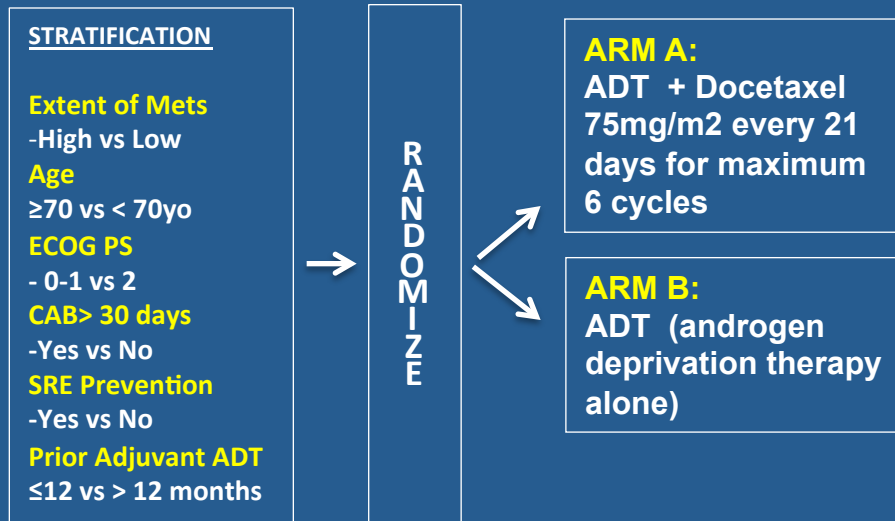
Charles Huggins recognized as an androgen -sensitive disease in 1941

21 patients metastatic prostate cancer → orchiectomy or administration of phenolic estrogens (stibestrol) resulted in regression in prostate cancer, extended life span, and decreased man-pain hours

Prostate Cancer Clinical States Model



E3805 CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer



HR=0.61 (0.47-0.80) p=0.0003

Median OS:

ADT + Docetaxel: 57.6 months

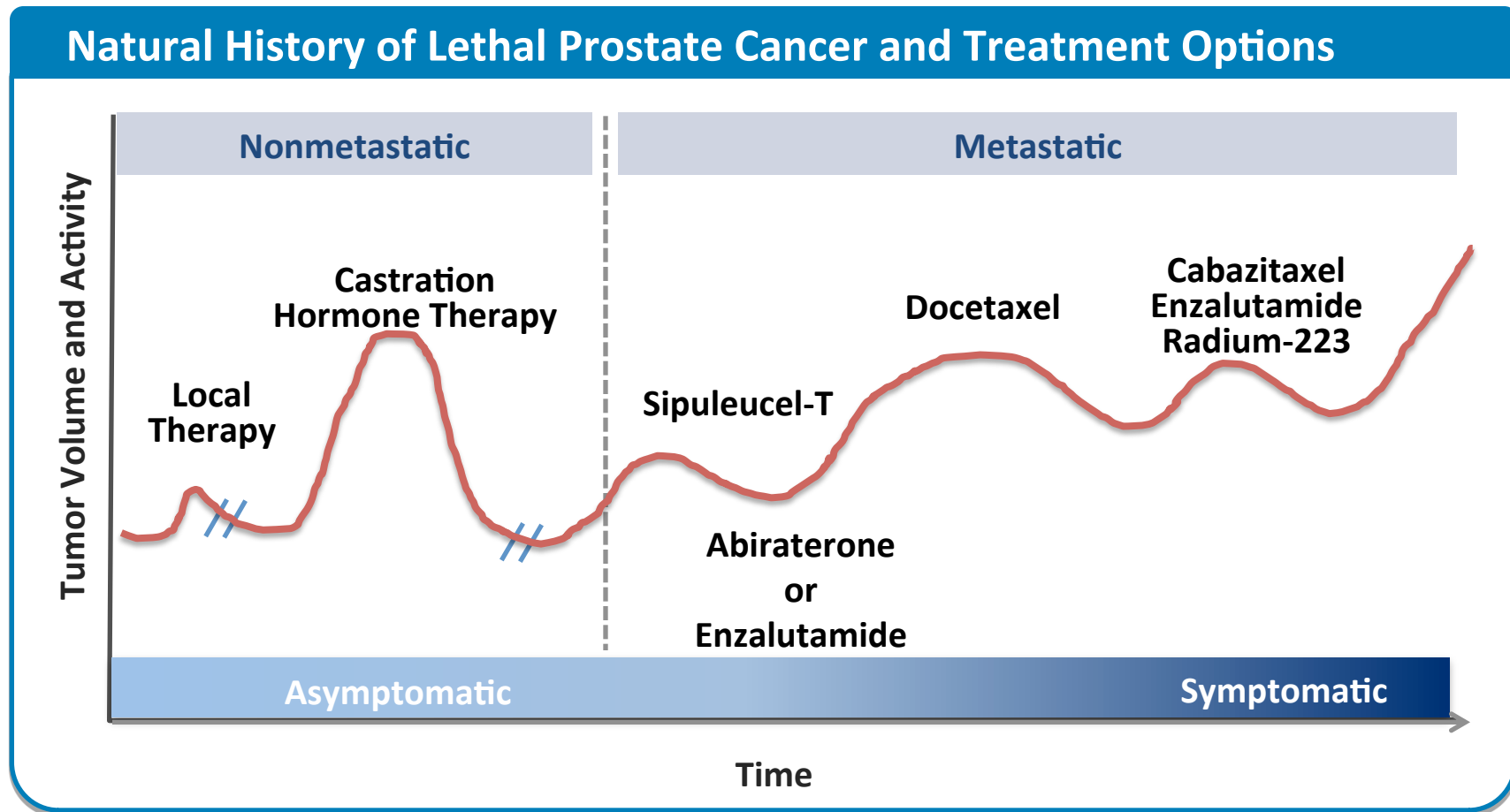
ADT alone: 44.0 months

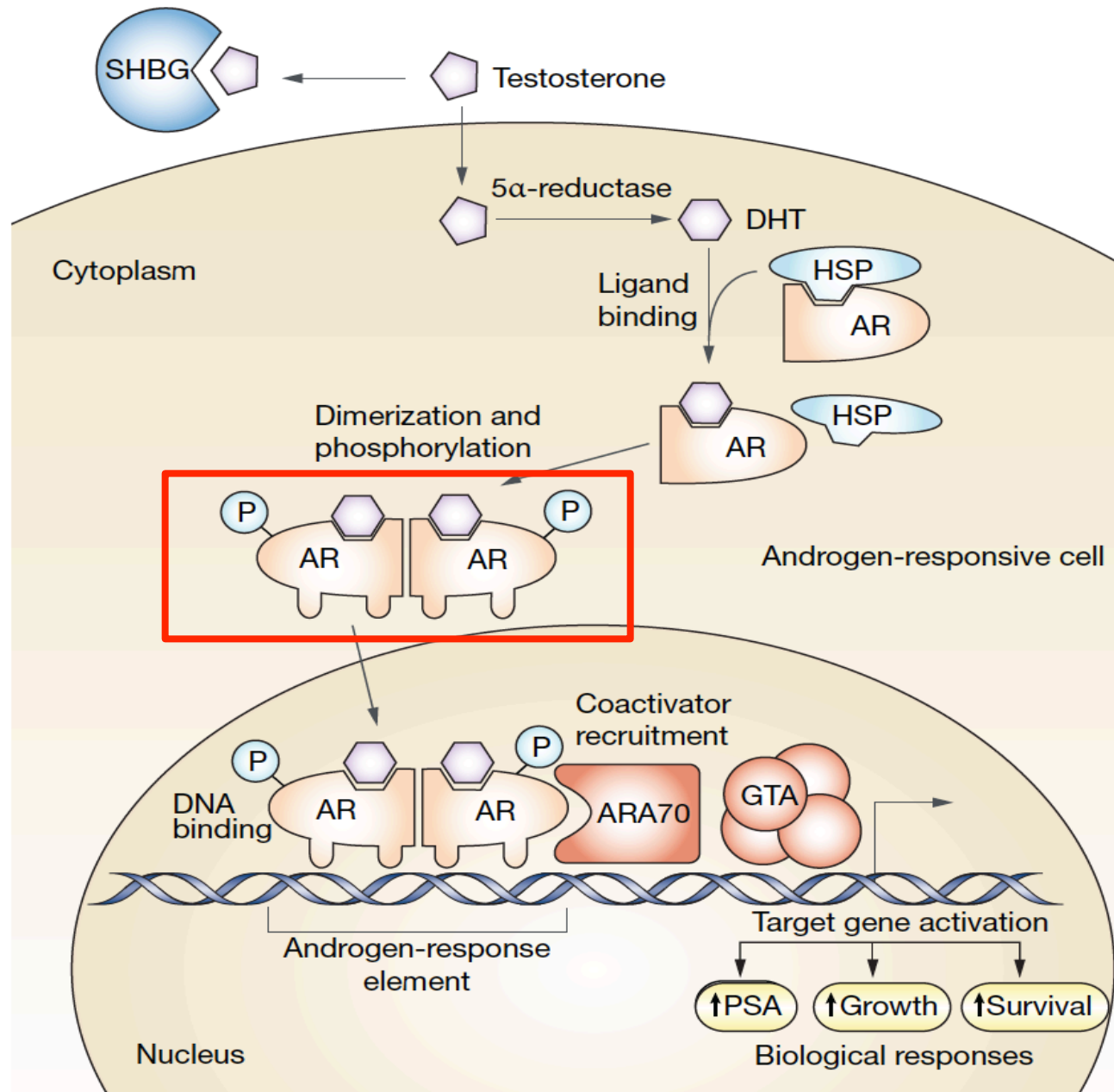
What's new in prostate cancer therapy?

- Targeting the androgen axis
- Immunotherapy
- Chemotherapy (what and when)
- Bone targeted therapies

- Molecular genetics
- Circulating Biomarkers
 - prostate cancer tumor cells
 - ctDNA

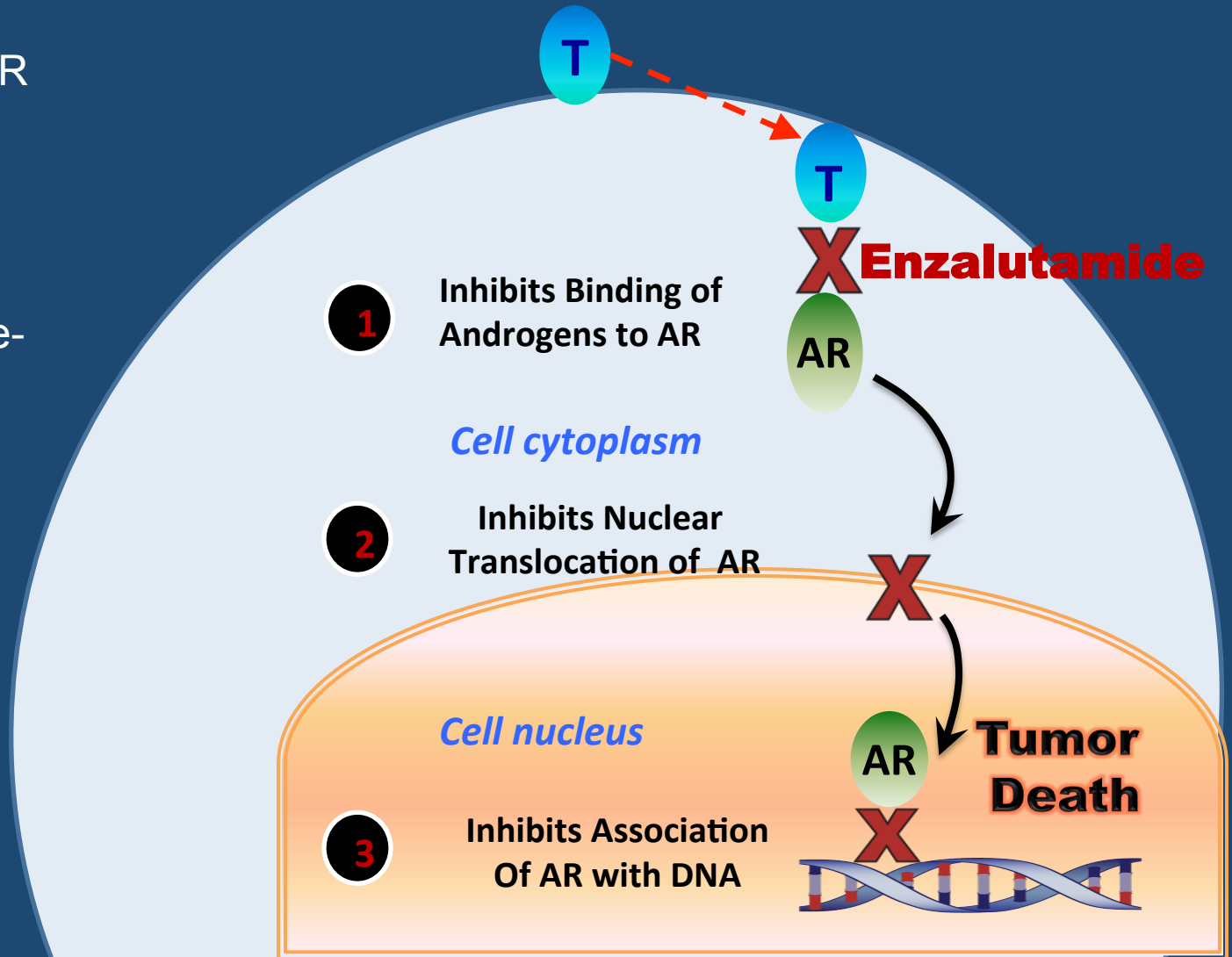
Multiple Treatment Options Are Now Available for Men With Metastatic Prostate Cancer



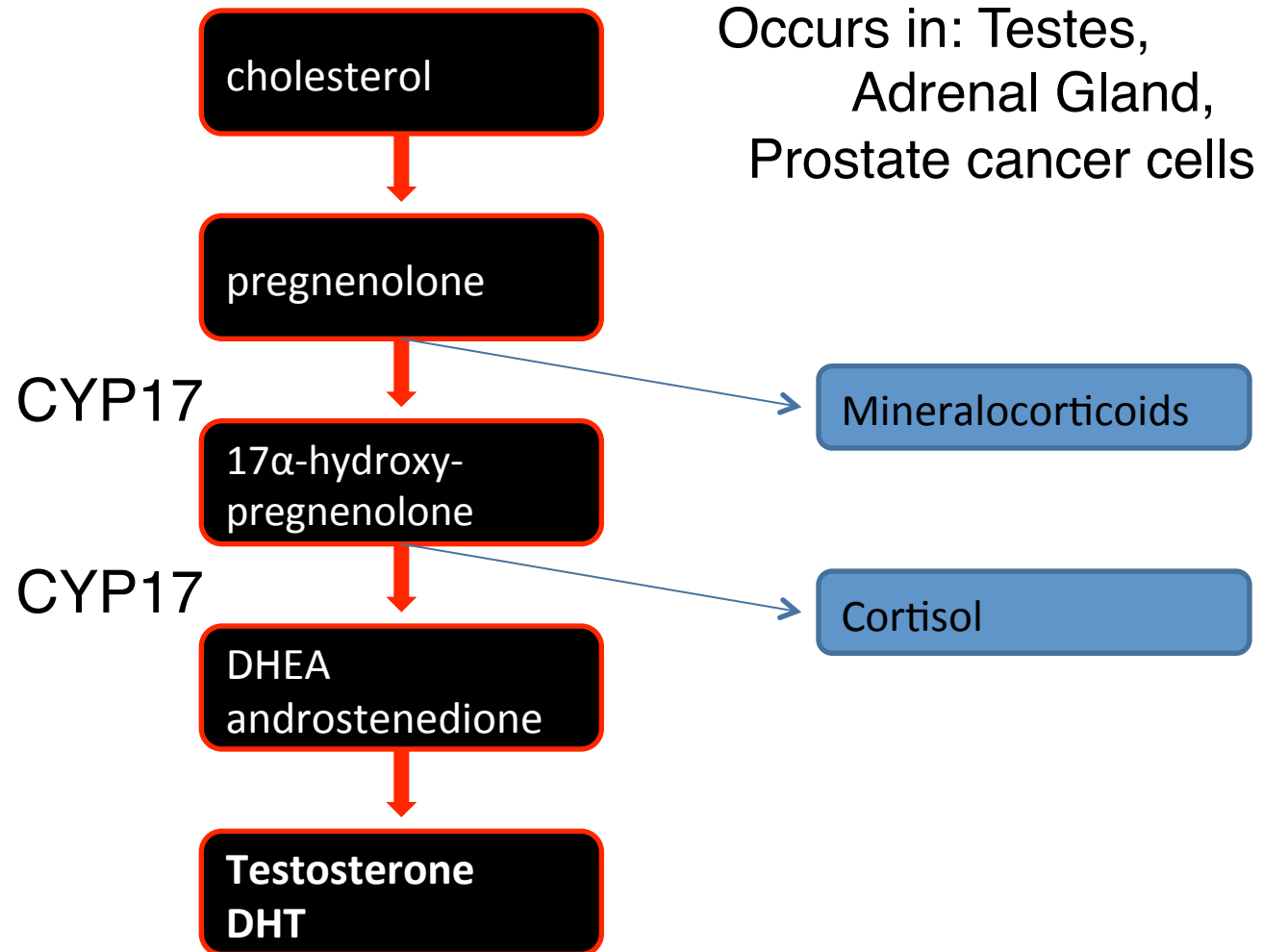


Enzalutamide (Xtandi)

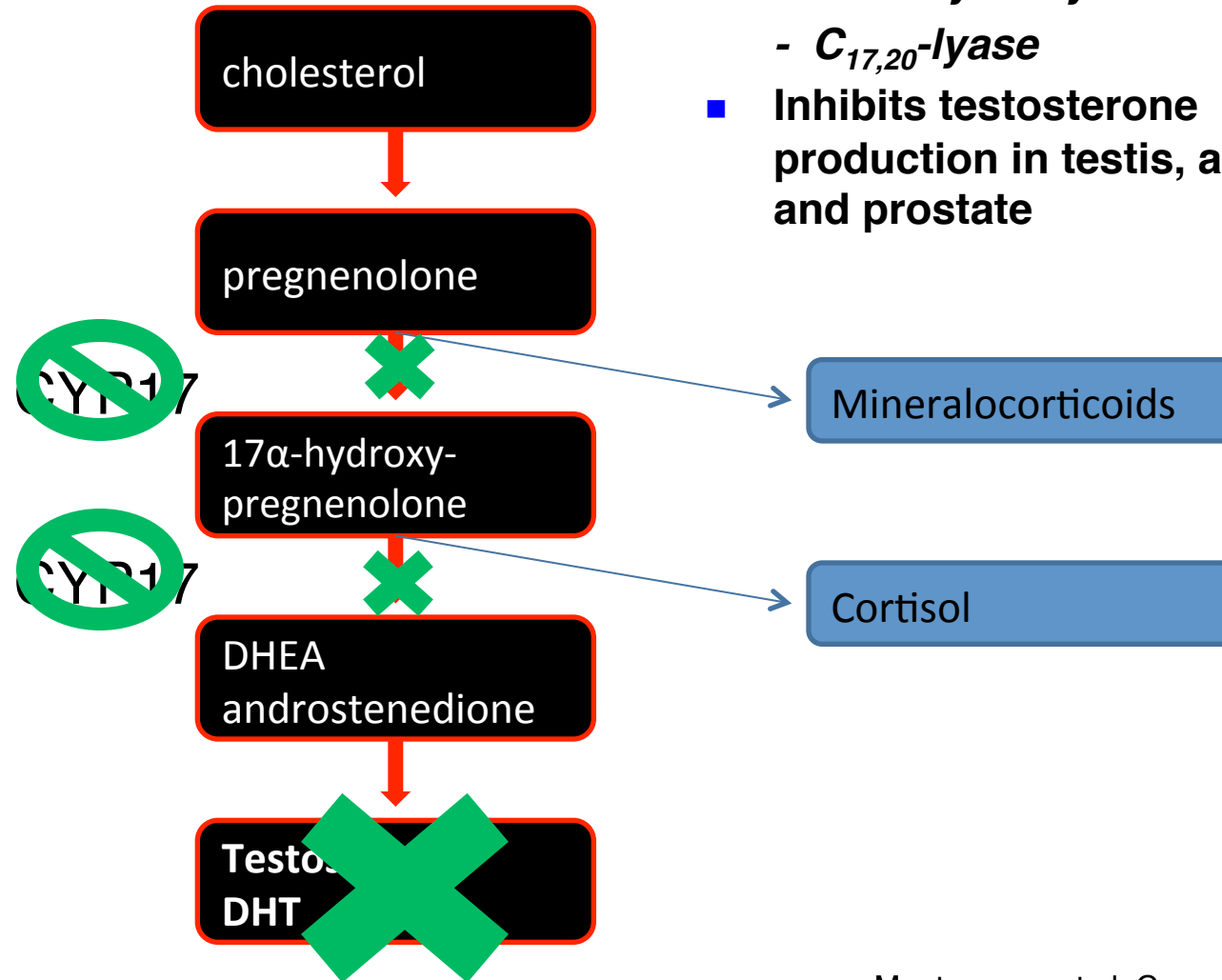
- Oral drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway.
- No demonstrated agonist effects in pre-clinical models.



Simplified view of cholesterol → testosterone synthesis

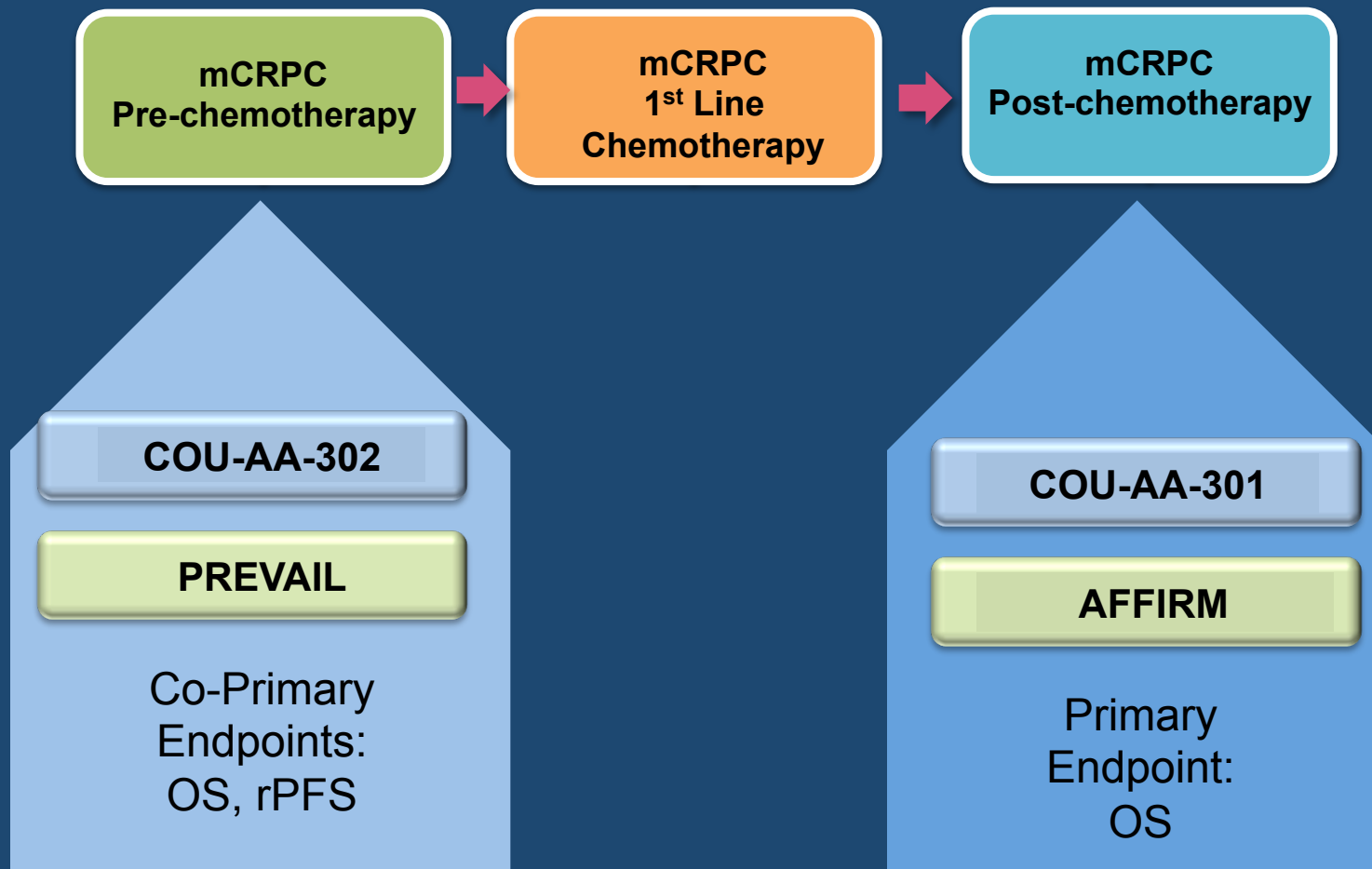


Abiraterone Acetate (Zytiga)



- **Oral irreversible inhibitor of CYP17**
 - 17 α -hydroxylase
 - C_{17,20}-lyase
- **Inhibits testosterone production in testis, adrenal, and prostate**

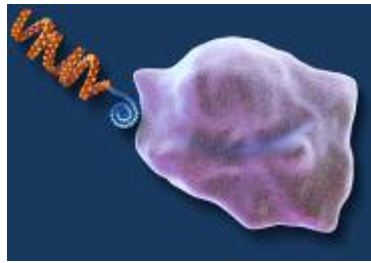
Abiraterone and Enzalutamide: Four Positive Studies!



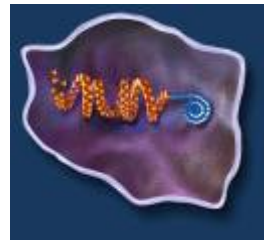
Immunotherapy

- Cancer vaccines
- Modulation of immune regulatory mechanisms
 - Blocking CTLA-4
 - Blocking PD-1 or PDL-1
- Monoclonal antibody targeting of tumour growth

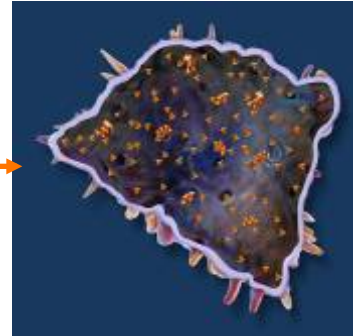
Sipuleucel-T: Autologous APC Cultured with PAP-cytokine Fusion Protein



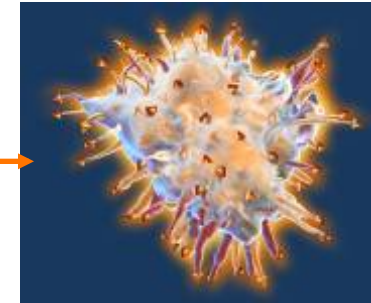
Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)



APC takes up the antigen

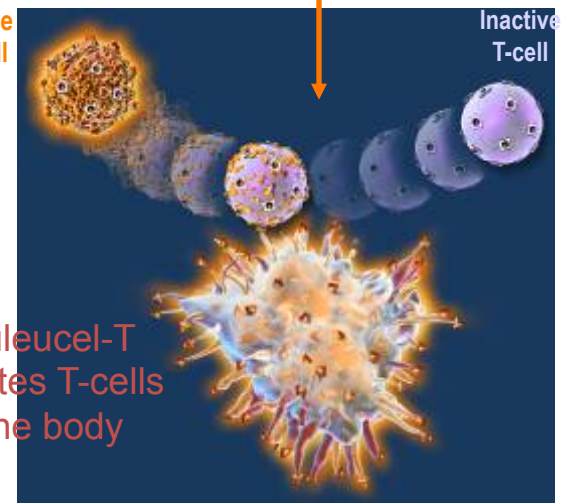


Antigen is processed and presented on surface of the APC

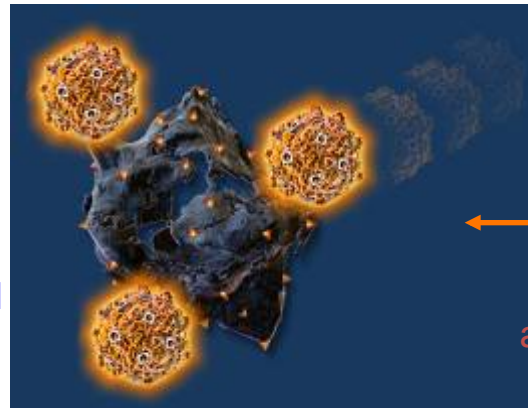


Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT



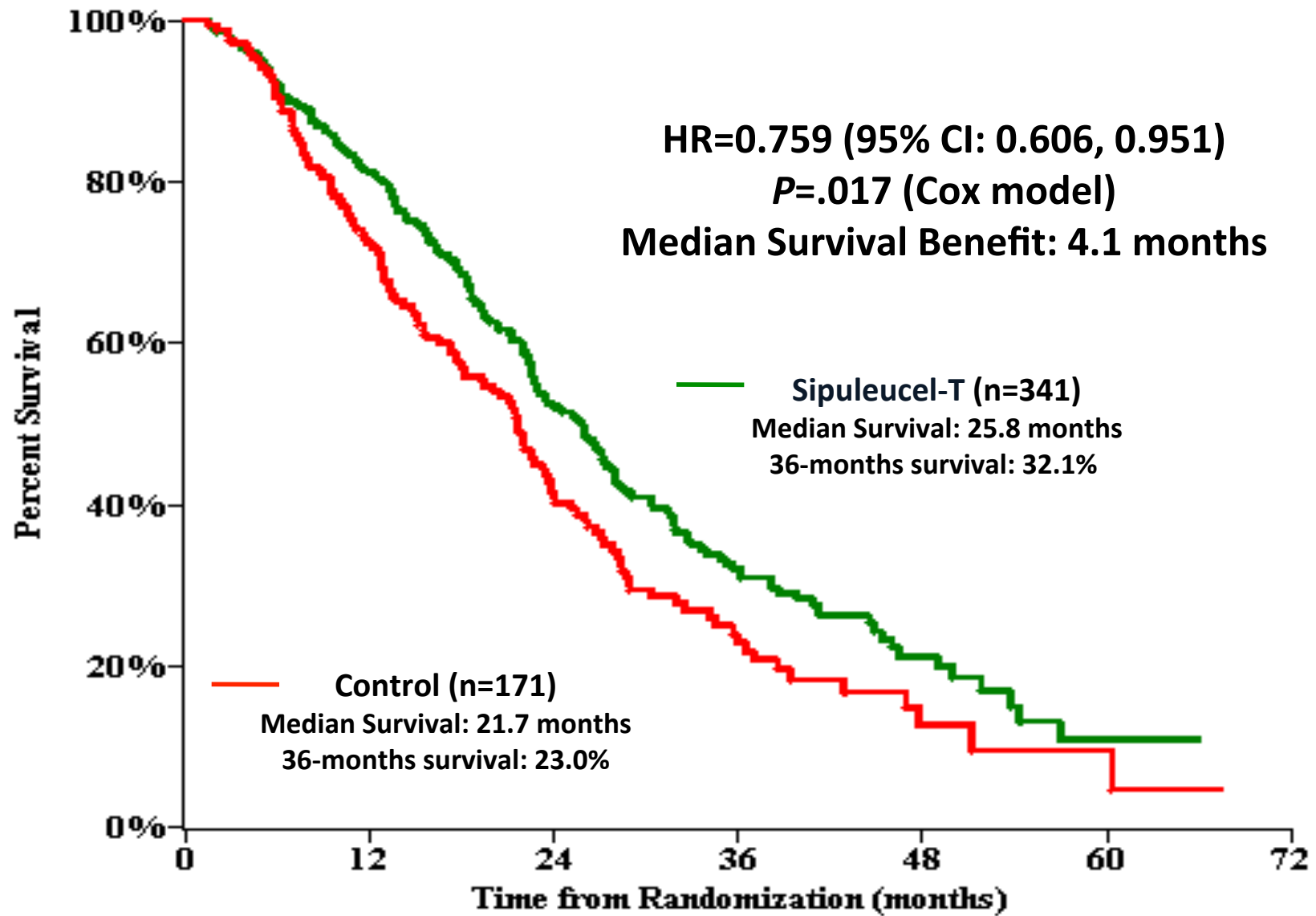
Sipuleucel-T activates T-cells in the body



T-cells proliferate and attack cancer cells

The precise mechanism of sipuleucel-T in prostate cancer has not been established.

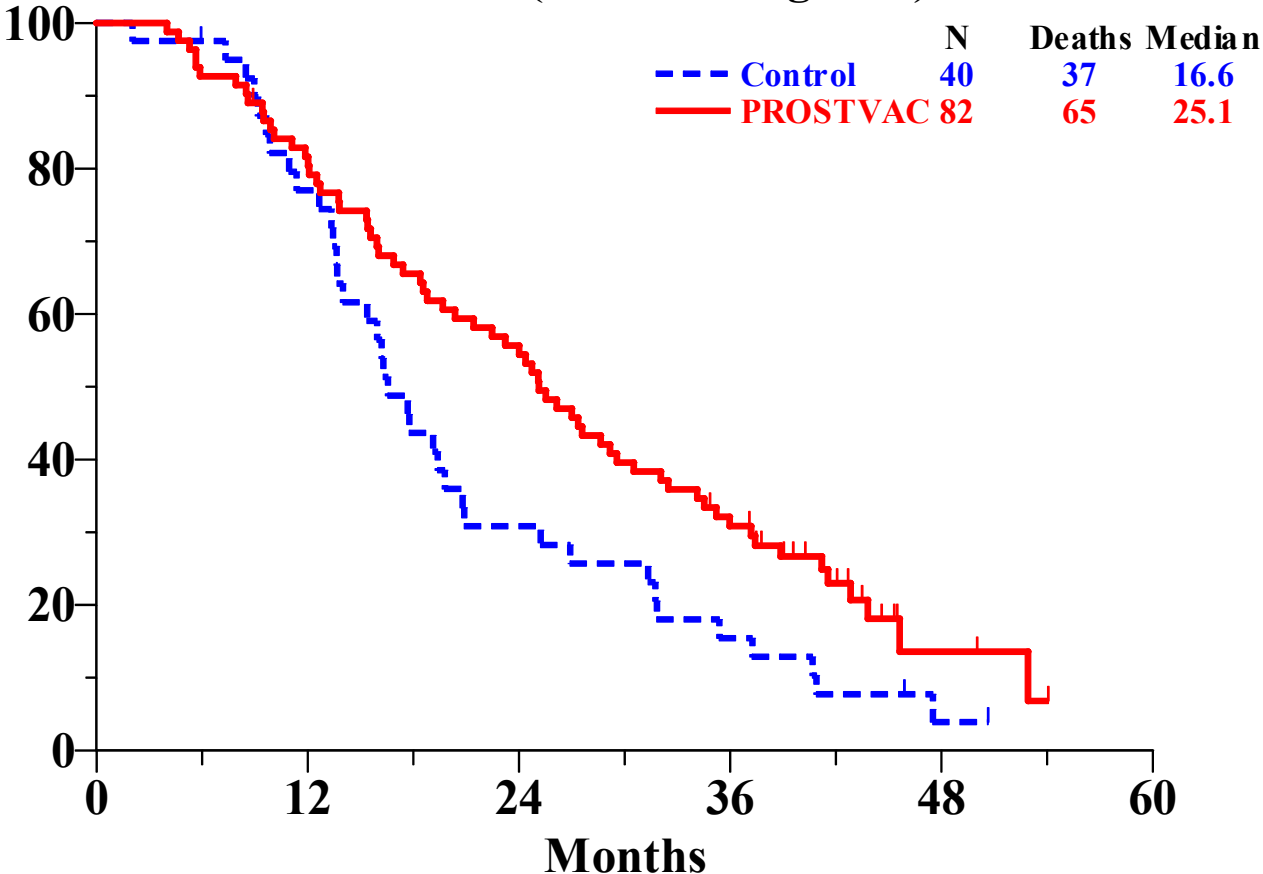
IMPACT Trial



PROSTVAC: Overall Survival

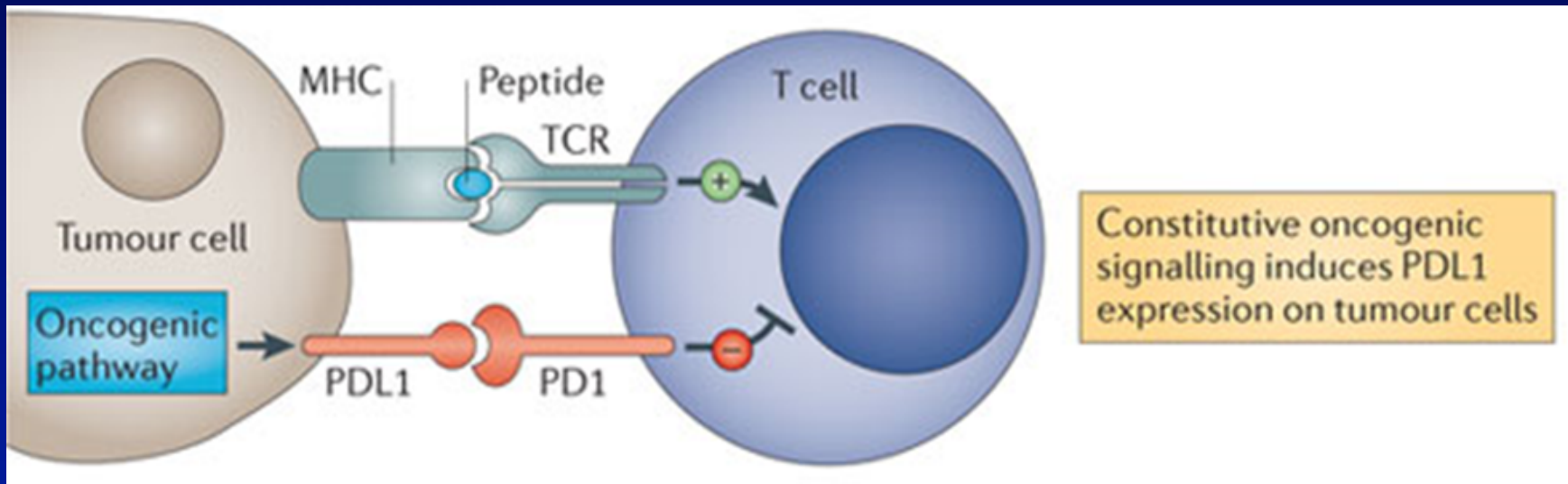
Hazard Ratio = 0.56 (95% CI 0.37 to 0.85)

P = 0.006 (stratified logrank)



Cancer Immunotherapy: Checkpoint Inhibitors

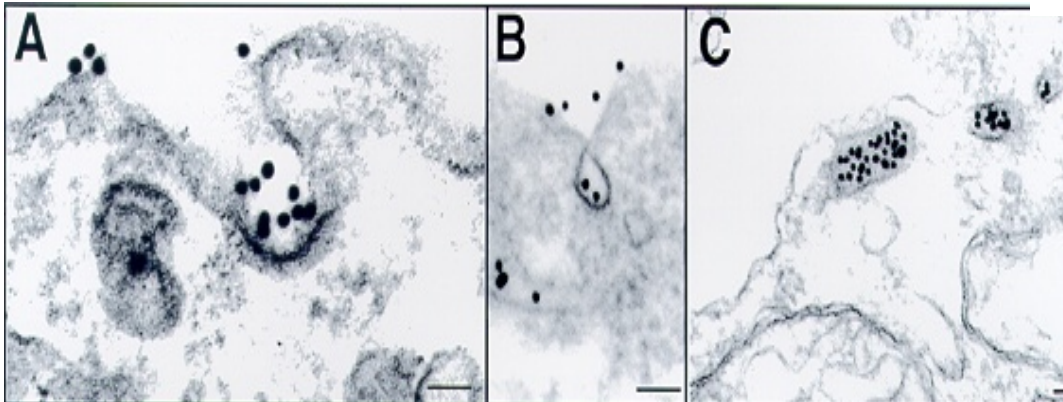
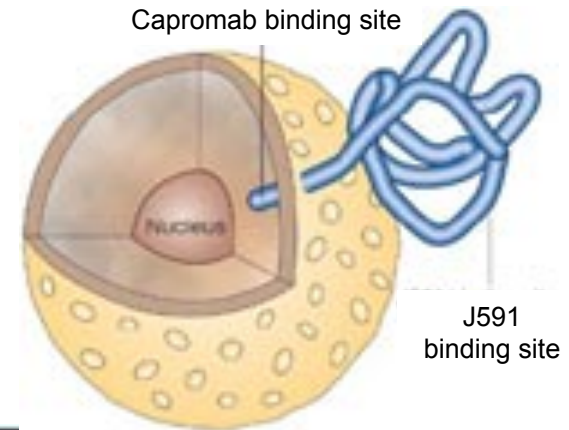
- Mutations make tumors recognizable by the immune system
- Oncogenic signaling in tumor cells can stimulate PD-L1 expression to help evade immune surveillance
- Inhibiting the PD-L1/PD-1 interaction (Checkpoint Inhibitors) can restore anti-tumor T-cell activity, potentially leading to long-lasting responses



Second Generation Anti-PSMA Abs: J591

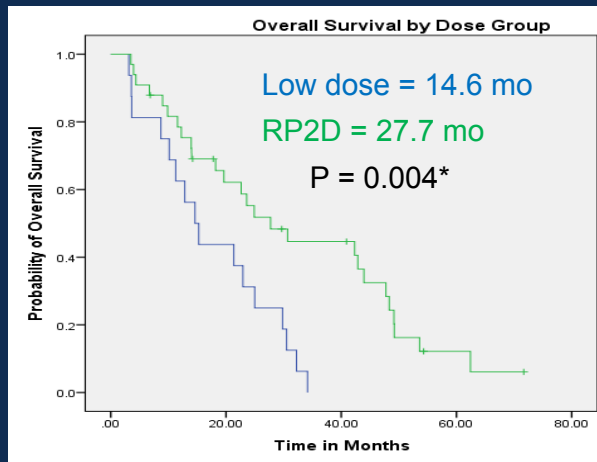
2nd generation mAbs

- Bind extracellular domain
- Bind viable PSMA⁺ cells
- Rapidly internalized

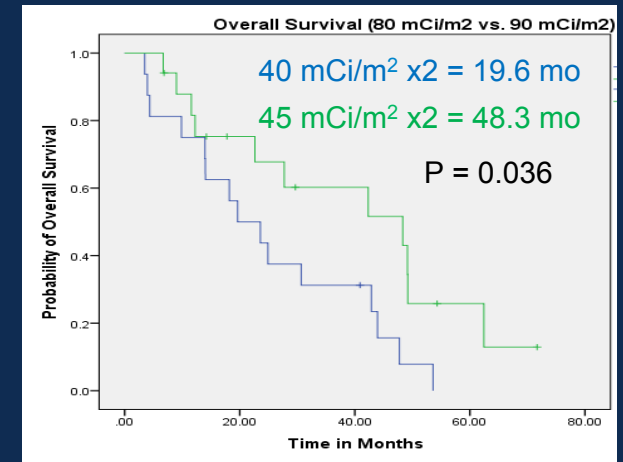


Liu H *et al.* Cancer Res 1997; 57: 3629
Liu H *et al.* Cancer Res 1998; 58: 4055





- At optimal dose:
- 87.5% with PSA decline
 - Median survival 48.3 months



Fractionated ¹⁷⁷Lu-J591

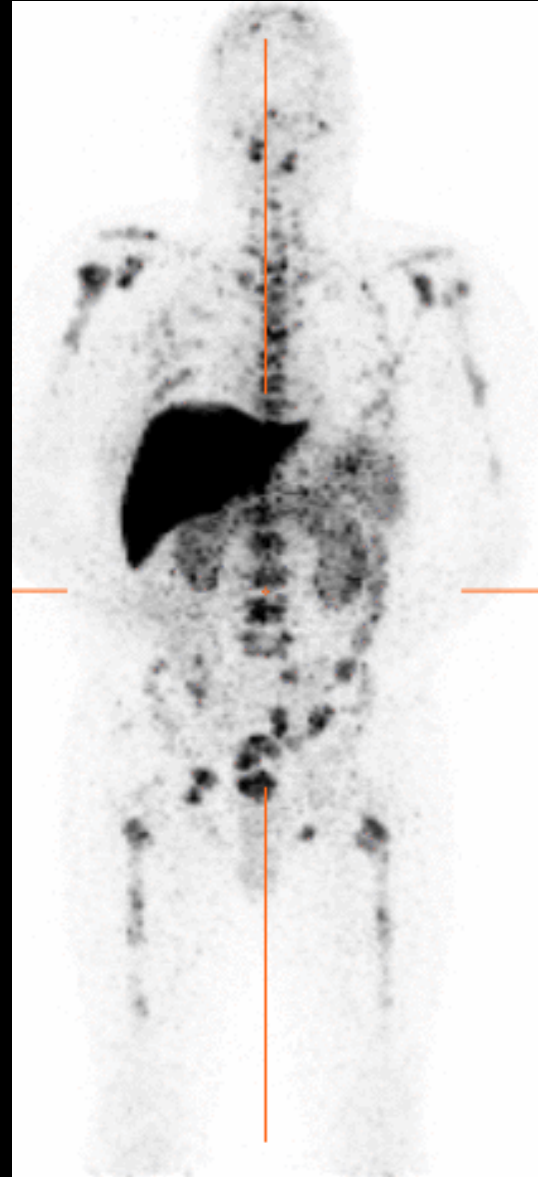
Presented by: Scott T. Tagawa

J591 PSMA-Targeted PET Scan

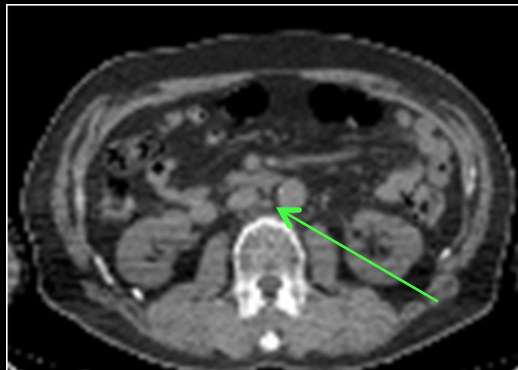
Substantial improvement over
conventional imaging (bone, CT, MR,
FDG)

Confirms ability of J591 to target PC
wherever it is in body

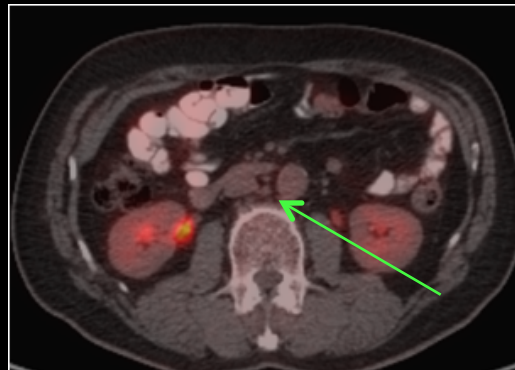
Allows quantitative imaging



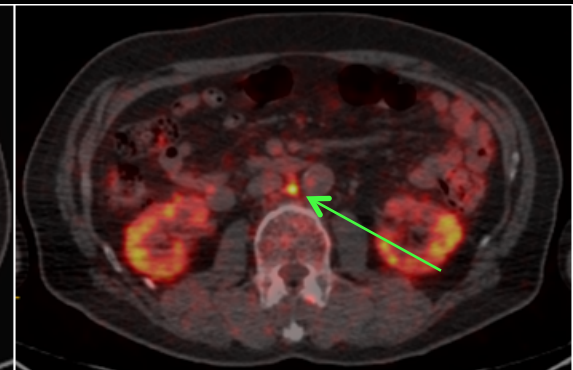
Pt with no known soft tissue disease until ^{89}Zr -J591 detected this LN met



CT (not detected)



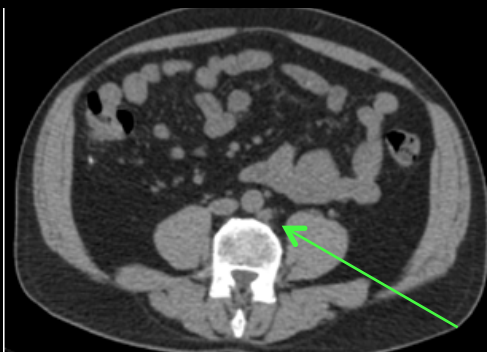
FDG PET (non avid)



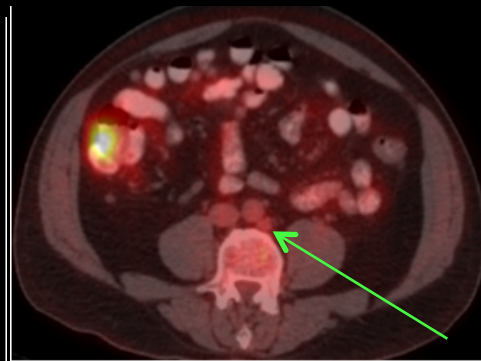
Zr89-J591 PET (avid)

Aortocaval node biopsy: Prostatic adenocarcinoma. Positive for PSA and PSAP by IHC.

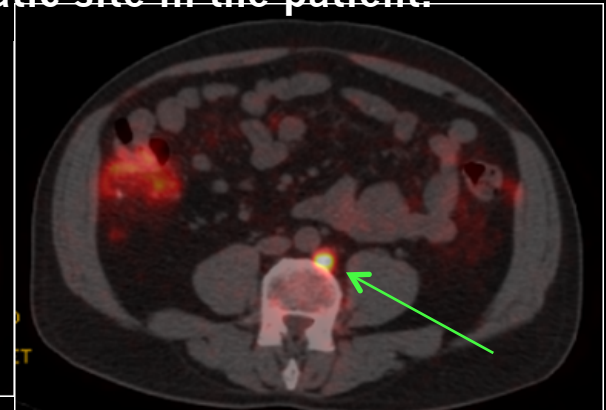
Patient with rising PSA, suspicious LN on MRI, but CT and FDG negative. ^{89}Zr -J591 avid; biopsy-proven as the first metastatic site in the patient.



CT (not detected)



FDG PET (non avid)



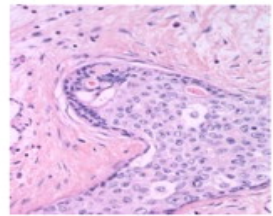
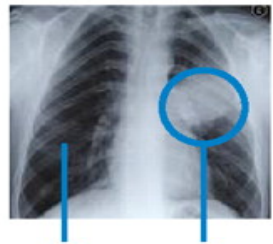
Zr89-J591 PET (avid)

Morris et al, 2013 Genitourinary Cancers Symposium

Molecular Markers

- Beyond the microscope
- May be diagnostic, prognostic, and/or predictive
- Gene fusions
- Expression of abnormal proteins
- Circulating Tumor Cells (CTCs)
- Circulating Tumor DNA

Molecular Classification of Prostate Cancer

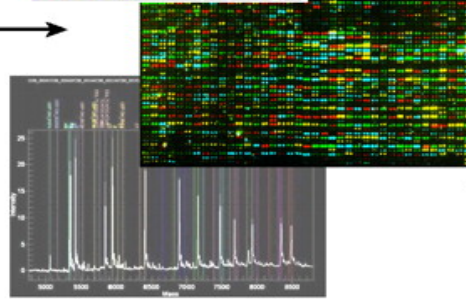
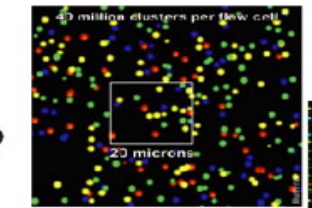


Cancerous

Tumor traditionally classified by histology, tissue site



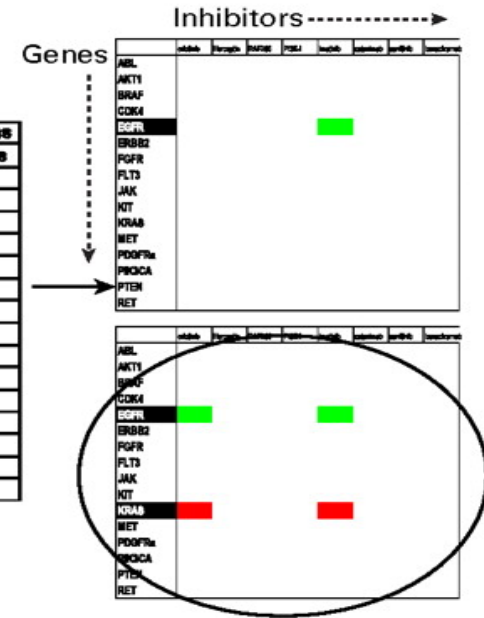
Extract tumor biopsy



Extract DNA from tumor to profile for somatic alterations

Gene	Mut	Amp	Del	Trans
ABL				yes
AKY1				
BRAF				
CDK4				
EGFR	yes			
ERBB2				
FGFR				
FLT3				
JAK				
KIT				
KRAS				
MET				
PDGFR α				
PIK3CA				
PTEN				
RET				

Define "actionable" mutation profile of tumor



Use genetic alteration profile to choose individualized targeted therapeutic

The NEW ENGLAND JOURNAL of MEDICINE

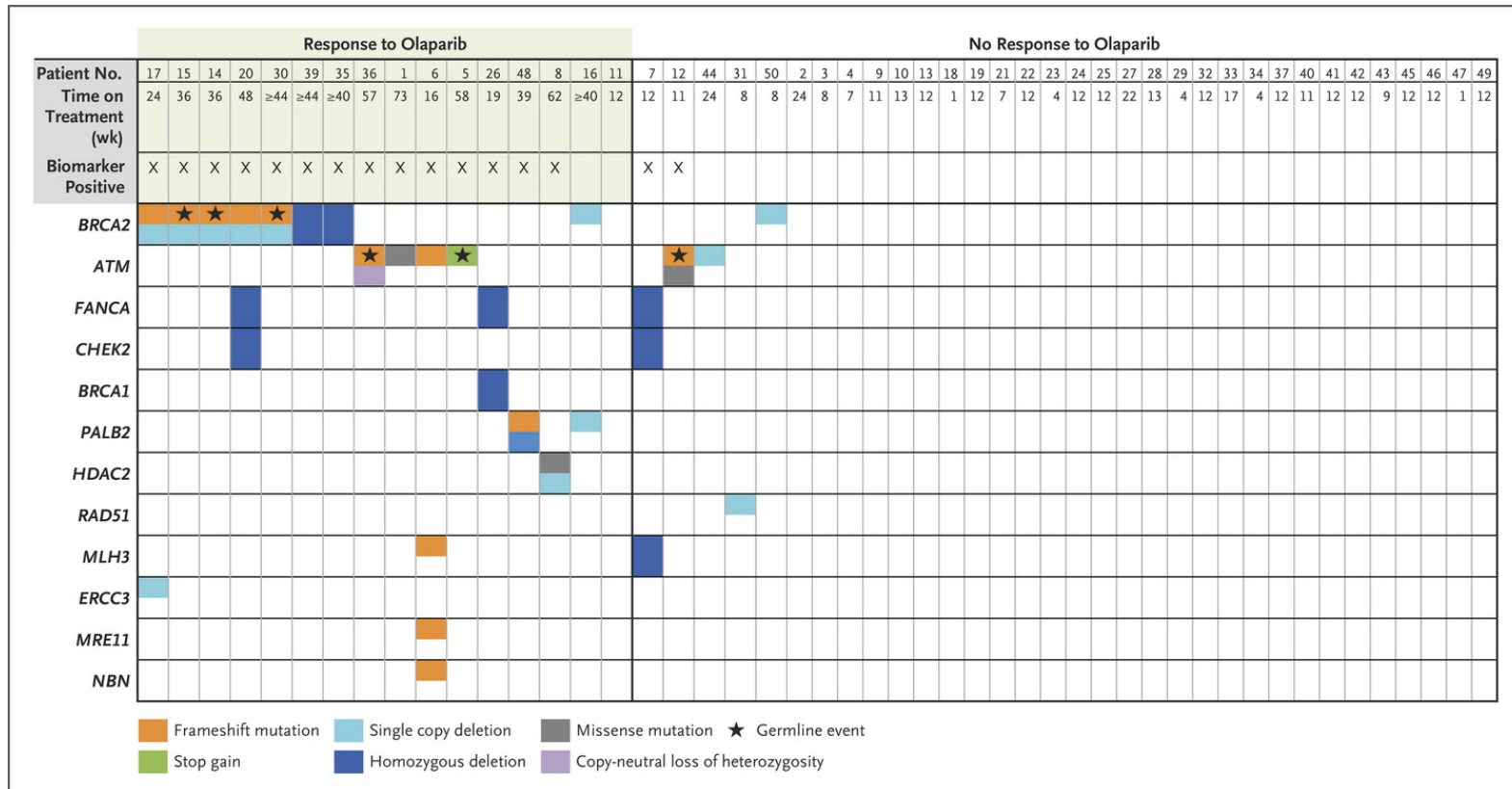
ESTABLISHED IN 1812

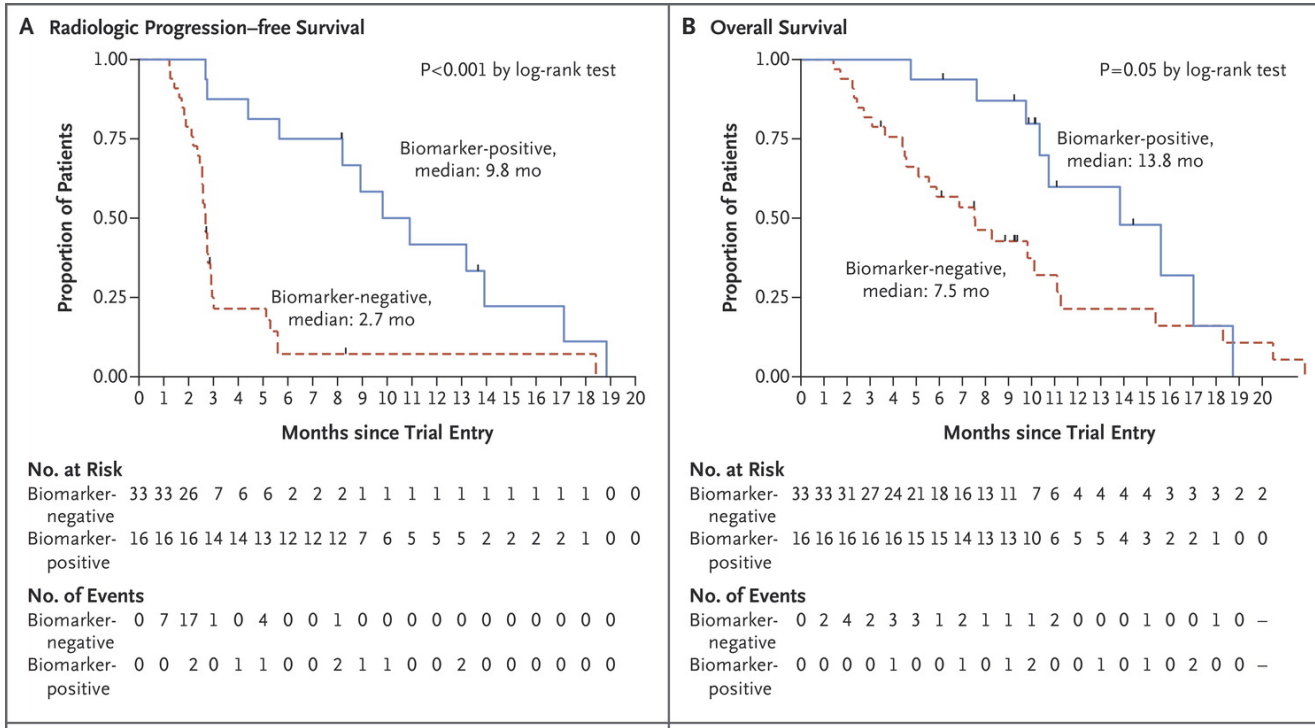
OCTOBER 29, 2015

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DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

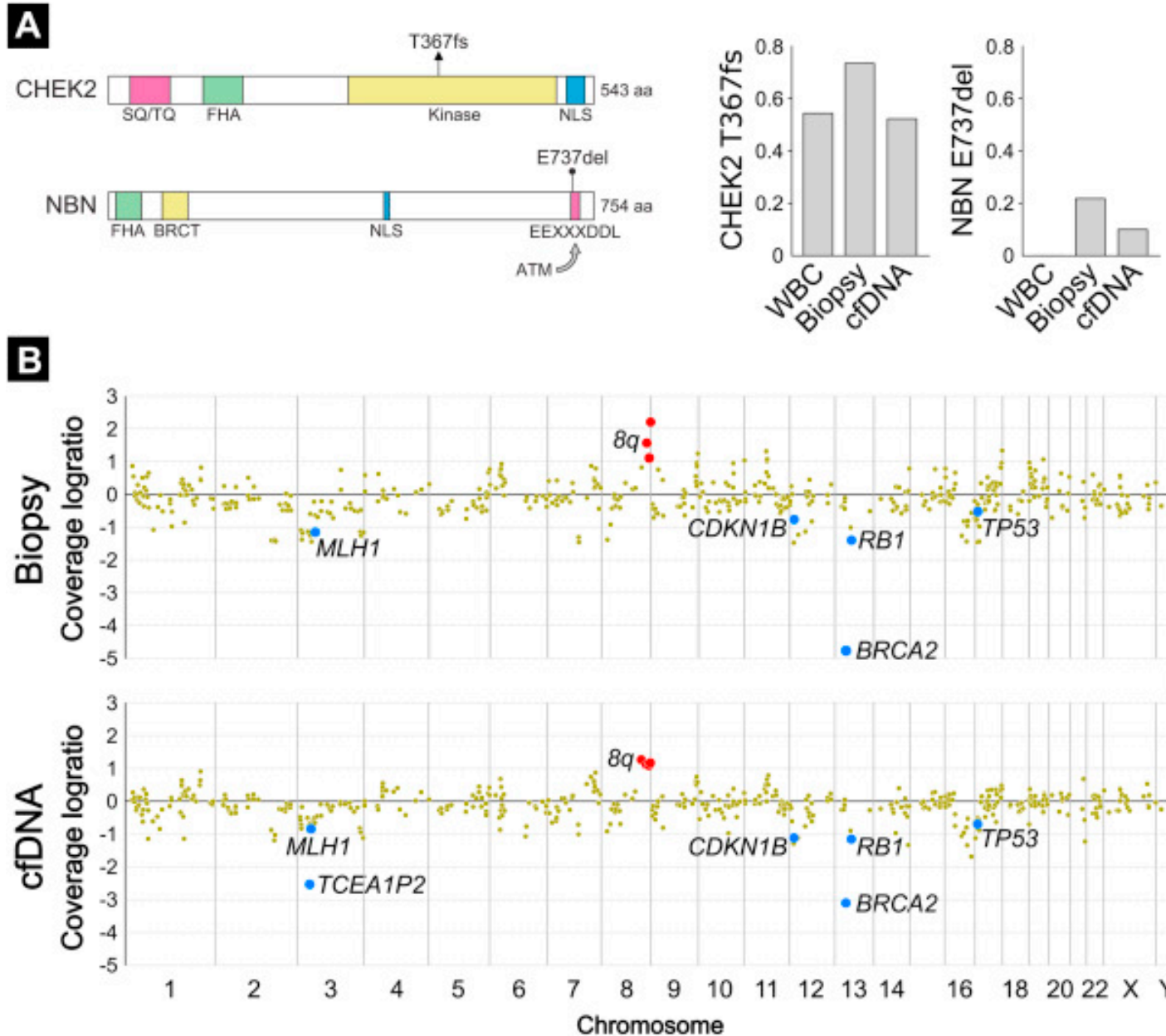
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson,



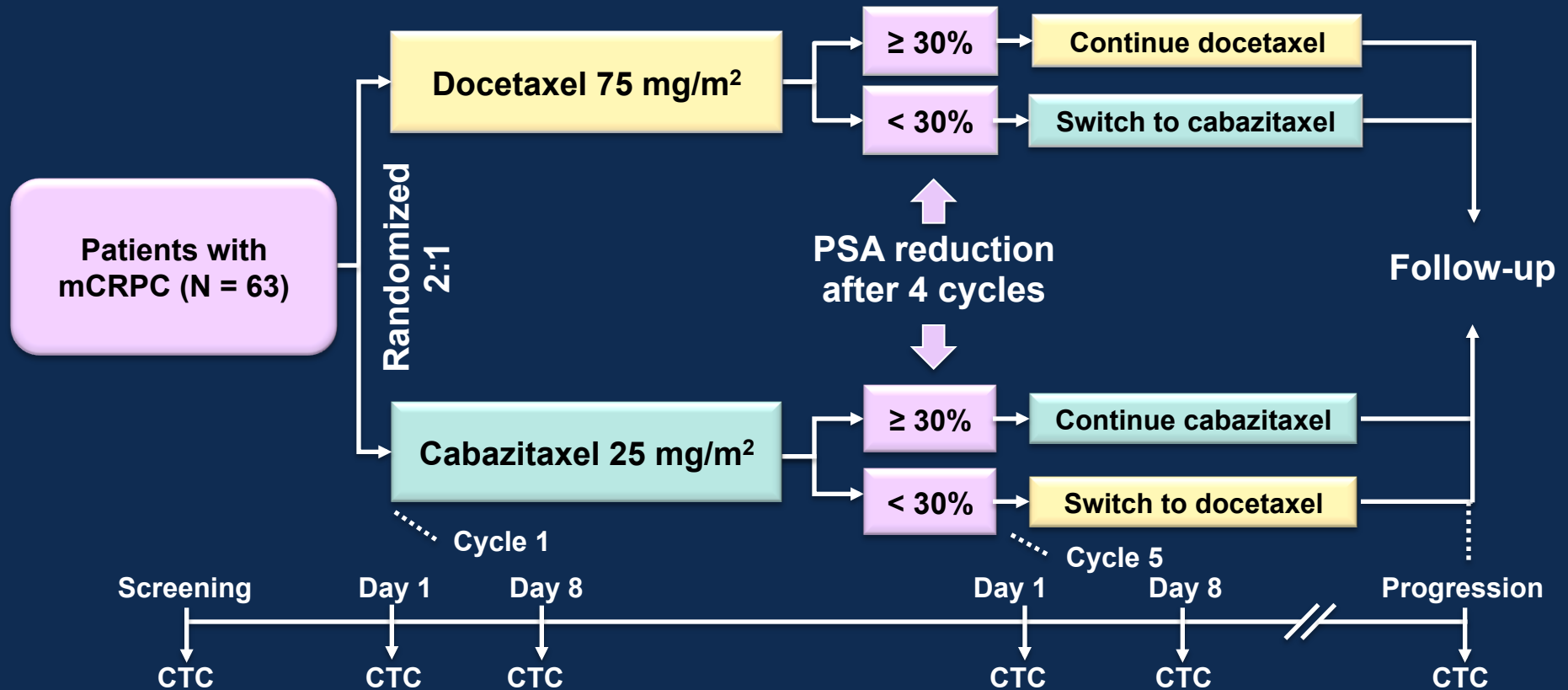


January 2016: olaparib granted FDA Breakthrough Designation for BRCA1/2 and ATM mutated CRPC

Detection of BRCA2 loss in tumor in circulating tumor DNA



TAXYNERGY: Study Design



Primary Endpoint: PSA response rate (≥ 50% reduction from baseline)

Co-primary Endpoint: DTE

Presented by: Scott T. Tagawa

CRPC Therapeutic Options

	Increase in median survival	Relative reduction in risk of death	Hazard ratio (95% CI; P-value)
Abiraterone/P vs. placebo/P	3.9 mos	35%	0.65 (0.54-0.77; P<0.001)
Enzalutamide vs. placebo	4.8 mos	37%	0.63 (P<0.0001)
Docetaxel(q3w)/P vs. Mitoxantrone/P	2.4 mos	24%	0.76 (0.62-0.94; P=0.009)
Cabazitaxel/P vs. mitoxantrone/P	2.8 mos	30%	0.70 (0.59-0.83; P<0.0001)
Sipuleucel T vs. placebo	4.1 mos	22%	0.78 (0.61- 0.98; P:0.03)
Alpharadin vs. placebo	2.8 mos	31%	0.70 (0.55-0.88; P: 0.00185)