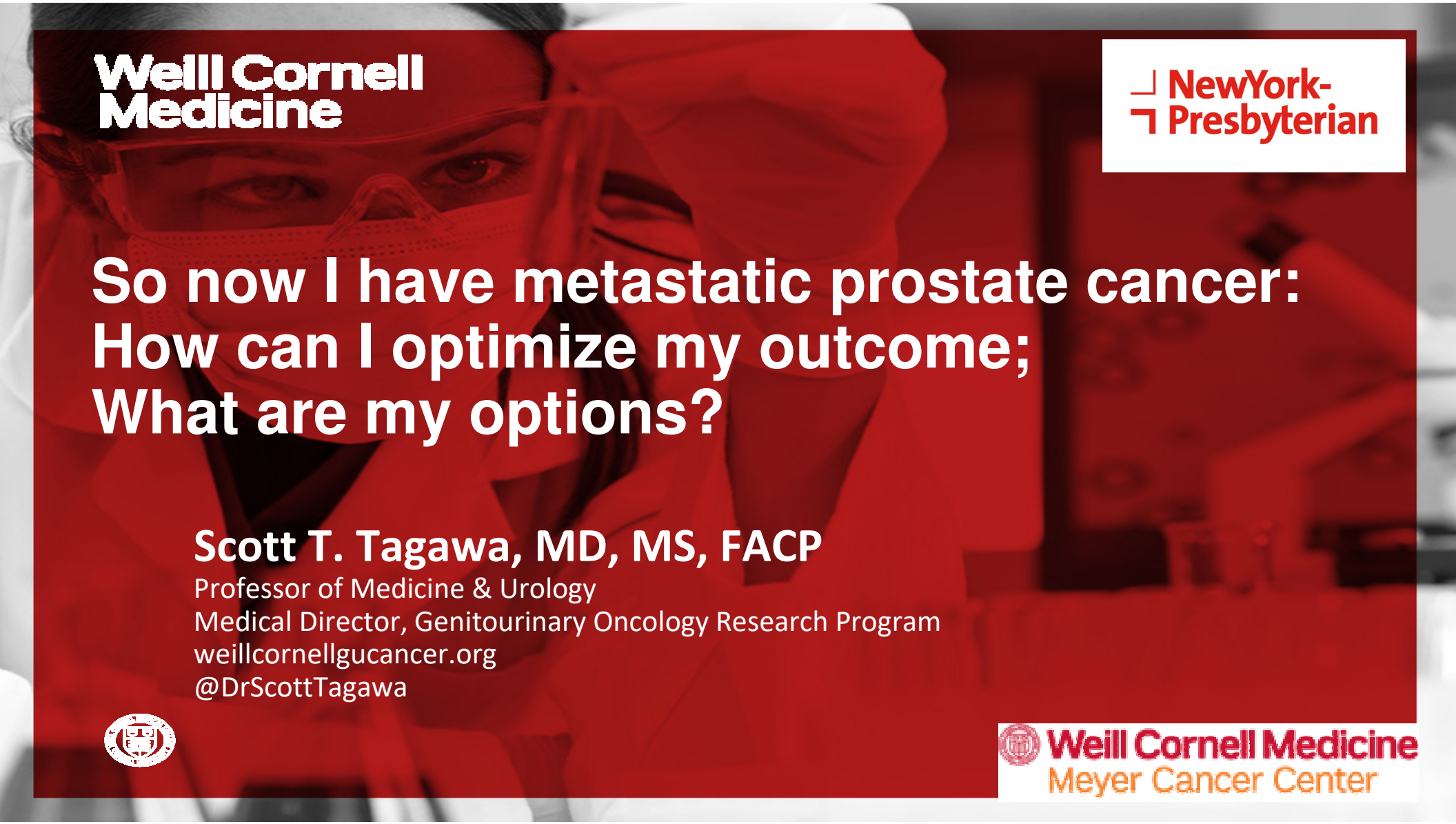

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NewYork-Presbyterian

So now I have metastatic prostate cancer: How can I optimize my outcome; What are my options?

Scott T. Tagawa, MD, MS, FACP
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Weill Cornell Medicine
Meyer Cancer Center

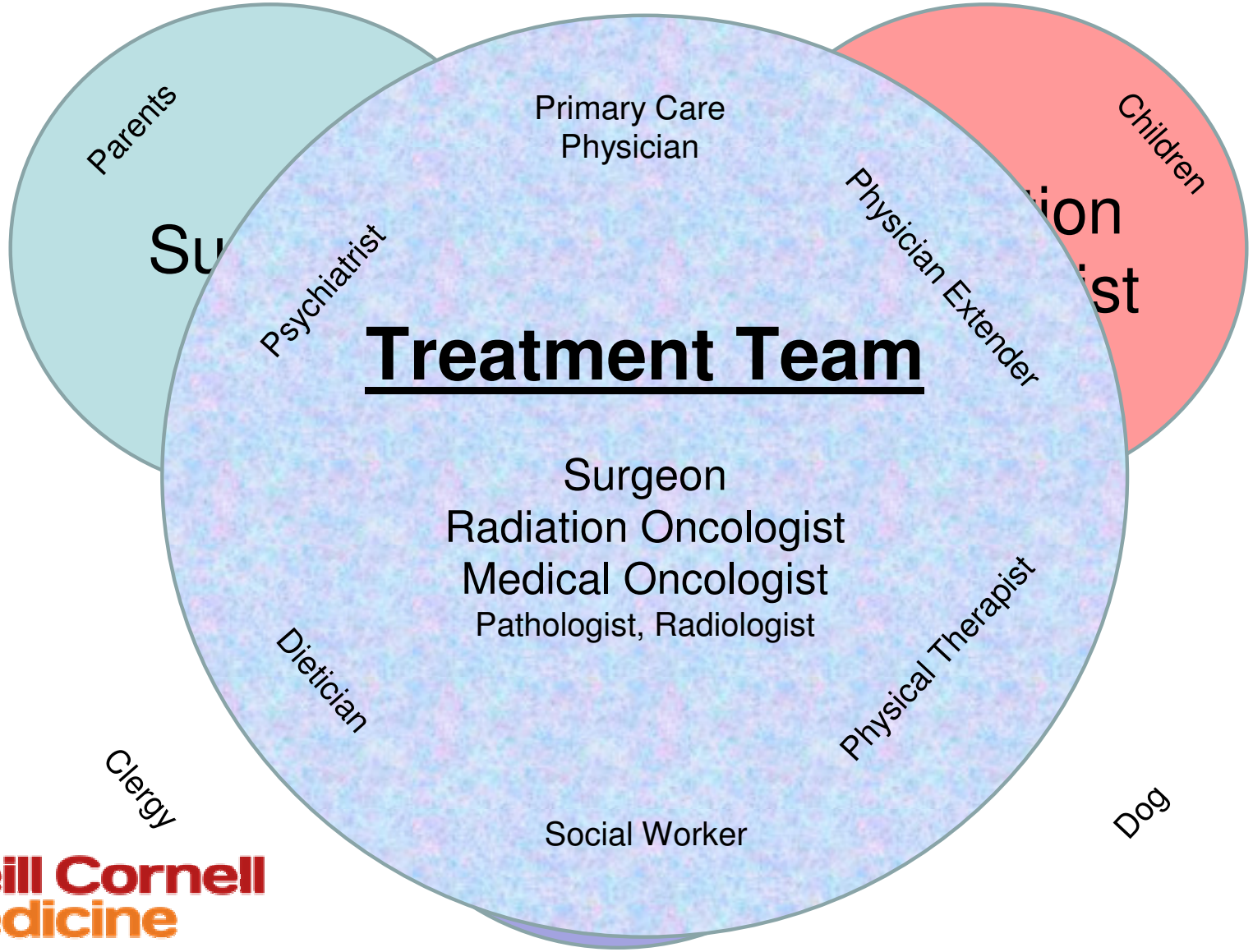
Disclosures

- Research support (to Weill Cornell):
  - Sanofi, Medivation, Astellas, Janssen, Amgen, Progenics, Dendreon, Lilly, Genentech, Newlink, BMS, Inovio, AstraZeneca, Immunomedics, Aveo, Rexahn, Atlab, Boehringer Ingelheim, Millennium, Bayer, Merck, Abbvie, Karyopharm, Endocyte, Clovis, Seattle Genetics, AAA/Novartis
- Paid Consultant (since 2007):
  - Sanofi, Medivation/Astellas, Dendreon, Janssen, Genentech, Bayer, Endocyte, Eisai, Immunomedics, Karyopharm, Abbvie, Tolmar, Seattle Genetics, Amgen, Clovis, QED, Pfizer, AAA/Novartis, Clarity, Genomic Health, POINT Biopharma, Blue Earth Diagnostics, Alkido Pharma, Telix Pharma
- Unpaid Consultant:
  - Atlab Pharma, Phosplatin Therapeutics, Amgen, Ambrx

Outline

- Introduction / Overview
- Quick run through some clinical trial data
- Summary of clinical trial data: What does it mean?
  - *What is the best systemic therapy?*
  - *What about my prostate tumor (if not previously treated)?*
  - *Am I getting unnecessary therapy?*
- Can we do better?
  - Tumor and germline (inherited profiling)
  - Advanced imaging
  - Highlight of some clinical trials

My bias…



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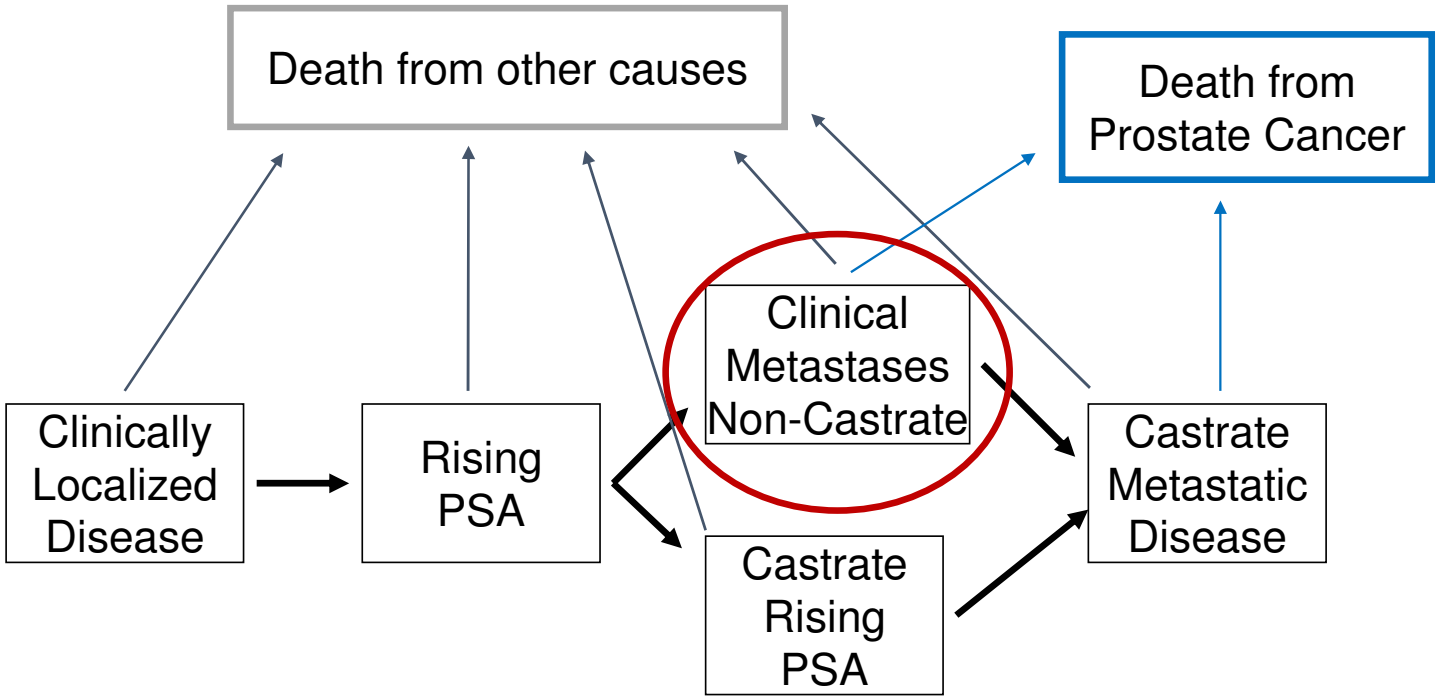
"Clinical states"



Metastases = spread of tumors
Most commonly lymph node and bone

Now what?

“Advanced prostate cancer”

Terminology

- **Advanced**: often synonymous with **metastatic** (meaning spread), but at least implies more than just prostate
- **Non-castrate**: prior to treatment with intact blood testosterone level; aka “hormone sensitive”, “hormone-naïve”, “castration-sensitive”
- **Castration-resistant**: following some treatment to lower blood testosterone levels, with some evidence of prostate cancer growth (PSA or scans)

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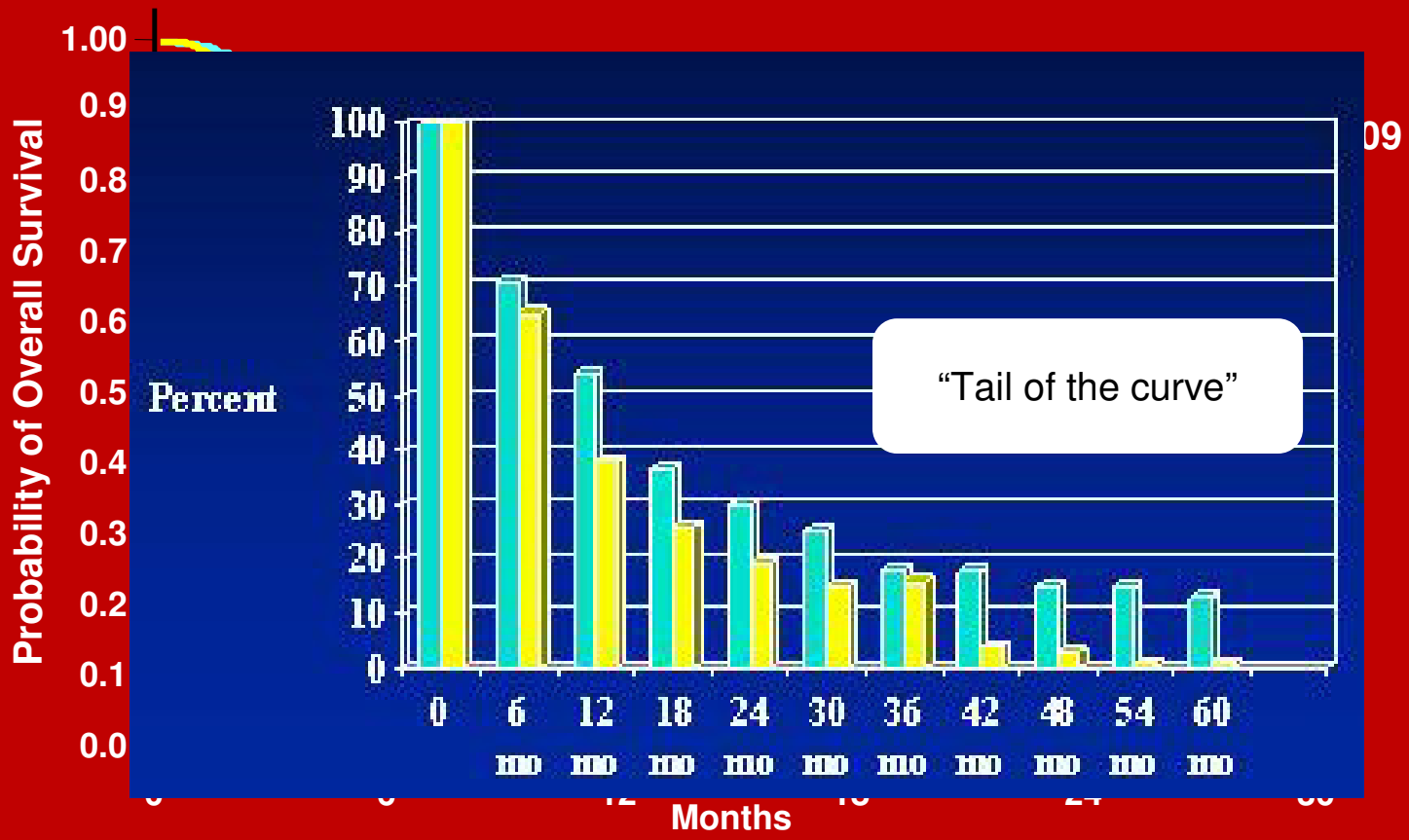
A word on medical clinical trial terminology and implications



Chemotherapy

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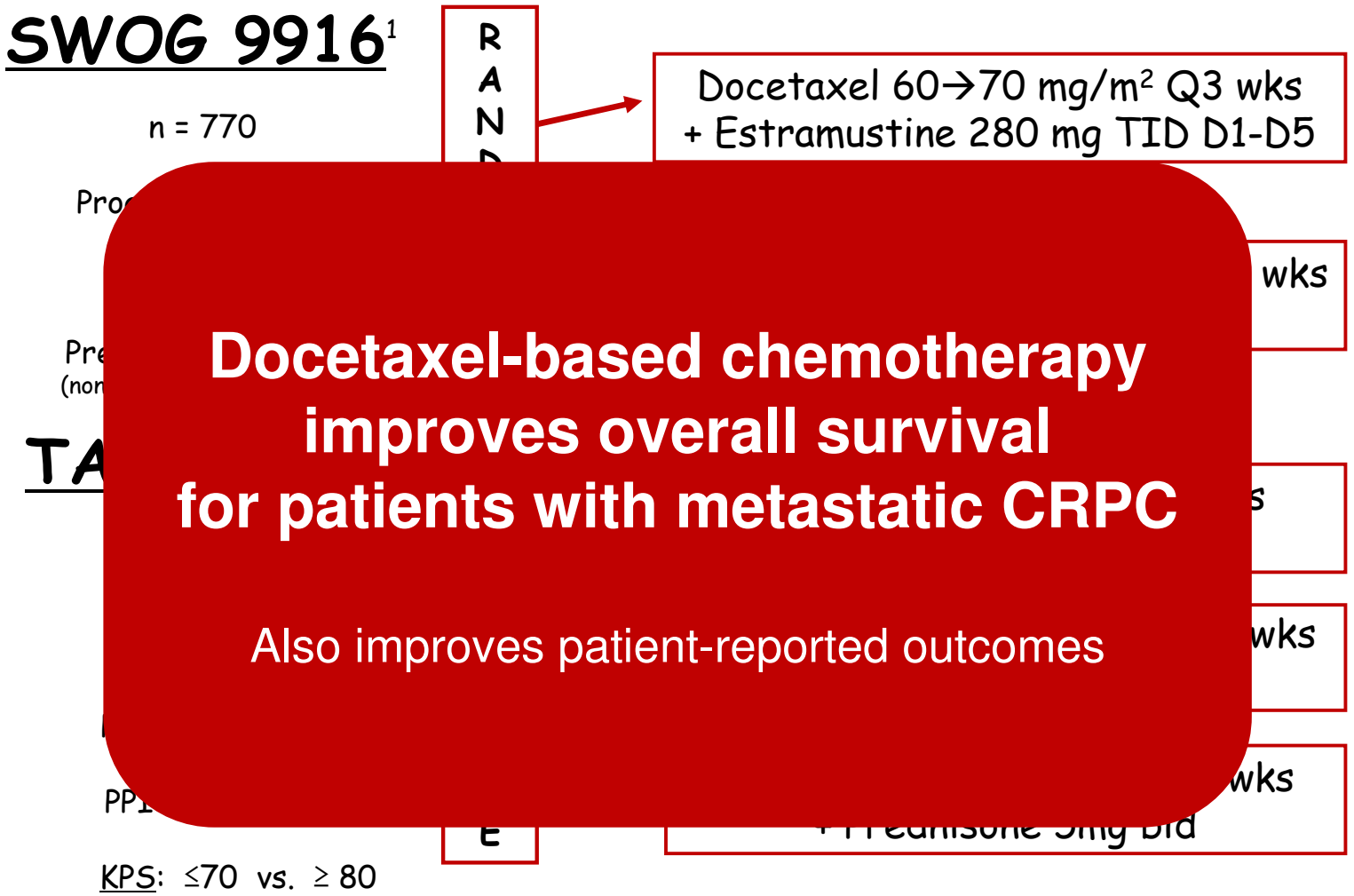

Docetaxel-based chemotherapy improves overall survival for patients with metastatic CRPC

Also improves patient-reported outcomes

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[1]Petrylak et al. NEJM 2004; 531: 1513
[2]Tanock et al. NEJM 2004; 531: 1502

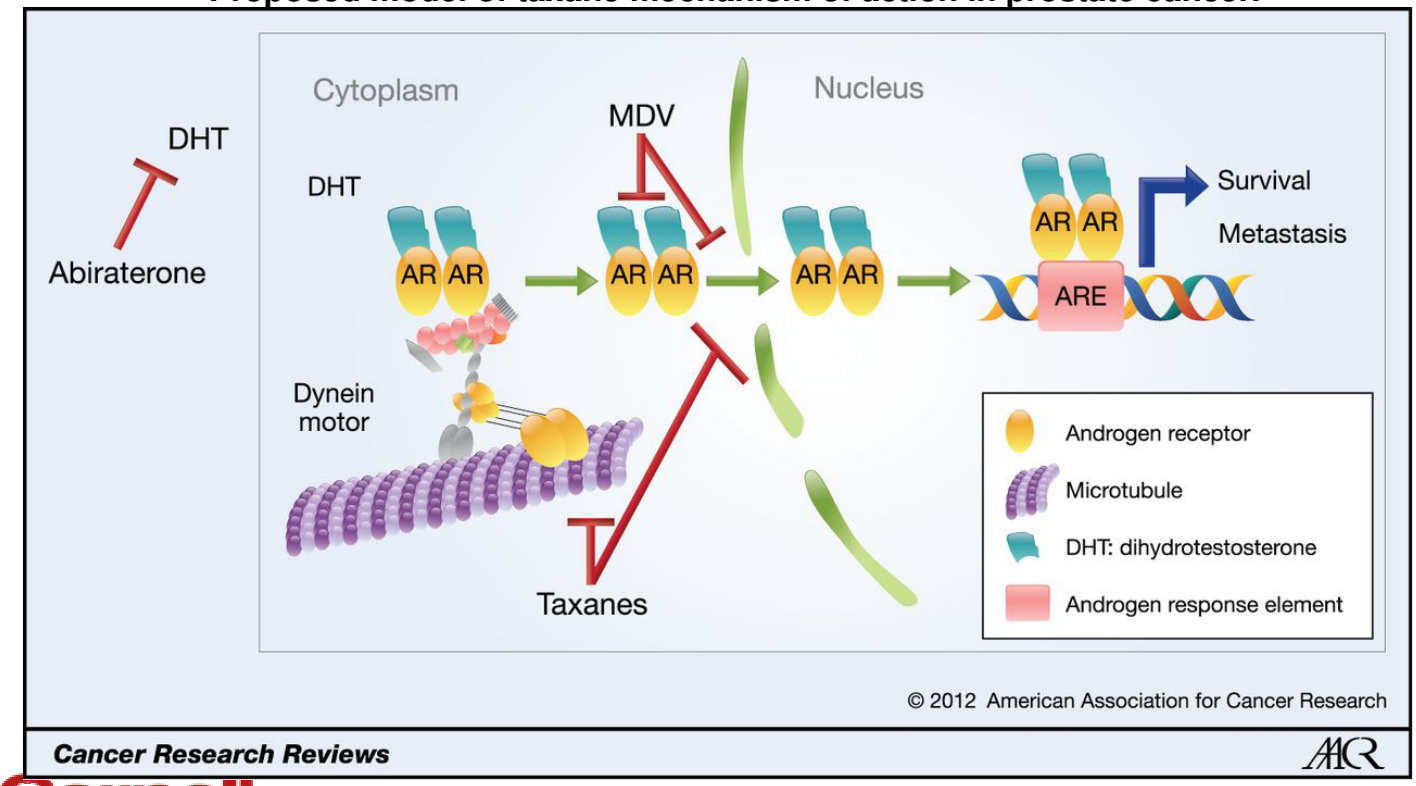
Review

Cancer Research

Androgen Receptor on the Move: Boarding the Microtubule Expressway to the Nucleus

Maria Thadani-Mulero[1], David M. Nanus[1,2], and Paraskevi Giannakakou[1,2]

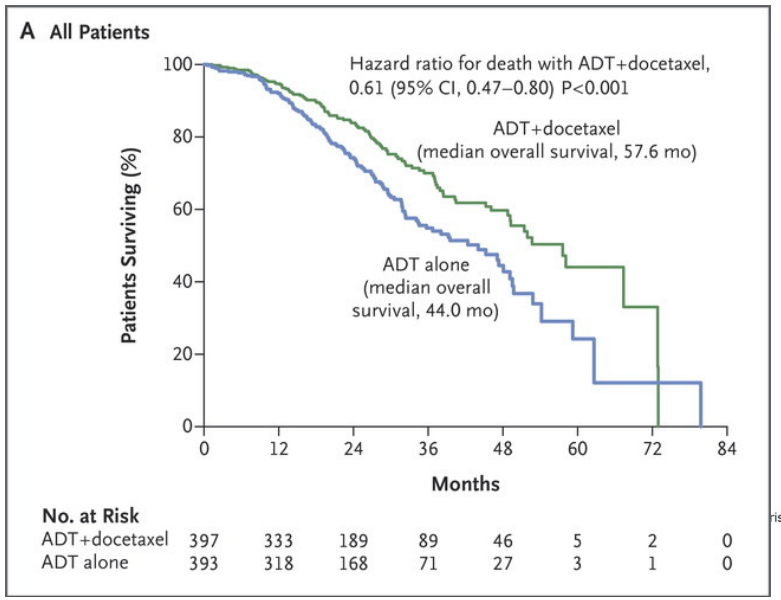
Proposed model of taxane mechanism of action in prostate cancer.



Thadani-Mulero M et al. Cancer Res 2012;72:4611-4615

Docetaxel for advanced non-castrate disease

E3805 “CHAARTED”



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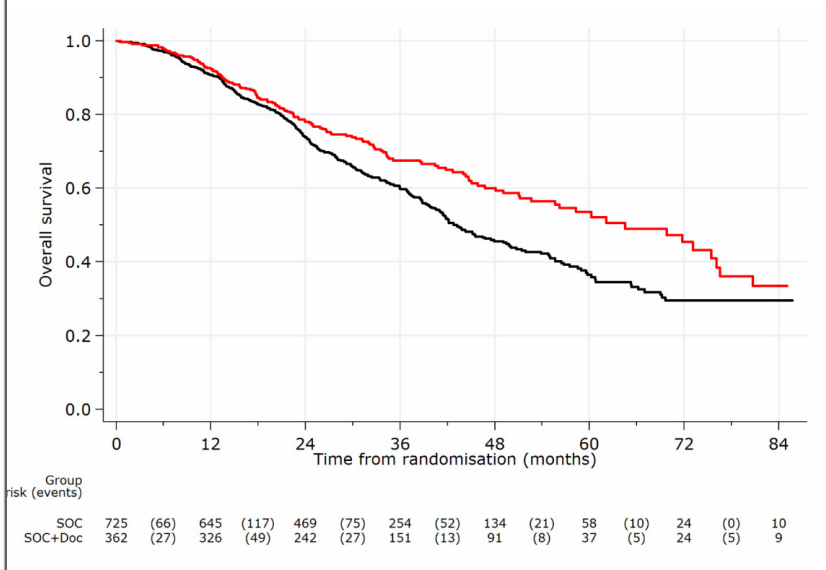

ADT + docetaxel superior to ADT alone for OS and PFS

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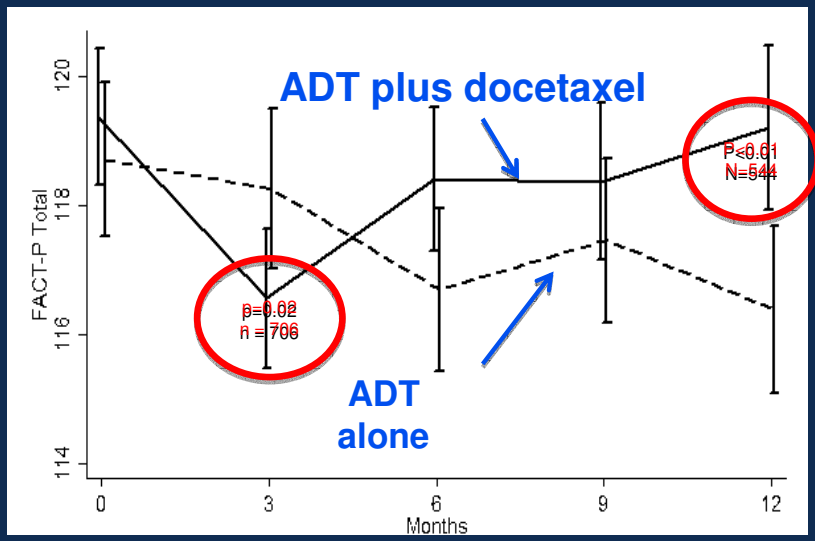
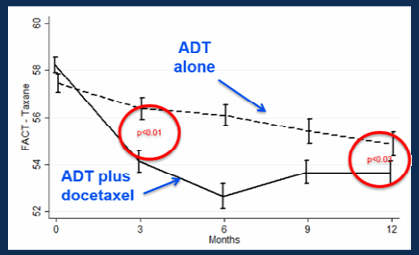
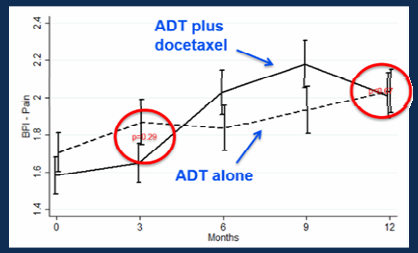
Sweeney NEJM 2015
James Lancet 2016

CHAARTED: Overall QOL on FACT-P

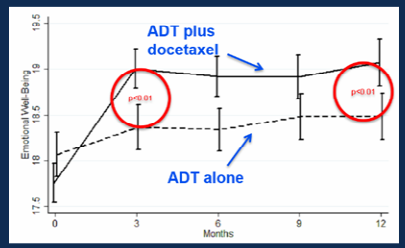




FACT-Taxane



Pain



Emotional Well-Being

Hormonal Therapy:

What's old is new again*

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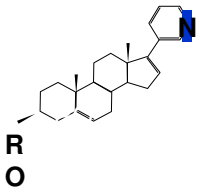
*Huggins & Hodges 1938 (animals) → 1941 (men) → Nobel Prize 1966

TERMINOLOGY

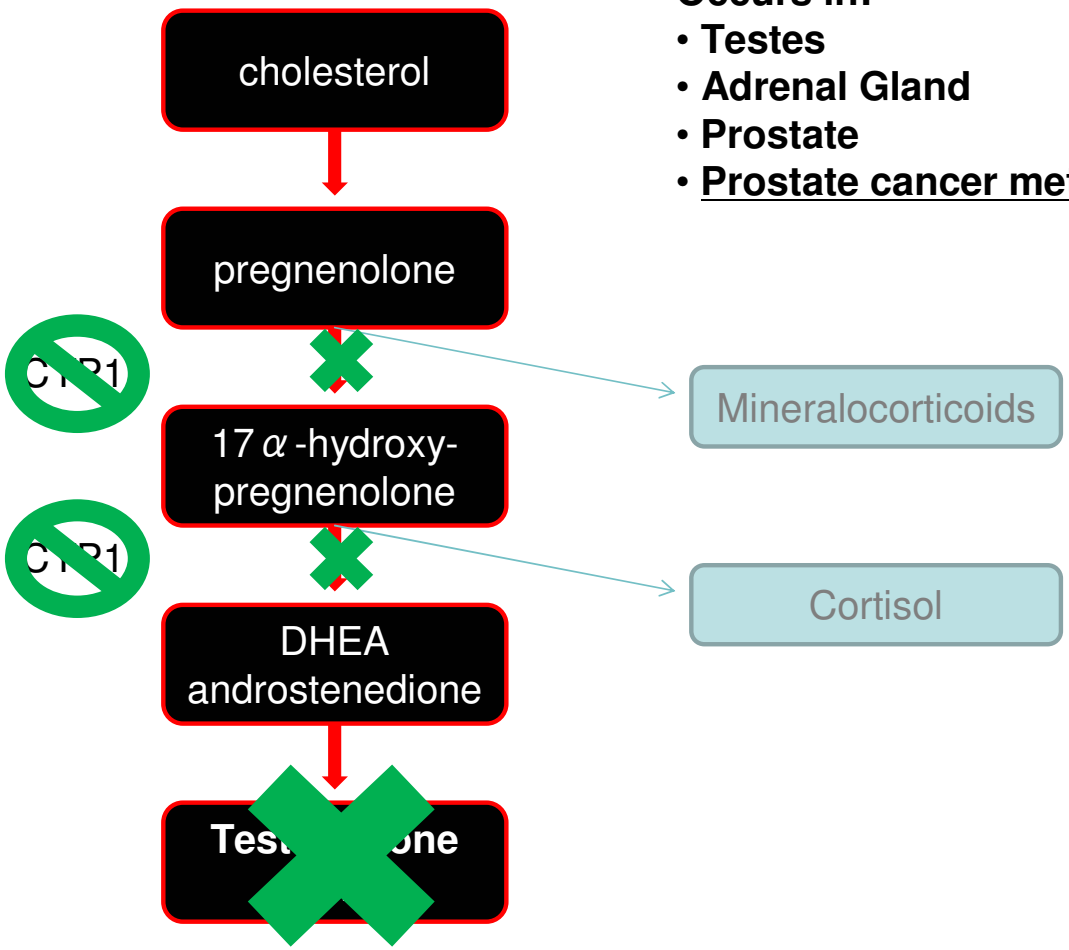
ADT = “androgen deprivation therapy”

- Bilateral orchiectomy = LHRH analog = estrogen (efficacy)
- LHRH analog most commonly used in US
  - **LHRH agonist** (leuprolide, goserelin, triporelin, histrelin, etc)
    - Block testosterone from testicles
    - Traditionally avoid flare with antiandrogen
  - **LHRH antagonist** (degerelix, relugolix)
    - Immediate reduction in testosterone production in testes
- Anti-androgens (traditional nonsteroidal = bicalutamide, flutamide, nilutamide)
  - Block testosterone action in cells (but can stimulate)
- “Combined androgen blockade” = CAB = combo of LHRH + antiandrogen

Abiraterone Acetate (CB7630)



- **Oral irreversible inhibitor of CYP17 (P450c17)**
  - **17α –hydroxylase**
  - **$C_{17,20}$-lyase**



Occurs in:
- **Testes**
- **Adrenal Gland**
- **Prostate**
- **Prostate cancer metastases**

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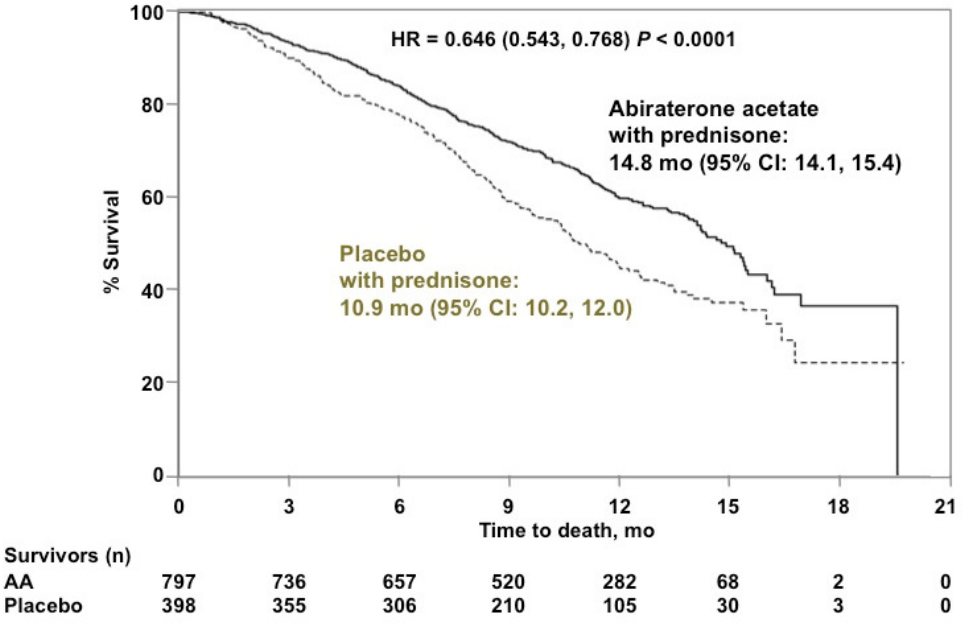
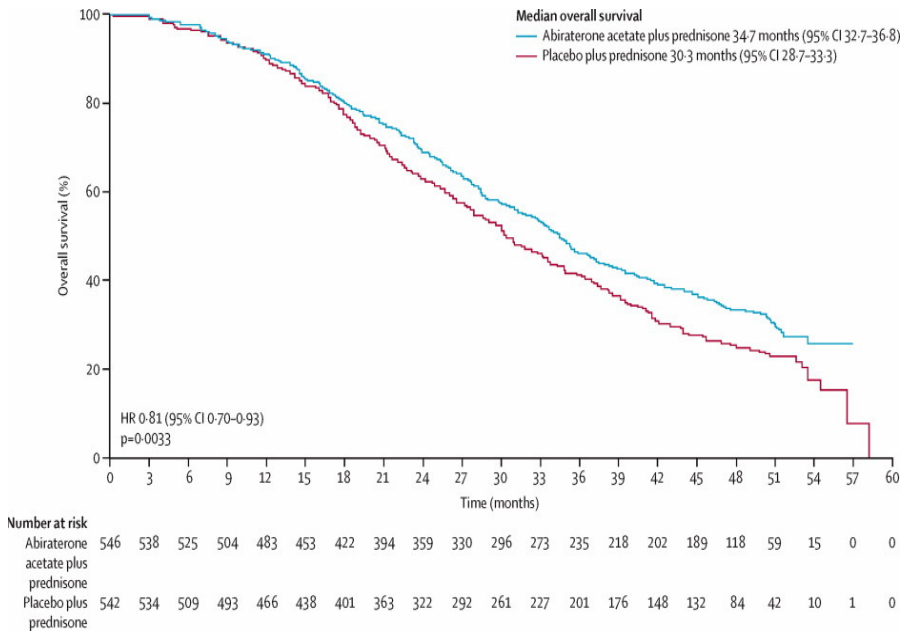
Abiraterone Acetate + prednisone vs Placebo + prednisone in men with progressive metastatic CPRC





Abiraterone + prednisone yields superior OS than prednisone + placebo in post-docetaxel mCRPC and chemo-naïve minimally symptomatic mCRPC

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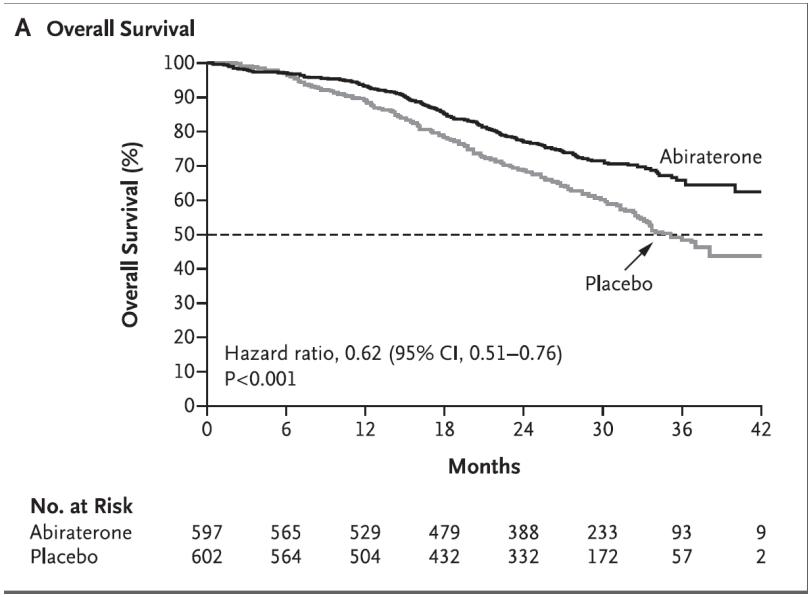
de Bono et al, NEJM 2011
Ryan et al, Lancet Oncol 2015

Abiraterone/Predisone for advanced non-castrate disease

LATITUDE



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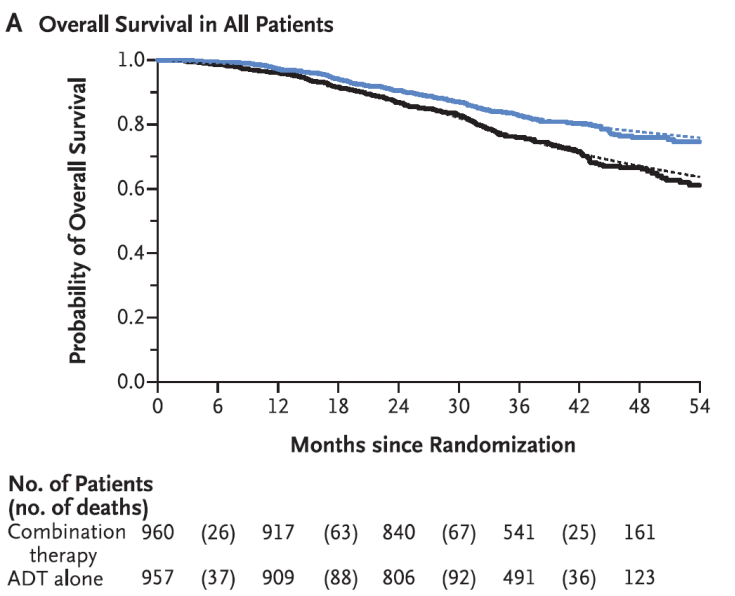

ADT + Abi/Pred superior to ADT alone for OS and PFS

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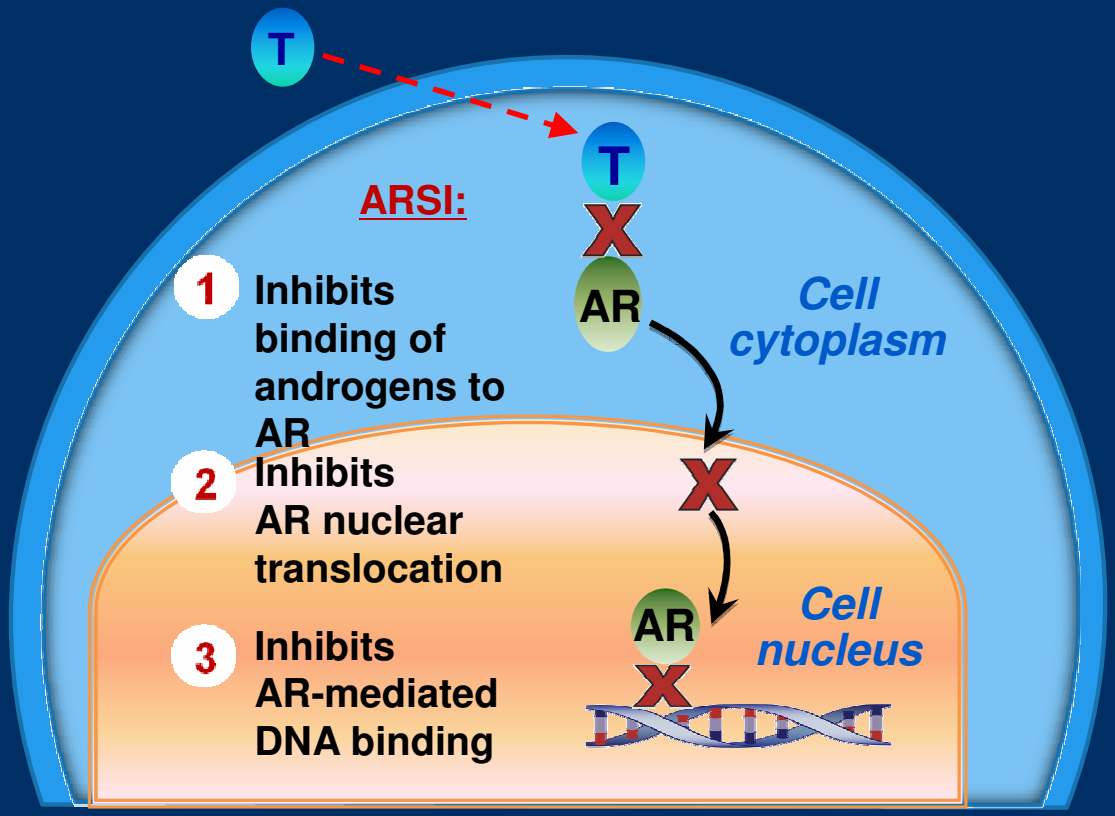
Fizazi NEJM 2017
James NEJM 2017

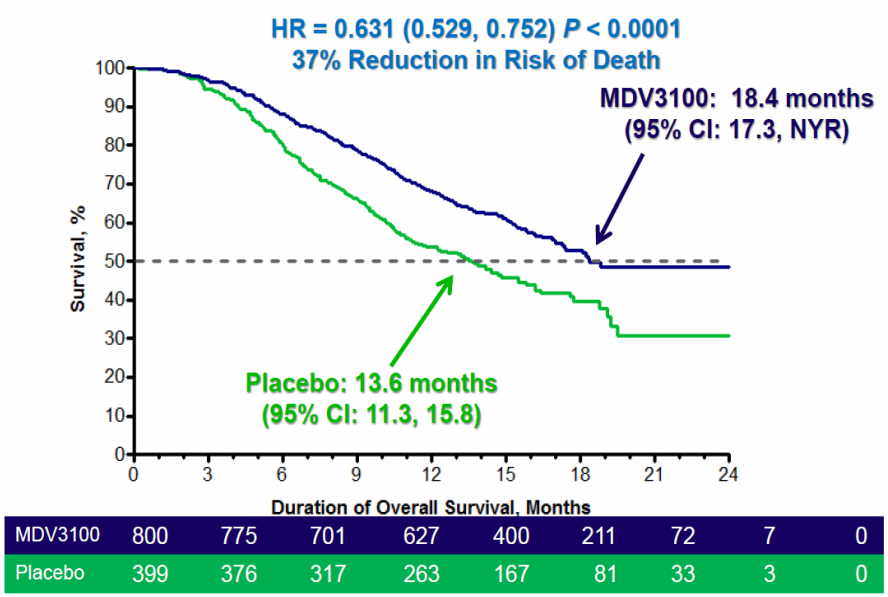
Androgen Receptor Signaling Inhibitor



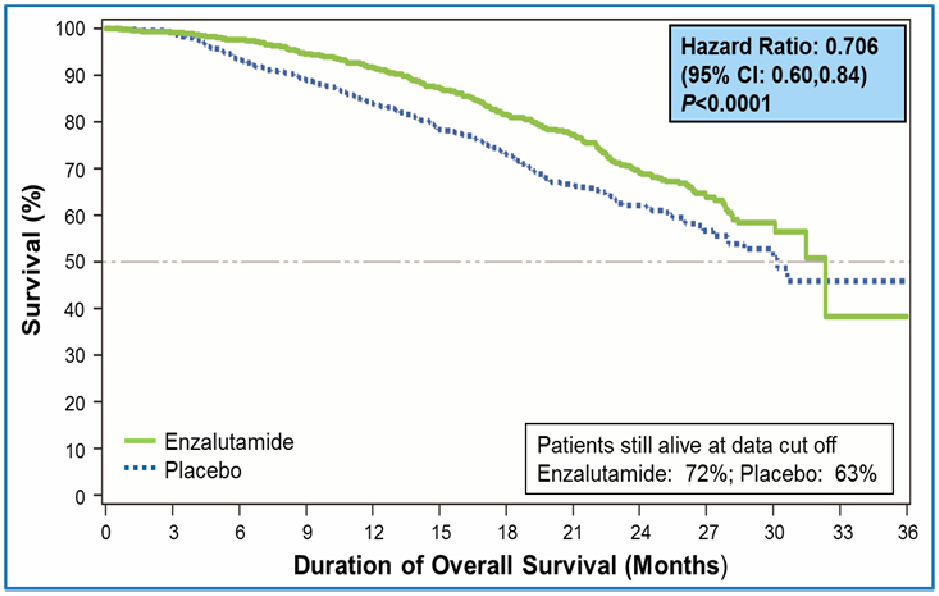
e.g.
Enzalutamide
Apalutamide
Darolutamide

AR=androgen receptor; T=testosterone

Enzalutamide vs Placebo in men with progressive metastatic CPRC



MDV3100	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0



Enzalutamide yields superior OS than placebo in post-docetaxel mCRPC and chemo-naïve minimally symptomatic mCRPC

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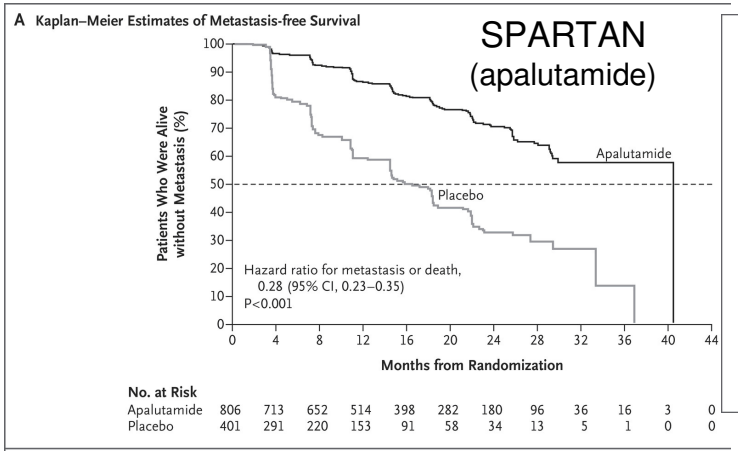
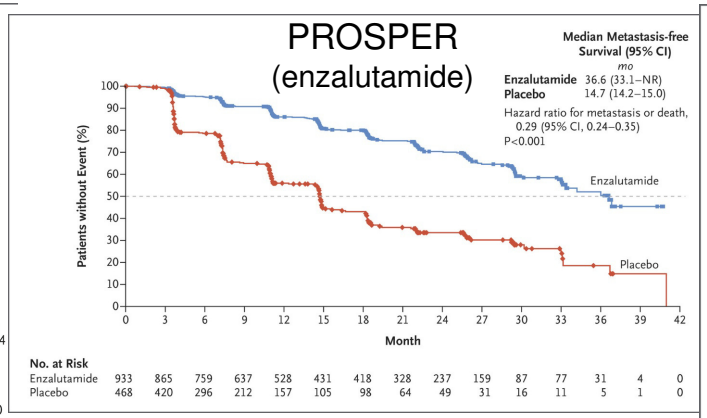
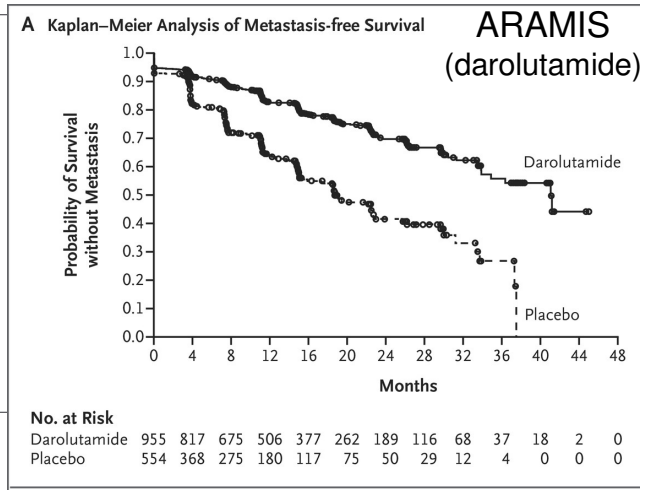
Scher et al, NEJM 2012
Beer et al, NEJM 2014

AR signaling inhibitors for non-metastatic (M0) castration-resistant prostate cancer

- nmCRPC = rising PSA despite LHRH analog or orchiectomy AND no metastases on CT/MRI and bone scan
- Trials compared ARSI to placebo in those with short PSA doubling time
- All showed significant improvement in metastasis-free survival
- And more recently (2020) overall survival







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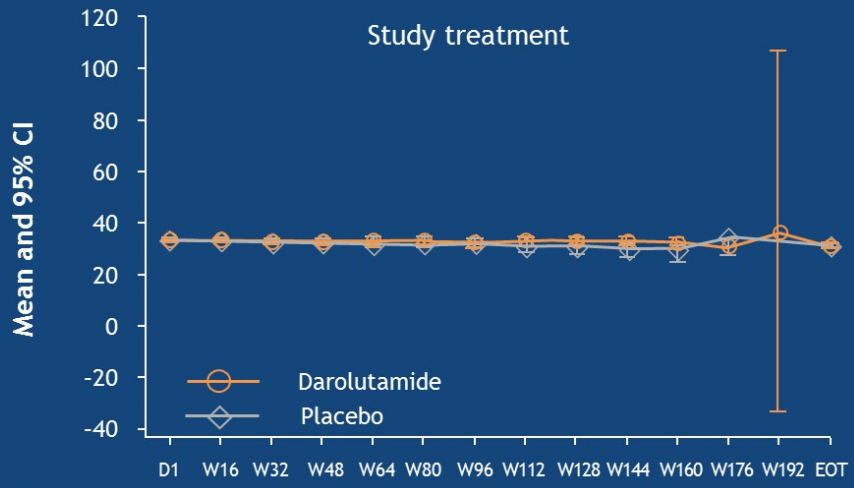
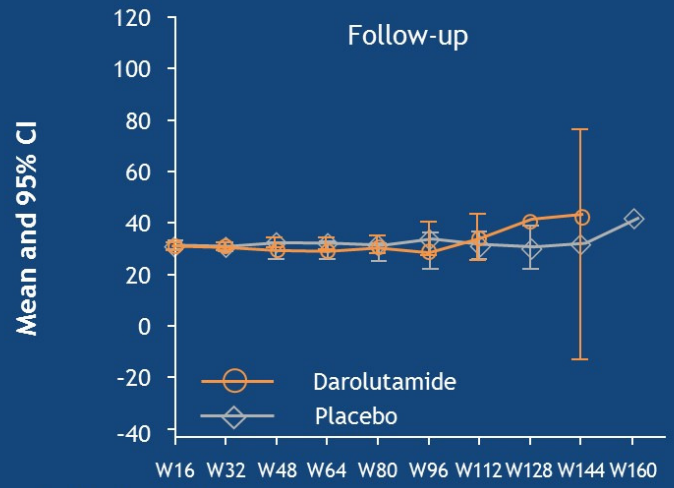
Hussain M, et al. *N Engl J Med.* 2018;378:2465-2474
Smith M, et al. *N Engl J Med.* 2018;378:1408-1418
Fizazi K, et al. *N Engl J Med.* 2019;380:1235-1246

ARAMIS (similar for apalutamide and enzalutamide vs placebo for nmCRPC)

Quality of life: FACT-P PCS

Mean scores* were maintained throughout the study





Number of subjects at risk

Darolutamide	938	882	820	669	512	387	270	199	121	73	37	19	2	191
Placebo	546	501	376	269	186	119	79	52	31	15	8	1	0	253

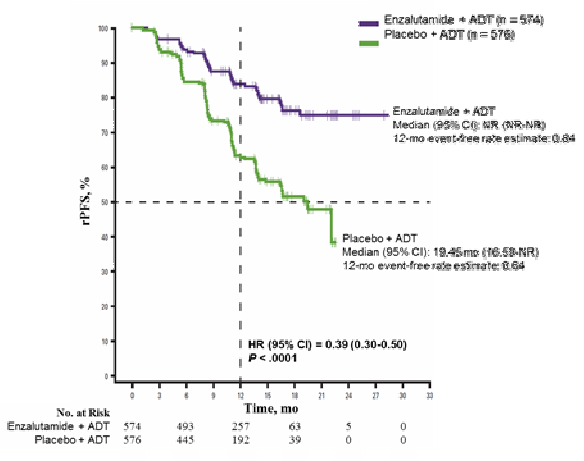
Number of subjects at risk

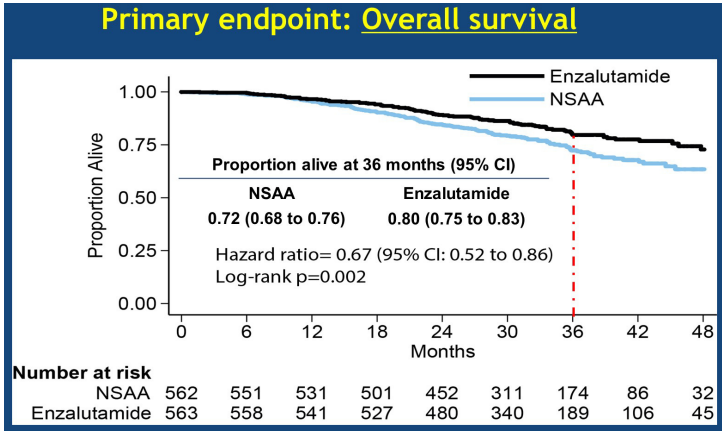
Darolutamide	85	59	31	17	14	8	4	1	1	0
Placebo	101	79	57	45	25	12	8	5	2	1

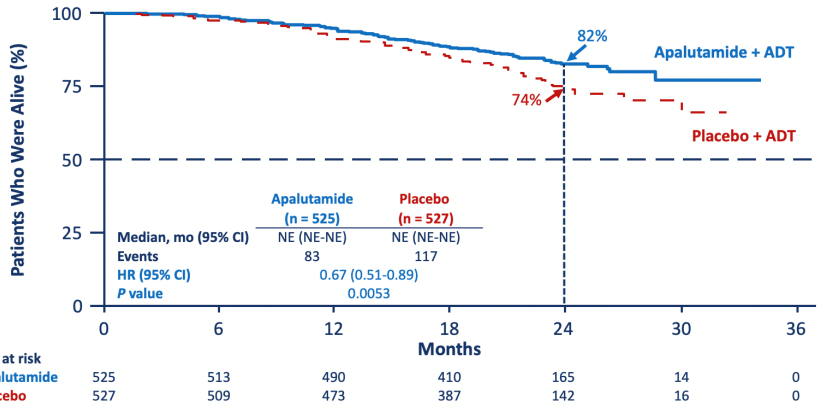
*Higher scores indicate better quality of life.
CI, confidence interval; EOT, end of treatment; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; PCS, prostate cancer subscale, W, week.

Fizazi K, et al. *J Clin Oncol.* 2019;(suppl 7S; abstr 140).

AR signaling inhibitors for metastatic non-castrate prostate cancer







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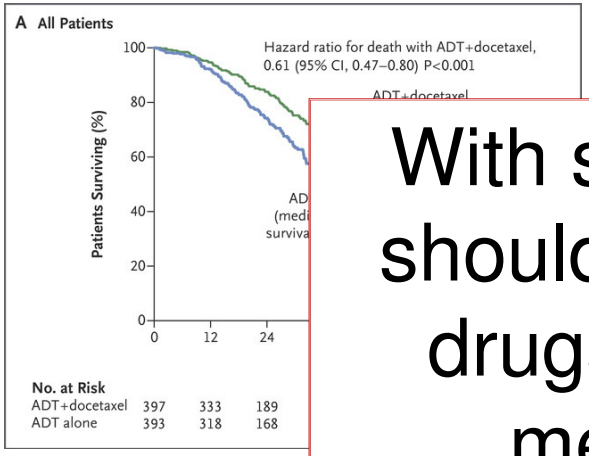
Armstrong et al. *J Clin Oncol* 2019
Sweeney et al, NEJM 2019
Chi et al, NEJM 2019

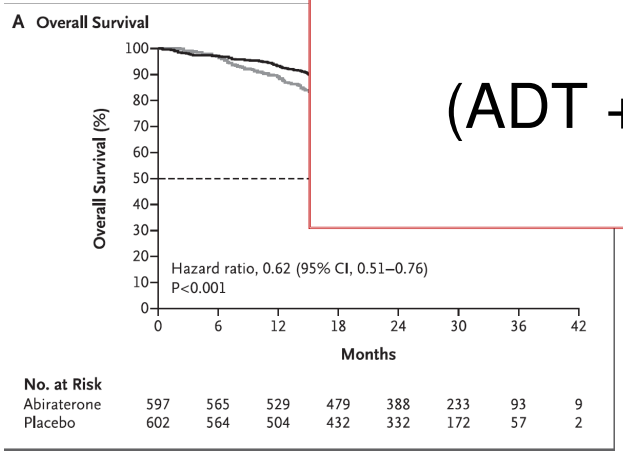
KEY POINT

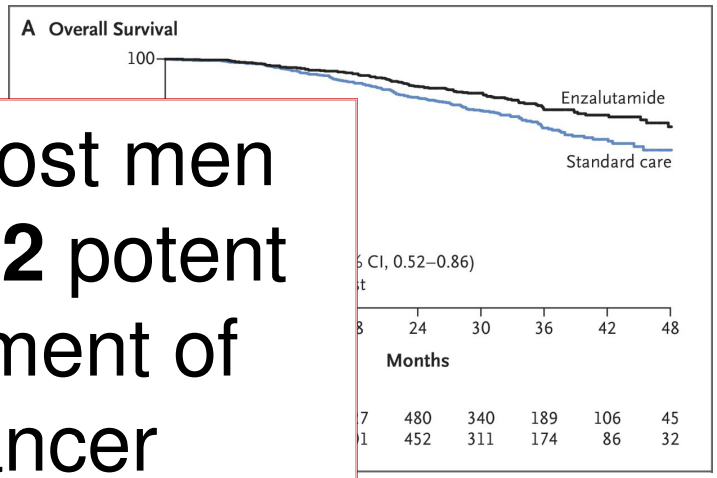
Initial treatment intensification for metastatic prostate cancer

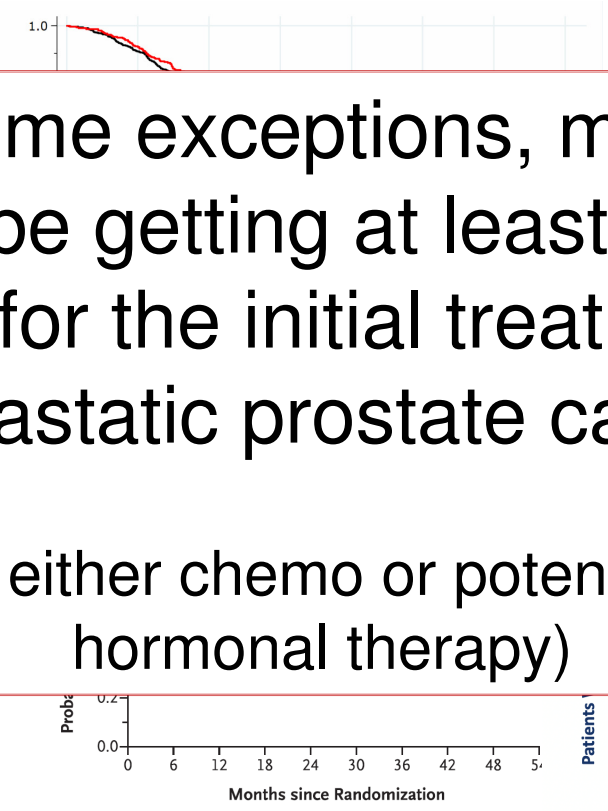
With some exceptions, most men should be getting at least **2** potent drugs for the initial treatment of metastatic prostate cancer

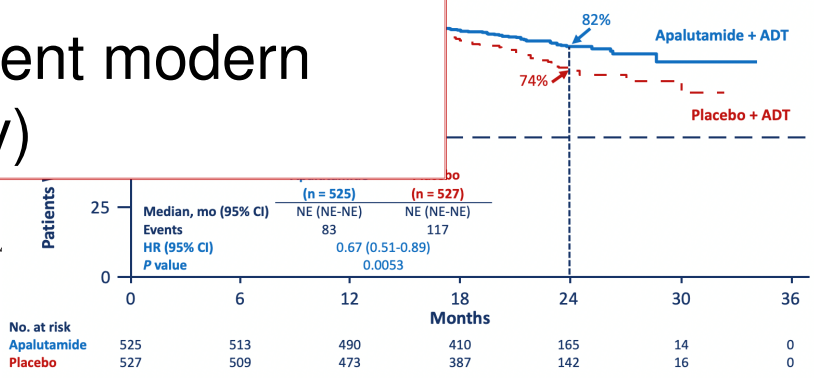
(ADT + either chemo or potent modern hormonal therapy)

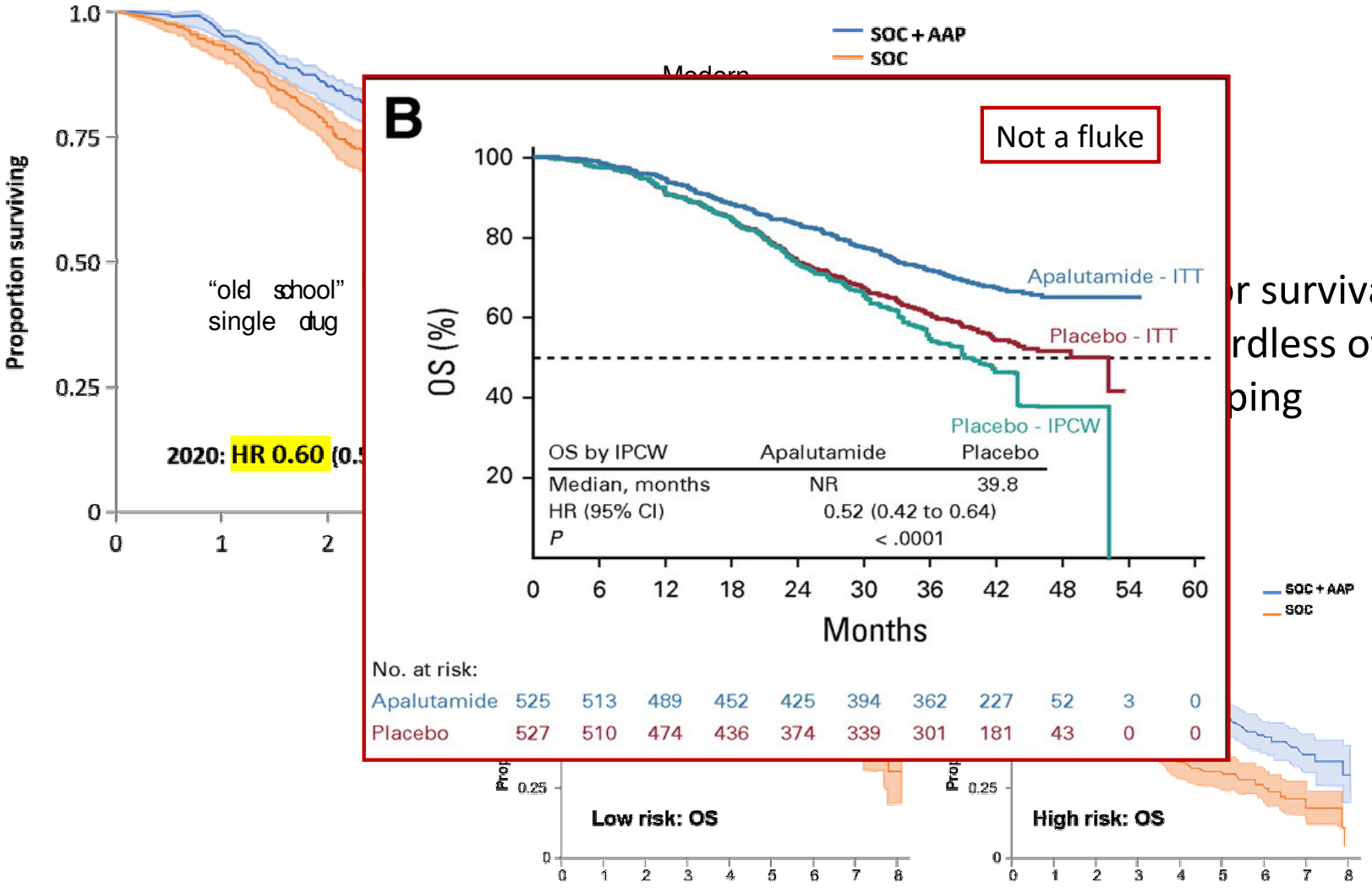










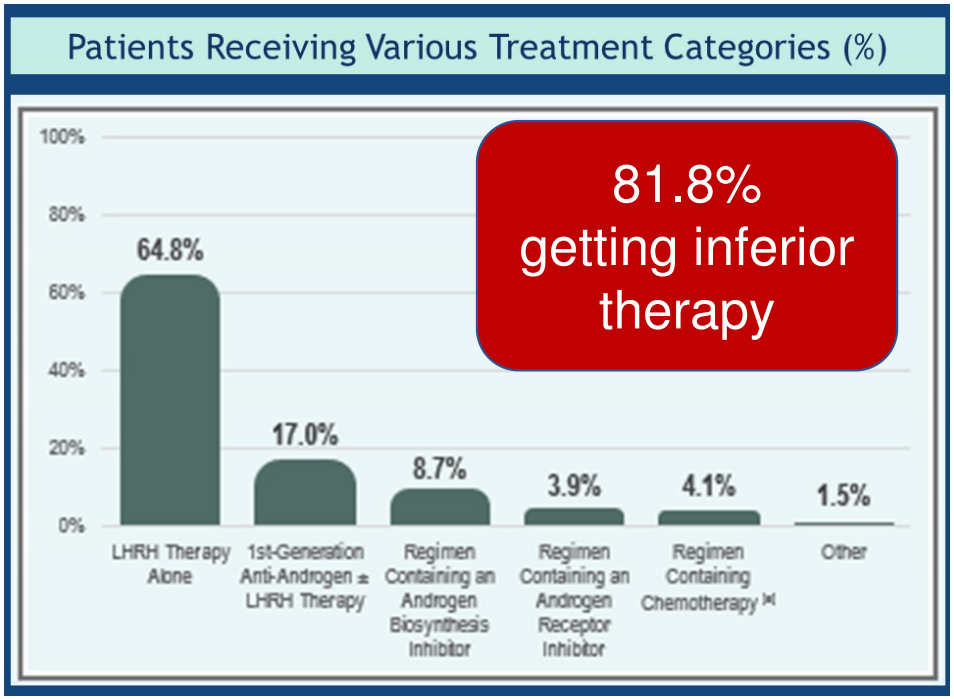


r survival difference
rdless of cancer risk
ping

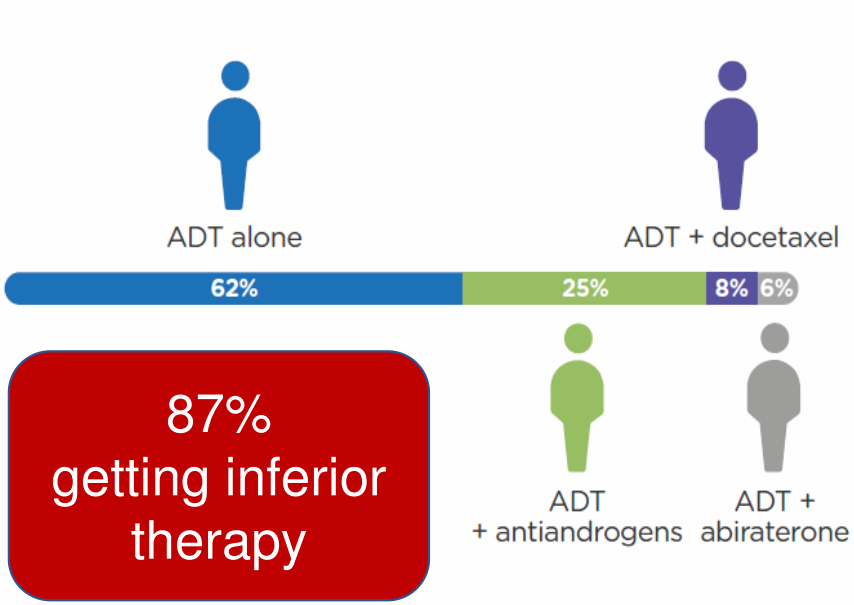
James et al, ESMO 2020

KEY POINT

Many men are getting the wrong treatment!



Ipsos Healthcare US Oncology monitor
June 2018 – June 2019, n=1360



VA claims analysis 2014 – 2018, n=1553

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Shore et al ASCO 2020
Tagawa et al ESMO 2020

Bone Targeted Therapy

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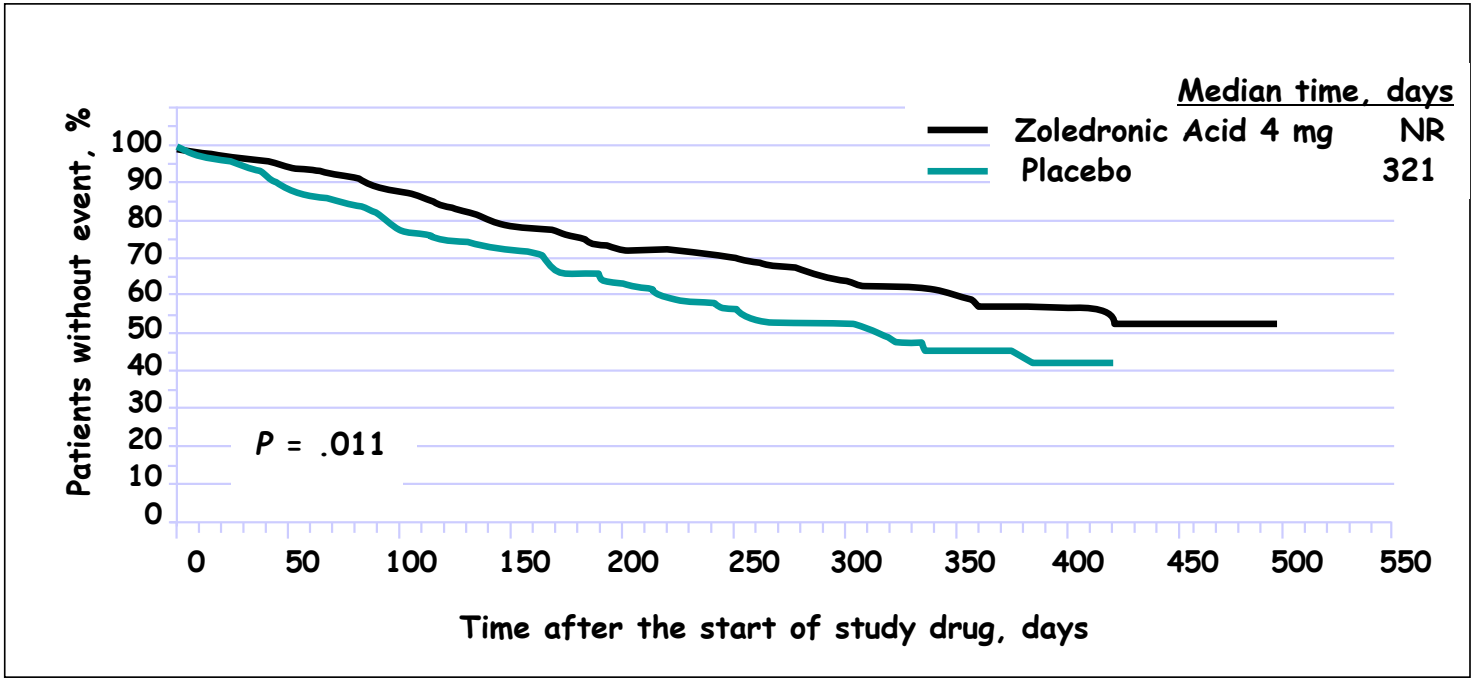
Time to First Skeletal Event in mCRPC by Treatment



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Saad et al; J Natl Cancer Inst 2002; 94: 1458

Denosumab Trials in PC

- HALT (Smith et al, NEJM 2009; 361: 745)
  - D'mab 60 mg vs placebo q6 mo without mets on hormones
  - Increased BMD, **decreased fractures**
- AMG 20050103 (Fizazi et al, Lancet 2011; 377: 813)
  - Denosumab/placebo vs zoledronic acid/placebo in men with CRPC with bone mets
  - **Decreased SRE's in denosumab arm**
- AMG 20050147 (Smith et al, Lancet 2011; Epub Nov 16)
  - Denosumab vs placebo in men with high-risk CRPC without radiographic evidence of bone mets
  - Increased bone met free survival by 4.2 mo (no change in OS)

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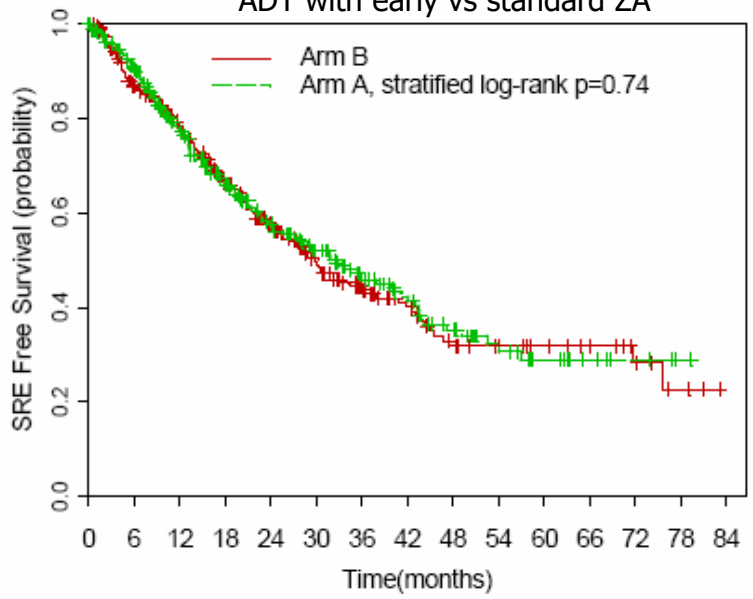
KEY POINT

No benefit from potent anti-resorptive bone therapy for Non-castrate bone metastases with ADT

CALGB 90202

ADT with early vs standard ZA

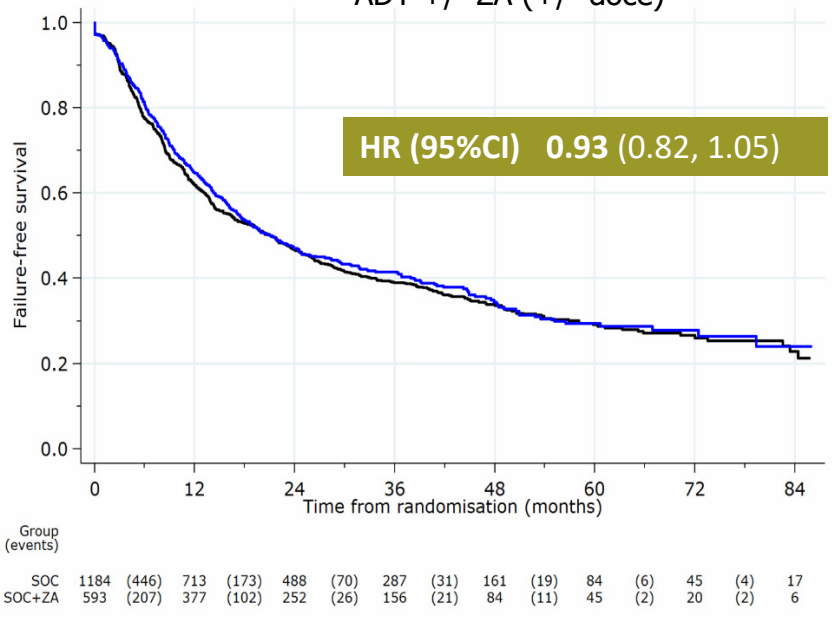


Number of Patients at Risk

Arm B	322	244	191	146	110	79	58	42	30	24	18	14	8	3	0
Arm A	323	257	195	141	108	84	61	45	31	20	13	7	4	1	0

STAMPEDE

ADT +/- ZA (+/- doce)



SRE-free survival

HR 0.89 [95% CI 0.73 – 1.07, p=0.221]

ASCO: "The Expert Panel is in agreement that the use of early zoledronic acid [with castration-sensitive bone metastases] is not supported by the evidence"

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Smith et al, JCO 2014
James et al, Lancet 2016
Saylor et al, JCO 2020

What about my prostate?

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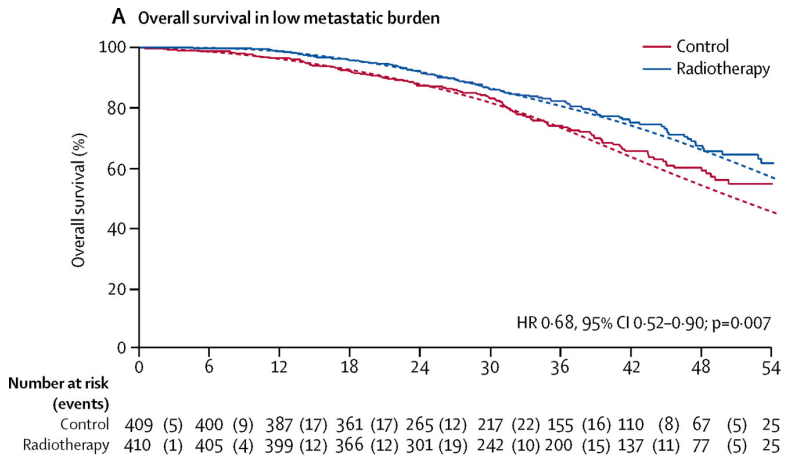
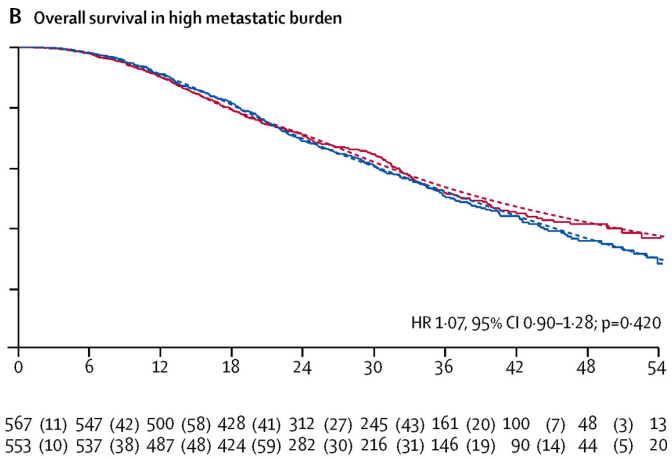
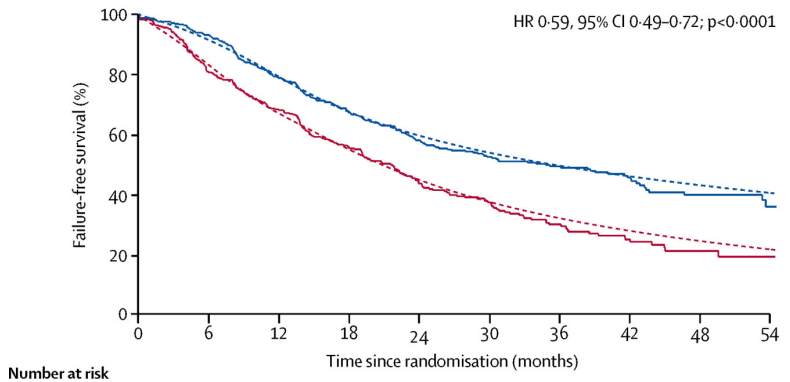
STAMPEDE

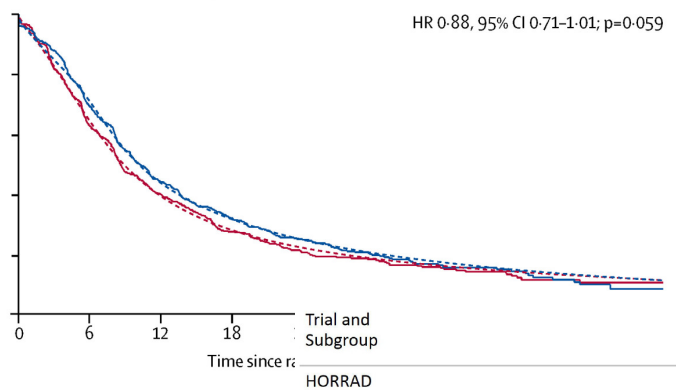




Number at risk (events)

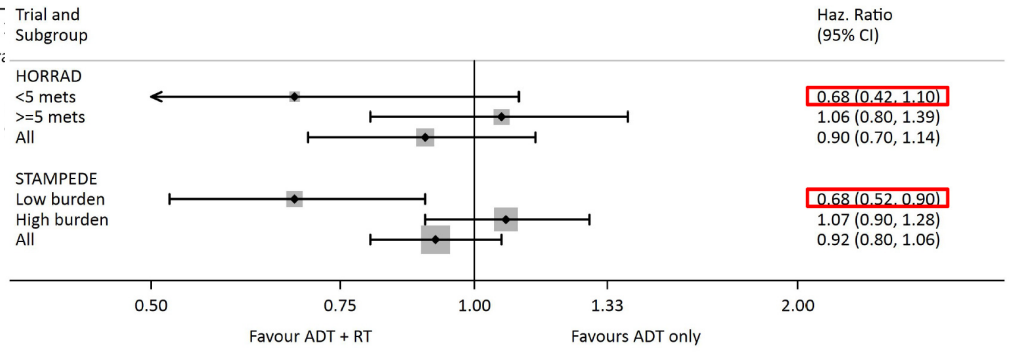
Control	409	(5)	400	(9)	387	(17)	361	(17)	265	(12)	217	(22)	155	(16)	110	(8)	67	(5)	25	567 (11)	547 (42)	500 (58)	428 (41)	312 (27)	245 (43)	161 (20)	100 (7)	48 (3)	13
Radiotherapy	410	(1)	405	(4)	399	(12)	366	(12)	301	(19)	242	(10)	200	(15)	137	(11)	77	(5)	25	553 (10)	537 (38)	487 (48)	424 (59)	282 (30)	216 (31)	146 (19)	90 (14)	44 (5)	20





Number at risk (events)

Control	409	(78)	324	(50)	269	(49)	211	(39)	121	(16)	83	(15)	53	(8)	32	(4)	16	(1)	6	567 (207)	350 (126)	223 (68)	147 (32)
Radiotherapy	410	(29)	377	(57)	318	(45)	255	(32)	178	(16)	142	(8)	113	(7)	75	(8)	35	(2)	12	553 (168)	379 (135)	237 (64)	166 (34)



Parker et al, Lancet 2018

Transition:

Can current diagnostic and therapeutic tools translate into major improvements in the initial management of advanced prostate cancer?

How much cancer do I actually have?

(or where is my PSA coming from?)

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Current imaging tools:

- Xray
- Ultrasound
- CT scans
- MRI
- Bone scan
  - ^{99m}Tc-MDP bone scintigraphy
- Other available/approved nuclear medicine techniques
  - ^{18}F-FDG-PET
  - ^{18}F-NaF bone PET
  - ^{11}C-choline PET
  - ^{18}F-fluciclovine (FACBC, Auxumin®) PET
  - ^{111}In-capromab penditide (Prostascint®)
  - ^{68}Ga-PSMA11 (California)
    - ^{18}F-DCFPyL PET (presumed next week)

PET combined with either CT or MRI

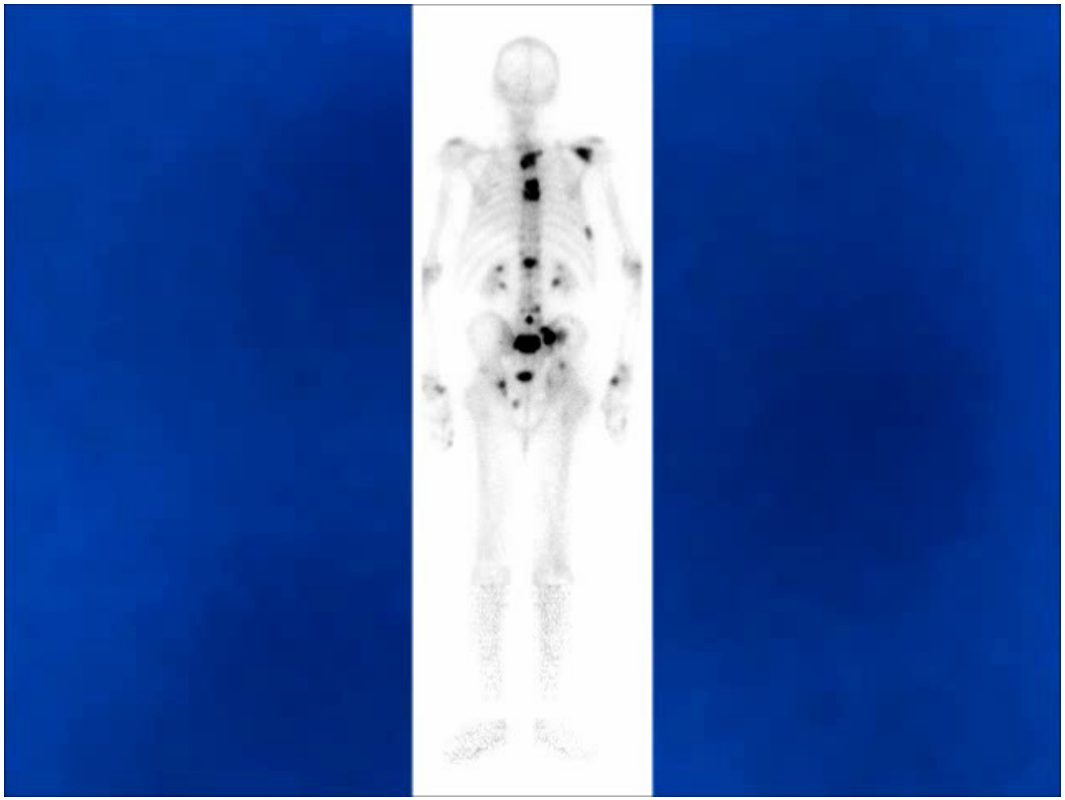
Problems with traditional imaging

- Not sensitive enough
- Not specific
- May not change treatment options

Targeted Diagnostics & Therapeutics

- PSMA = a very specific lock present on tumor
- We have engineered specific “keys” that only target PSMA “locks”

  and we can attach cancer killers or other molecules to keys that enter via locks



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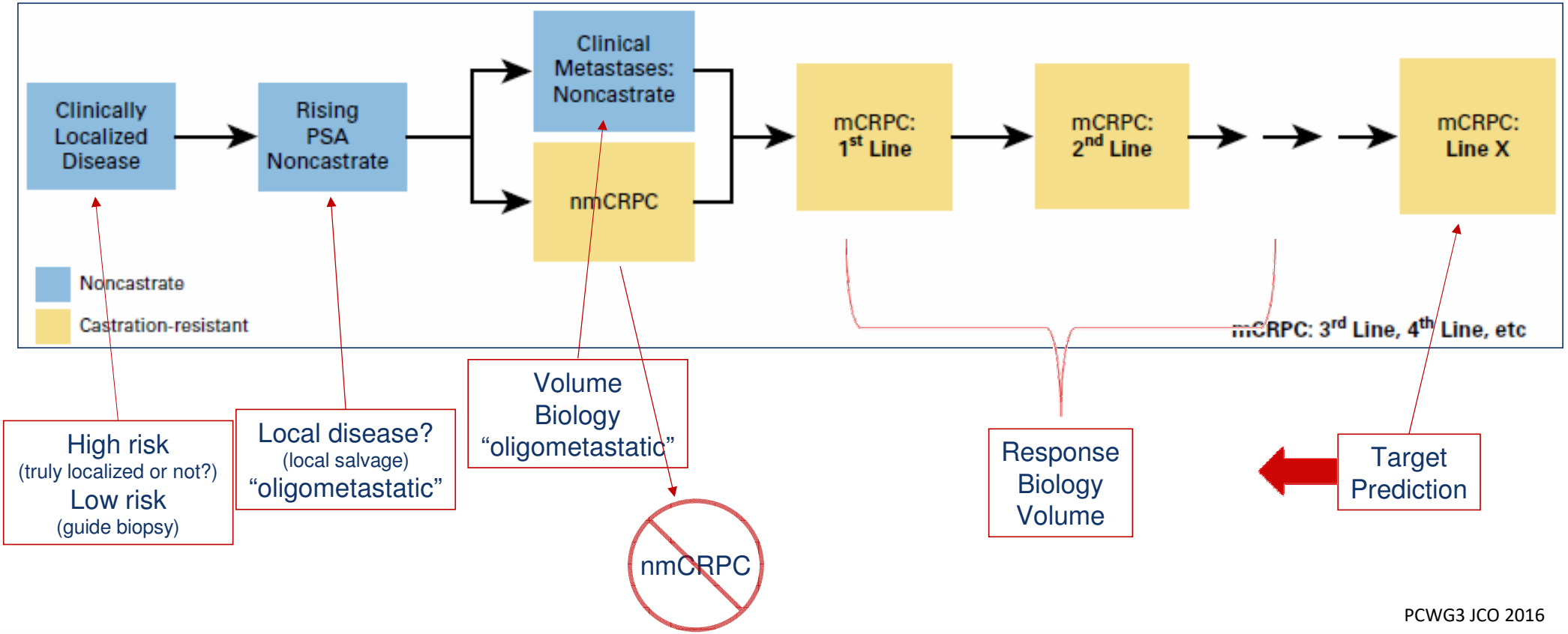
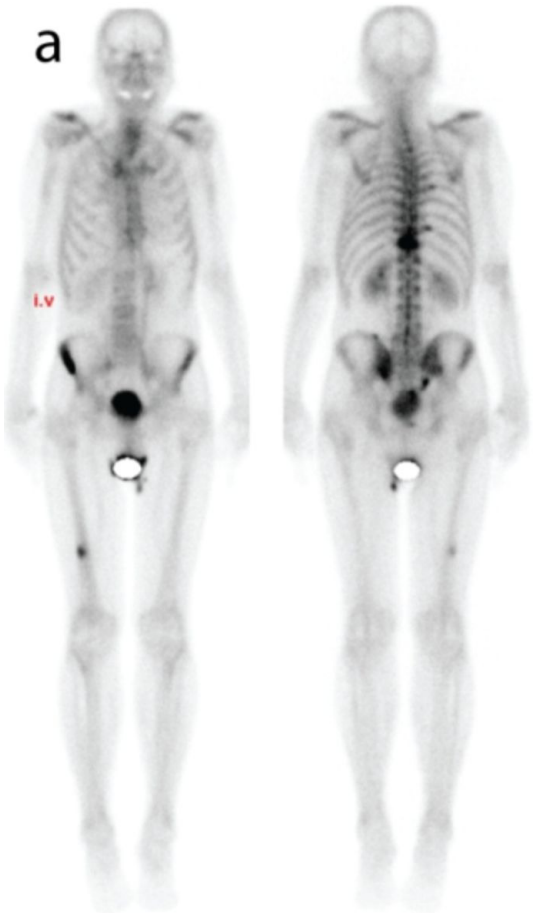
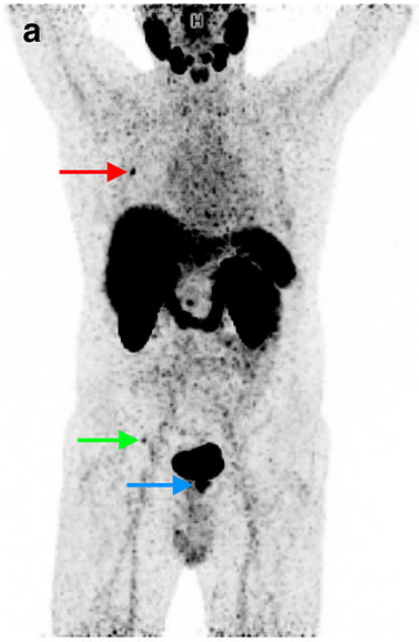
Imaging deficiencies for men with prostate cancer

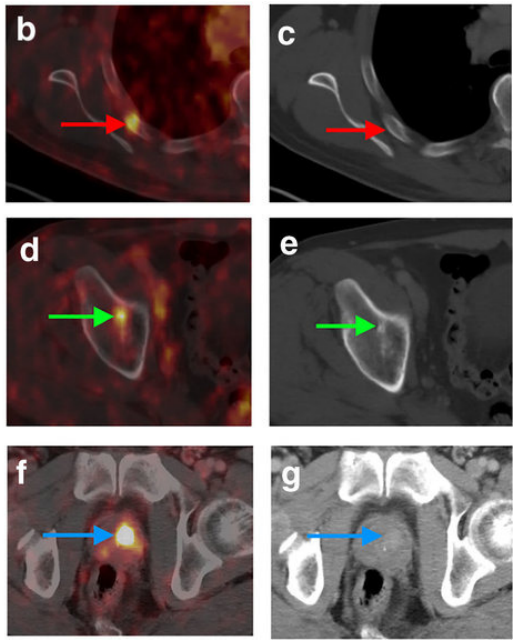


PCWG3 JCO 2016

Examples: PSMA PET vs “standard” imaging







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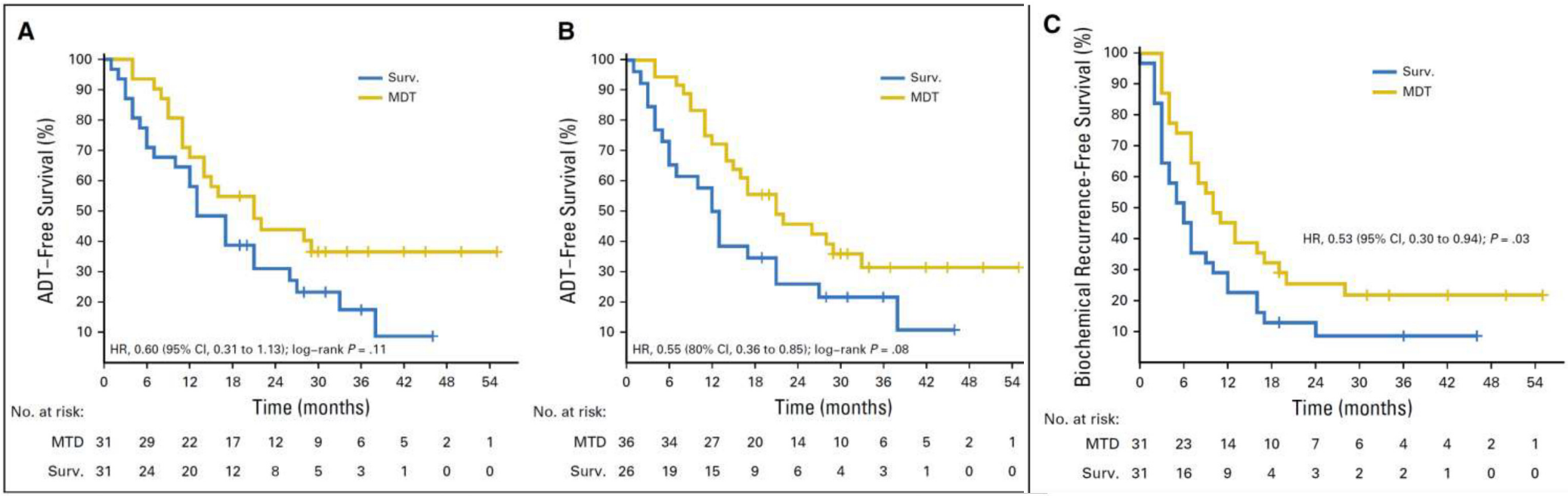
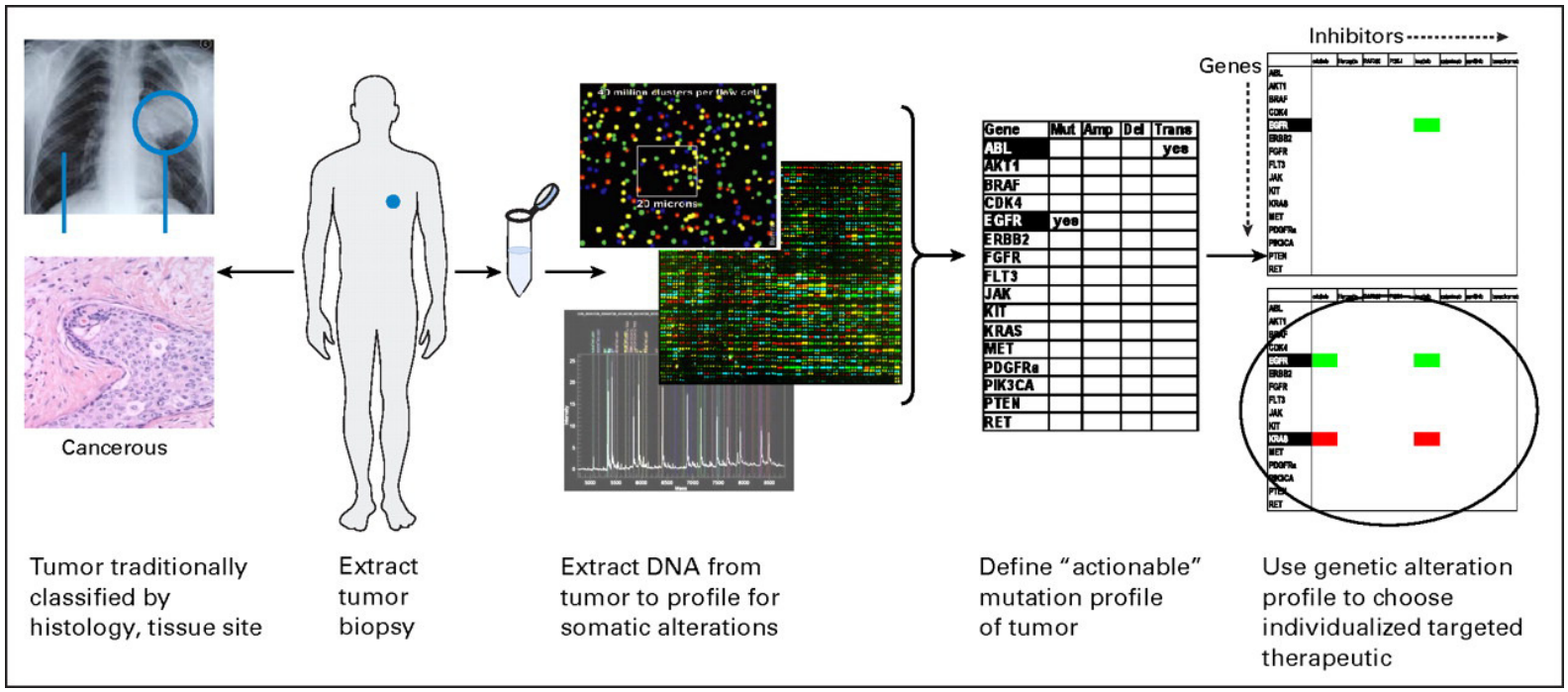
Radiation to “oligometastatic” sites



Molecular Classification of Prostate Cancer



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KEY POINT

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Germline = Inherited from mom & dad

Why test / get tested?

1)Might impact prostate cancer prognosis or treatment choices

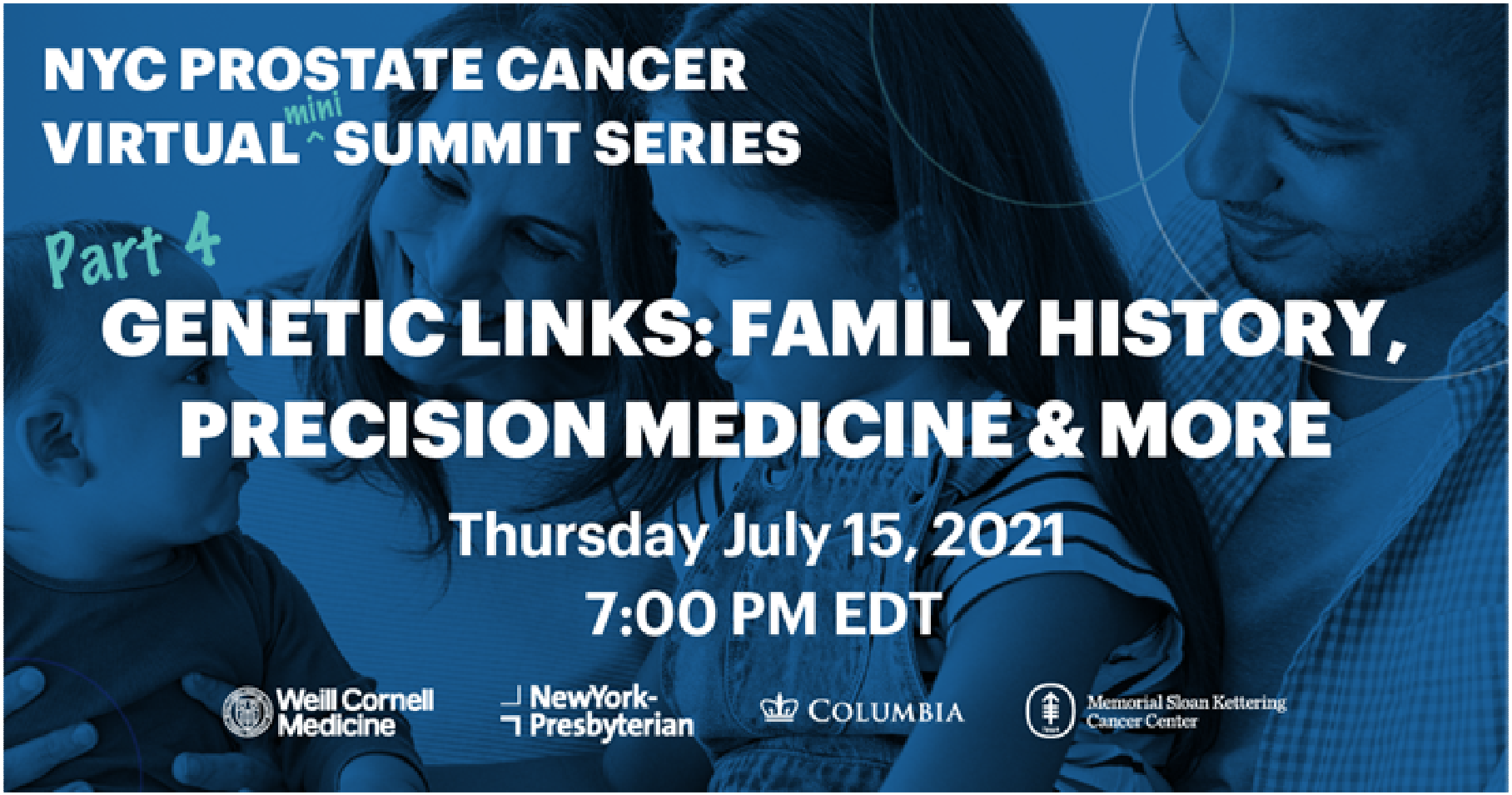
2)Might impact other cancer screening / prevention

3)Cascade testing (1st degree relatives)

How: Genetic counselor or physician

And/Or panel testing (usually commercial)

PLUG



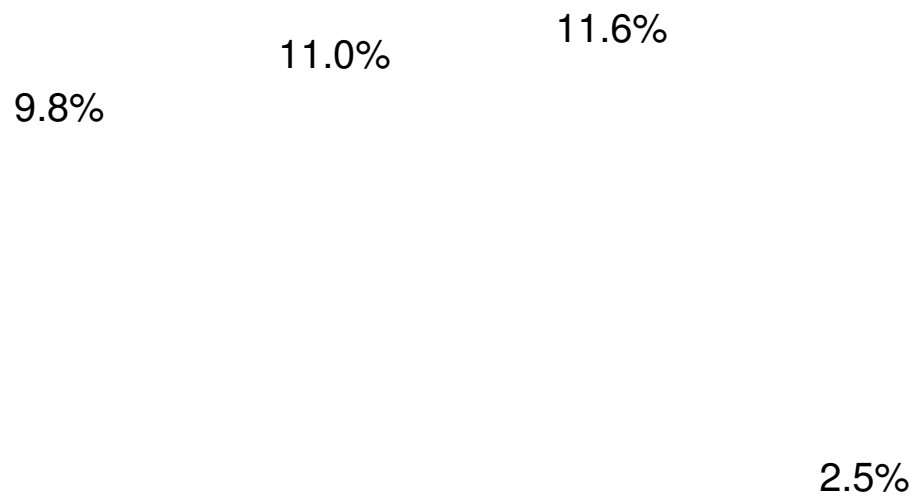
If you missed any of the earlier webinar sessions or would like to re-watch the recordings, **Part 1 "Living with Prostate Cancer"**, **Part 2 "Newly-Diagnosed: What Are My Treatment Options"**, and **Part 3 "Advanced Prostate Cancer Treatment Updates"** available on demand.
Learn more and sign up for the entire webinar program series at **prostatesummit.org**.

How do we make improvements in medicine?

OR

How can I utilize these newer discoveries for my or my loved on?

Percent of patients participating in clinical trials



Wassenaar et al, ASCO 2008

Patient satisfaction with care

Cancer Type	Treated with standard care	Treated on clinical trial	Statistical significance
Prostate Cancer	60.1%	69.4%	P=0.03
Colorectal Cancer	45.5%	58.9%	P=0.009
Lung Cancer	37.7%	63.6%	P=0.001

Wassenaar et al, ASCO 2008

Why don’t more patients participate in clinical trials?

Primary reason for not participating in clinical trial

Wassenaar et al, ASCO 2008

How can I (we) help?

Two very important elements
to make progress:

Awareness /Advocacy

and

Funding

Selected current trials to “definitively” answer questions about management of advanced prostate cancer

- Should we treat the prostate (mostly surgically) in setting of modern systemic therapy (S1802)
- Should we add abiraterone and/or radiation to ADT/docetaxel (PEACE-1)
- Should we add darolutamide to ADT/docetaxel (ARASENS)
- Should we add pembrolizumab immunotherapy to ADT/enzalutamide (KEYNOTE-991)
- Should we add ^{177}Lu-PSMA-617 to ADT/ARPI (AFT53 / PSMAddition)

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TAKE HOME MESSAGES

Management of "non-castrate" (aka "hormone-sensitive" or "castration-sensitive") advanced prostate cancer: ***Am I getting the right treatment?***

- Most should get 2 potent drugs at beginning
- Most should NOT be getting potent bone therapy
  - But assess fracture risk and treat/prevent as appropriate
- Consider treatment of the prostate
  - If not previously treated in setting of limited metastases
- Most should have germline (inherited) testing
- Regular scans in addition to PSA testing
- Is there a trial available?

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Prostate Cancer 2021:

We have seen translational therapy lead to real, **clinically relevant improvements** for patients

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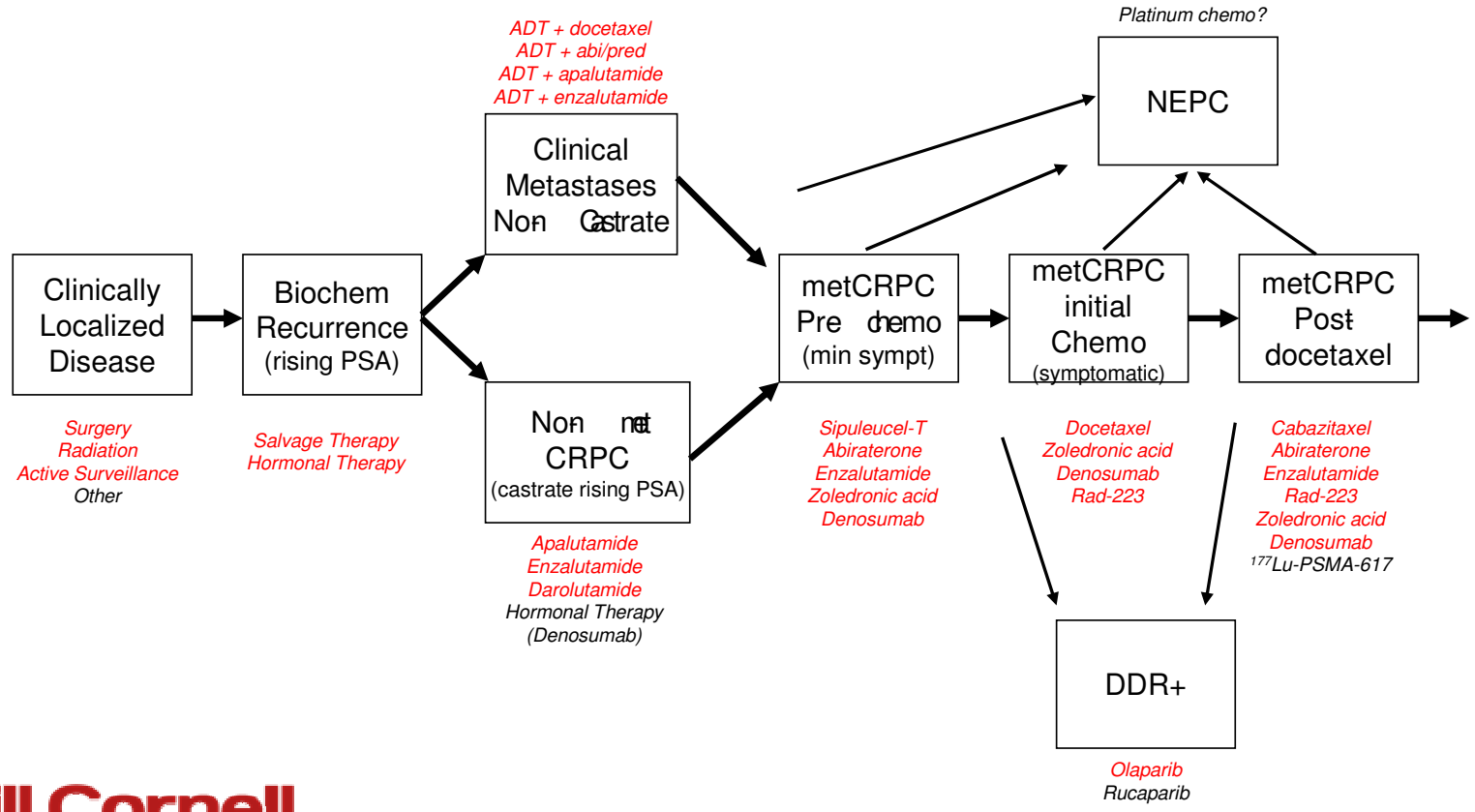
Prostate Cancer
Evidence / Approved Recommendations



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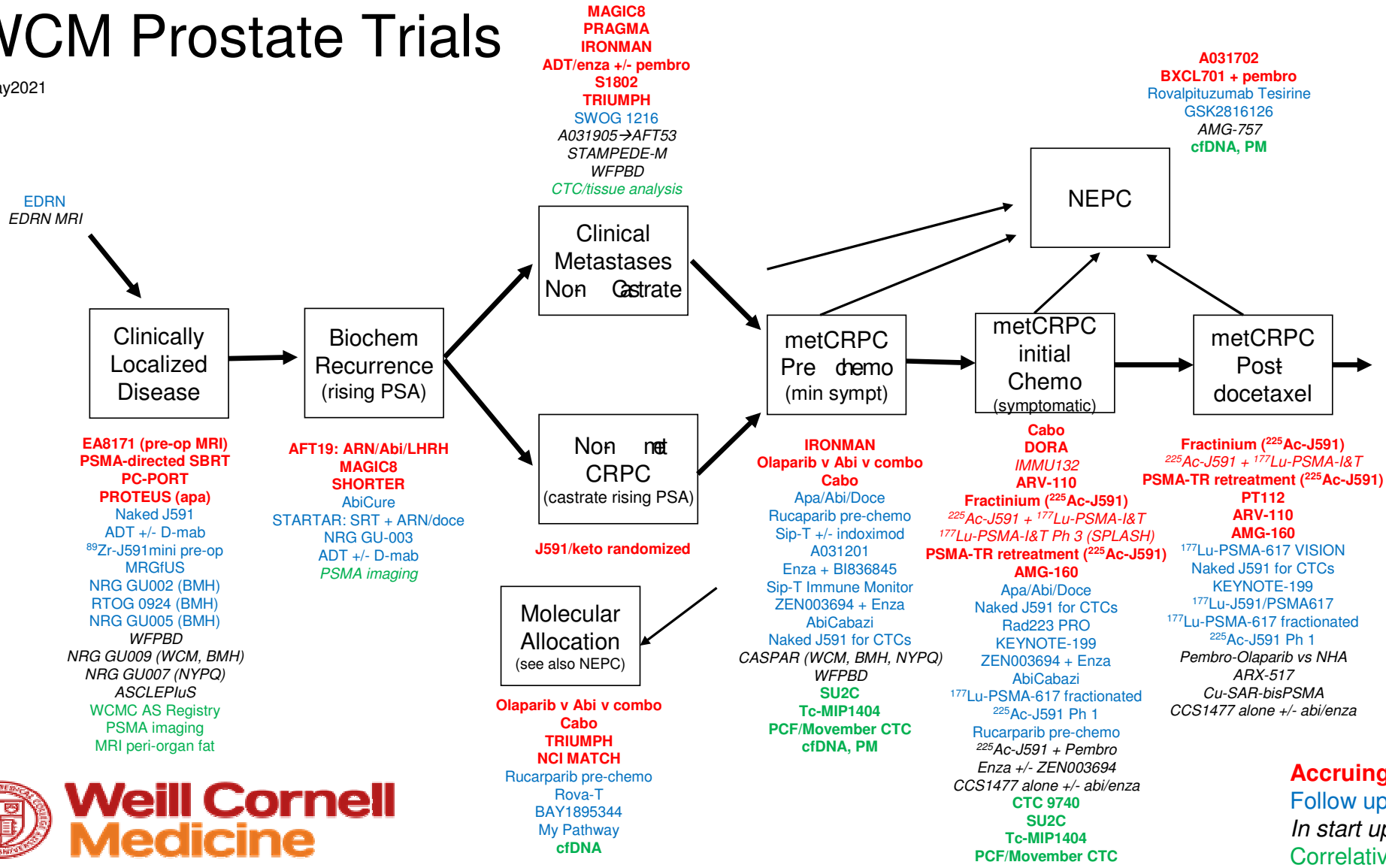
Standard
Alternative

WCM Prostate Trials

17May2021



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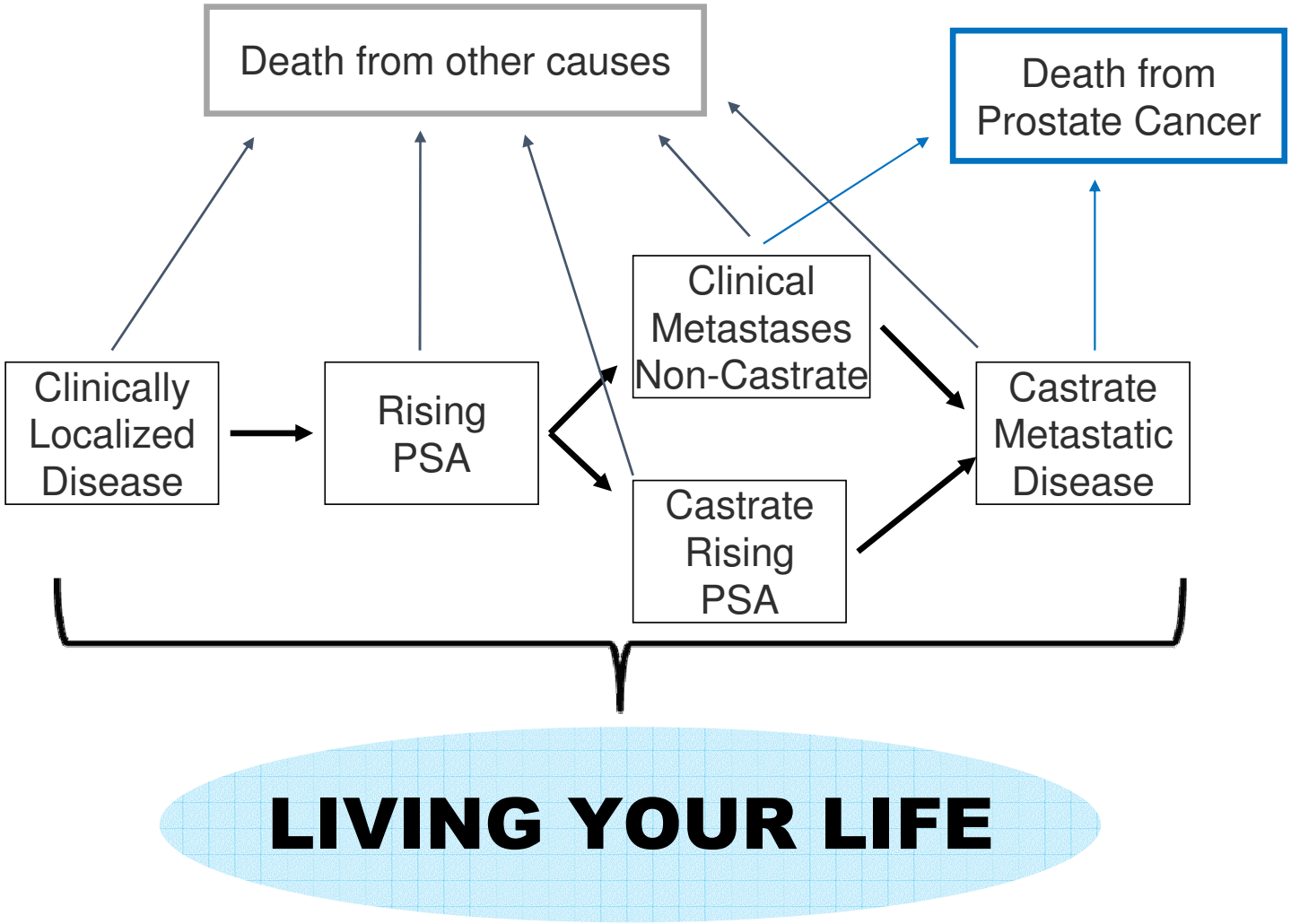
Accruing
Follow up / analysis
In start up / planned
Correlative

"Clinical states"



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PATIENTS AND THEIR FAMILIES