Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Tanya Dorff, MD
Associate Clinical Professor of Medicine
Head of Genitourinary Cancer Program
City of Hope Comprehensive Cancer Center

Prostate Cancer Oncology Board Review August 2020

Disclosures

Consultant: Advanced Accelerator Applications, Abbvie, Bayer, BMS, Dendreon, Exelixis, Janssen, Seattle Genetics

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Overview: highlighting major changes in Prostate Cancer management

Early stage Prostate Cancer

- Avoid overtreatment.
- XRT and surgery equally effective. ADT + XRT >XRT

Biochemical recurrence

- Add ADT to salvage radiation – but not all of the time
- PSA doubling time is critical to choosing treatment

Metastatic hormone sensitive

- Up front intensification: abiraterone, apalutamide, docetaxel, enzalutamide are all options

mCRPC

- Sequence remains preferred over combination
- New FDA approvals: PARP inhibitors

Epidemiology/ Risk Factors

- 1 in 9 men will be dx prostate CA
- 2x risk if 1st degree relative
  - 4x risk if ≥2 relatives affected age < 70
- Higher risk from high fat diet (α-linoleic acid)
  - Lower risk with lycopene, cruciferous vegetables
- African American
- Prostatitis, HG PIN

Siegel RL et al.
CA Cancer J Clin 2019; 69:7-34

Estimated New Cases

	Males	
Prostate	174,650	20%
Lung & bronchus	116,440	13%
Colon & rectum	78,500	9%
Urinary bladder	61,700	7%
Melanoma of the skin	57,220	7%
Kidney & renal pelvis	44,120	5%
Non-Hodgkin lymphoma	41,090	5%
Oral cavity & pharynx	38,140	4%
Leukemia	35,920	4%
Pancreas	29,940	3%
All Sites	**870,970**	**100%**

Estimated Deaths

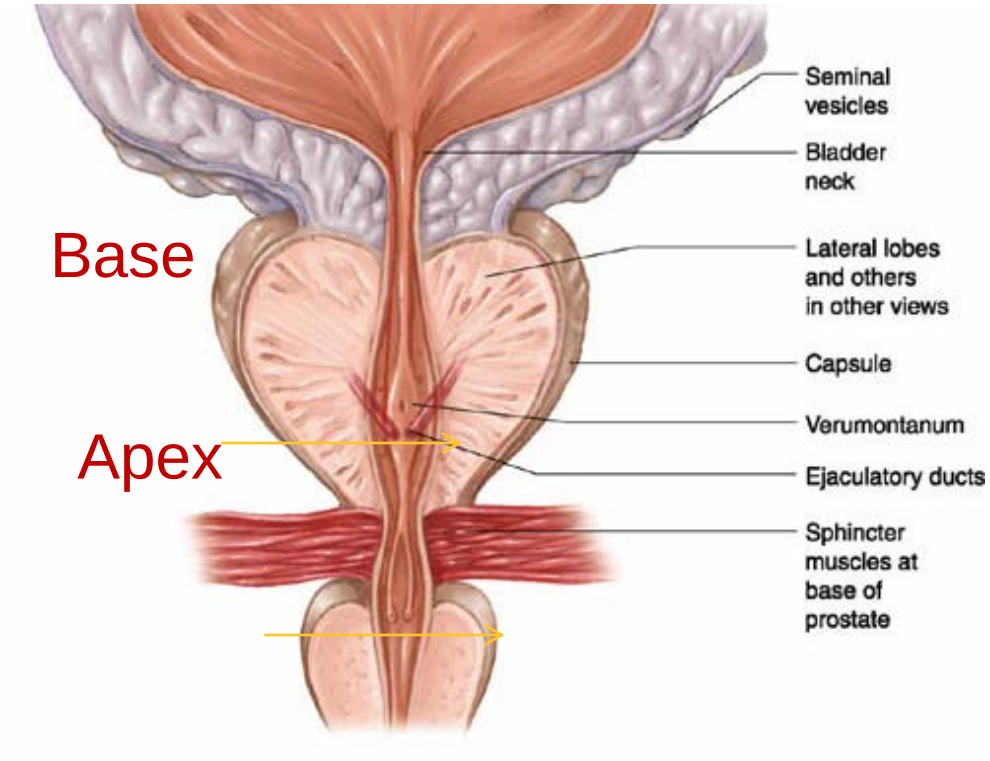
	Males	
Lung & bronchus	76,650	24%
Prostate	31,620	10%
Colon & rectum	27,640	9%
Pancreas	23,800	7%
Liver & intrahepatic bile duct	21,600	7%
Leukemia	13,150	4%
Esophagus	13,020	4%
Urinary bladder	12,870	4%
Non-Hodgkin lymphoma	11,510	4%
Brain & other nervous system	9,910	3%
All Sites	**321,670**	**100%**

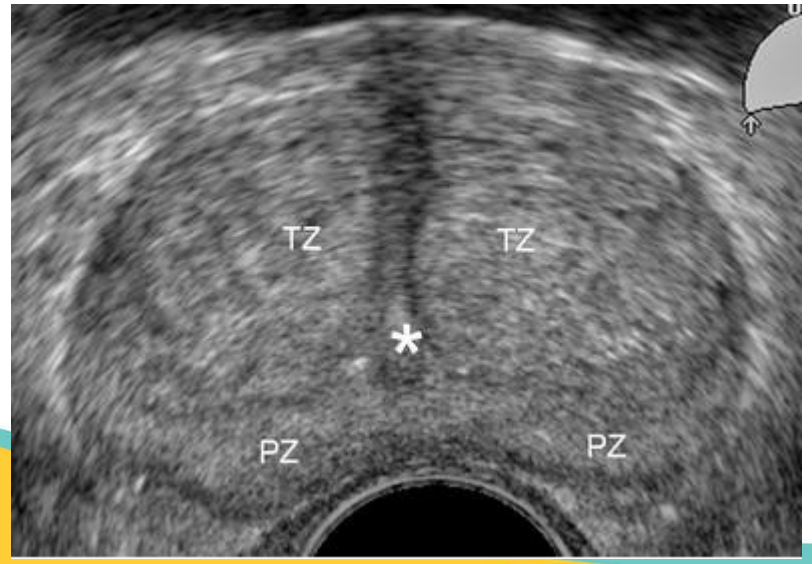
Prostate Cancer Prevention

	PCPT[1]	SELECT[2]
Number enrolled	18,000	35,553
Intervention	Finasteride 5 mg Placebo	Vit E (400 IU), Selenium, Both, or Neither
Results	22.9% risk PC for placebo vs 16.6% risk PC for finasteride RR 0.7 (0.64 – 0.76) p<0.0001	17% increased risk PC in Vitamin E group

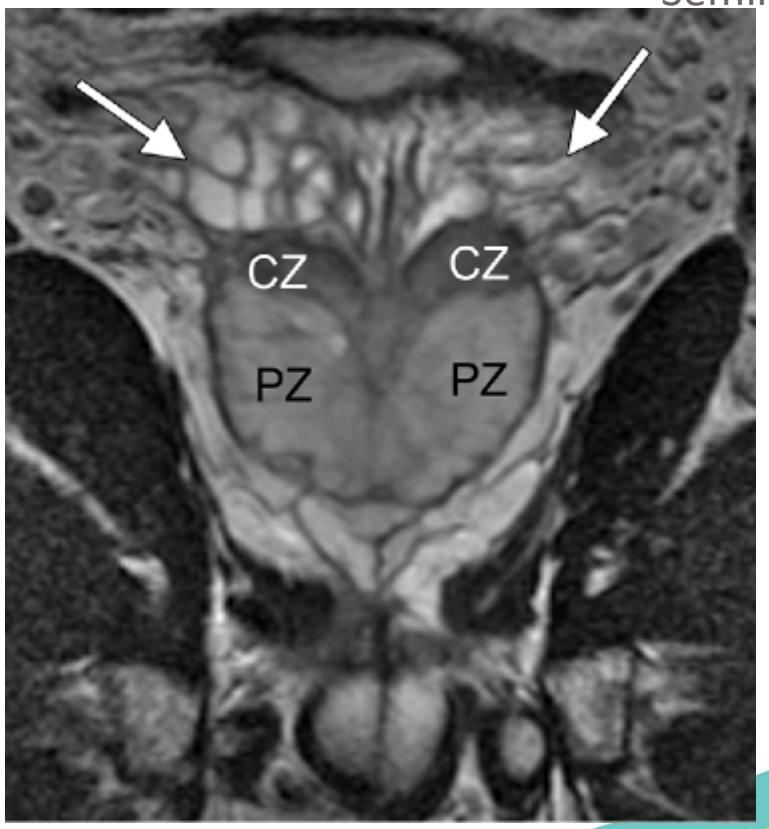
1. Thompson IM et al. NEJM 2003; 349:297
2. Lippman SM et al. JAMA 2009; 301:39

Anatomy of the Prostate Gland



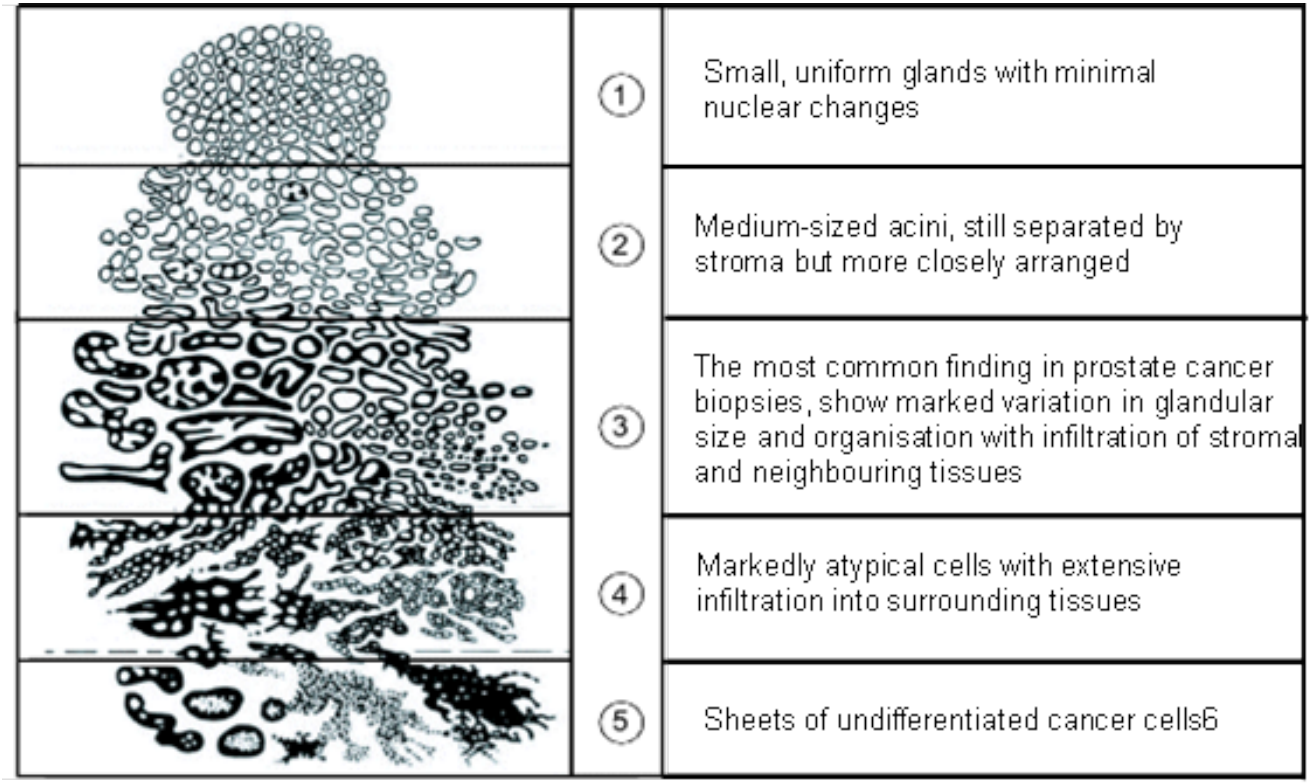


Seminal vesicle



CZ = central zone
PZ = peripheral zone

Gleason Grading



Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Prostate Cancer Staging

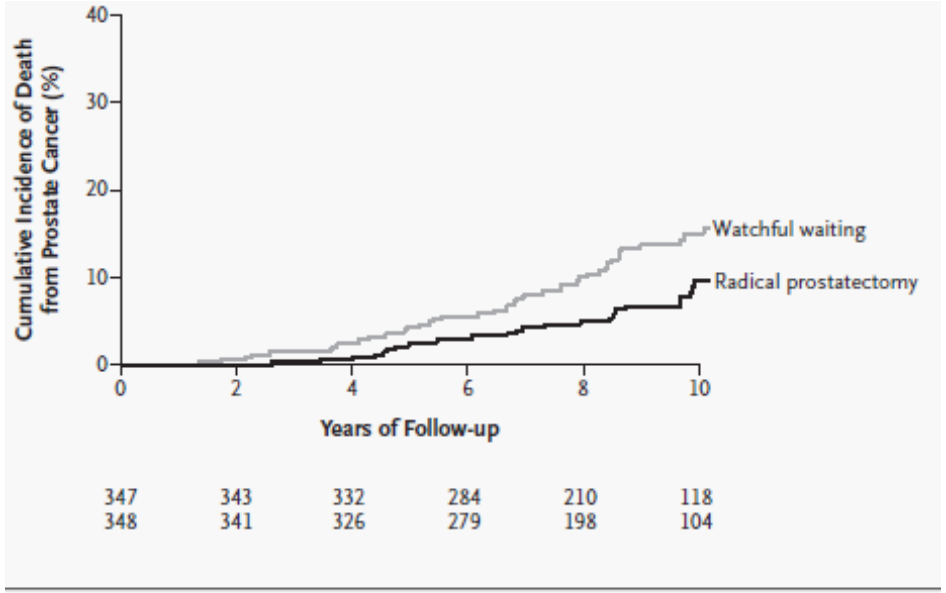
When T is...	And N is...	And M is...	And PSA is...	And Grade Group is...	Then the stage group is...
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

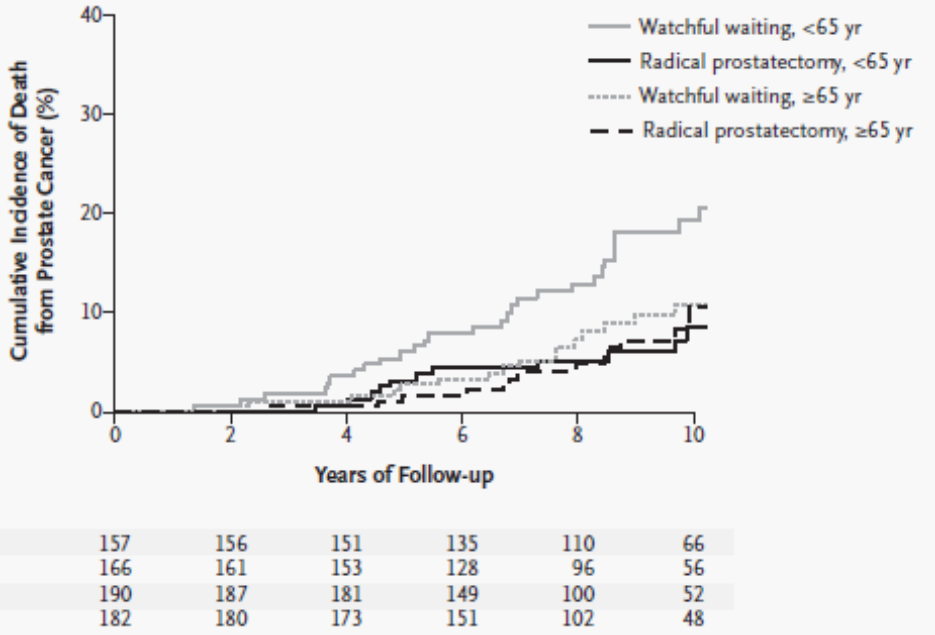
NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk Group	Clinical/Pathologic Features			Imaging[f,g]	Germline Testing[c]	Molecular/ Biomarker Analysis of Tumor[c]	Initial Therapy
Very low[d]	Has all of the following: • T1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Not indicated	See PROS-3
Low[d]	Has all of the following but does not qualify for very low risk: • T1–T2a • Grade Group 1 • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-4
Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-6
High	Has no very-high-risk features and has at least one high-risk feature: • T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Consider if life expectancy ≥10 y[j]	See PROS-7
Very high	Has at least one of the following: • T3b–T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended	See PROS-7

What is the Role of Prostatectomy for low risk prostate cancer?





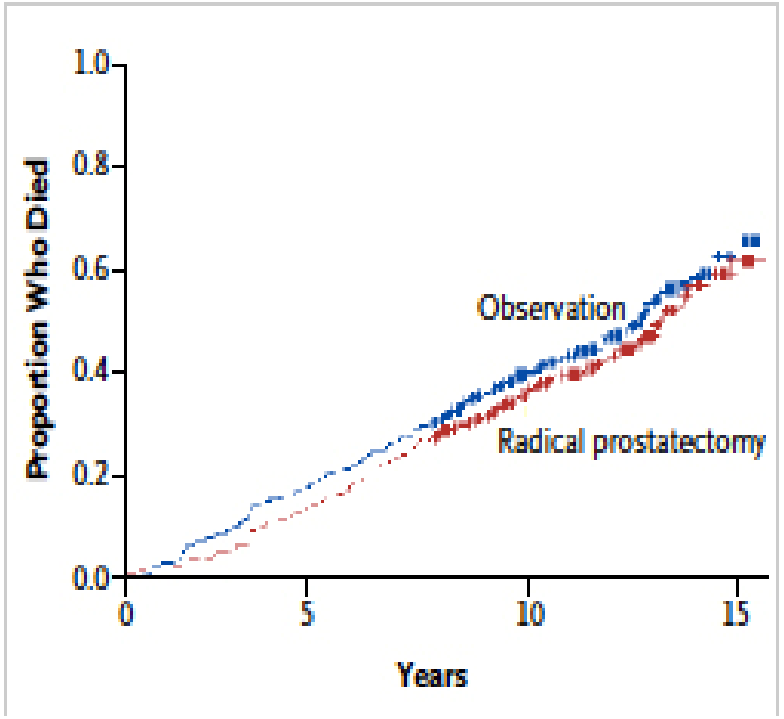
Bill-Axelson A et al.
NEJM 2005; 352:1977-84

Table 3. Probabilistic Sensitivity Analysis

Strategy	QALYs (95% Confidence Interval)	Incremental QALY
Active surveillance	11.00 (6.93-13.90)	
Brachytherapy	10.65 (5.57-14.29)	−0.35
IMRT	10.54 (5.55-14.27)	−0.09
Radical prostatectomy	10.30 (4.89-14.36)	−0.24

Abbreviations: IMRT, intensity-modulated radiation therapy; QALY, quality-adjusted life-year.

Hayes JH et al JAMA 2010 304:2373



ORIGINAL ARTICLE

Treatment or Observation for Localized Prostate Cancer

July 19, 2012 | T.J. Wilt and Others

Over 700 men were assigned to radical prostatectomy or observation after receiving a diagnosis of prostate cancer, usually on the basis of elevated PSA levels. After a median of 10 years, between-group differences in all-cause and prostate-cancer mortality were not significant.

CME | Comments

SPECIALTIES Hematology/Oncology, Surgery

Wilt TJ et al. NEJM 2012; 367:203-12

"If there is no difference in mortality [between active surveillance and immediate treatment], then quality of life is the defining issue."

— Mark Litwin, MD, MPH

Criteria for Inclusion in Active Surveillance

- **Epstein criteria for VERY low risk:**
  - **T1c, Gleason ≤ 6**
  - **PSA density <0.15 ng/cc**
  - **Fewer than 3 cores with cancer, <50% involvement of any one core**
- Other groups have criteria:
  - Gleason 3+4 becoming possible (with molec testing)
  - T2a OK in some series
  - Fewer than 2 cores or <1/3 of cores involved
  - * for boards, <10 years life expectancy

How To: Active Surveillance

Table 3. National Active Surveillance Guidelines

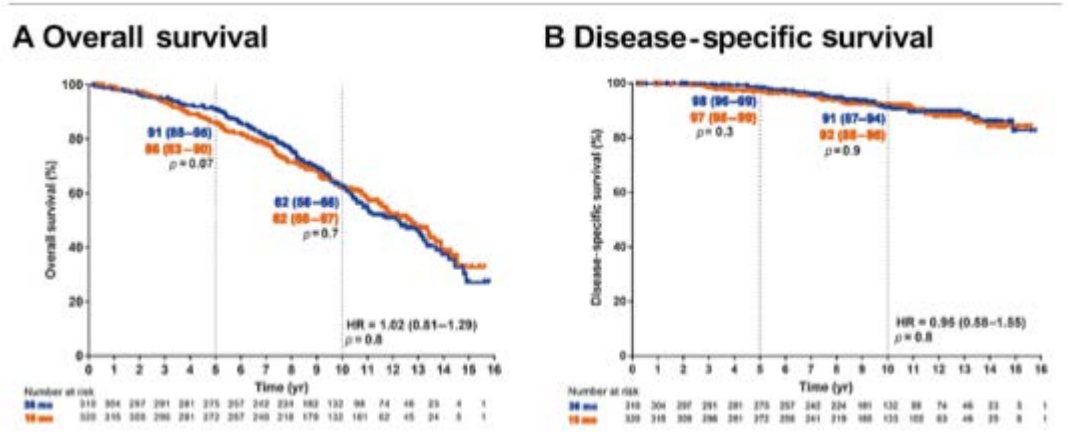
Group	Recommendations for Low-Risk Prostate Cancer	Recommendations for Intermediate-Risk Prostate Cancer	Tests Recommended for Use In Active Surveillance	Recommendations Regarding Other Tests	Role of 5-α Reductase Inhibitors
Cancer Care Ontario[27]	Active surveillance is preferred management	Active treatment; active surveillance for selected pts	PSA every 3–6 mo DRE annually Systematic bx within 6–12 mo of diagnostic bx, then every 3–5 yr	MRI when clinical and pathology findings discordant	May have a role
ASCO[28]	Active surveillance is preferred management	Active treatment; active surveillance for selected pts	PSA every 3–6 mo DRE annually Systematic bx within 6–12 mo of diagnostic bx, then every 3–5 yr	Other tests remain investigational	No clear role
NCCN[29]	Very-low-risk prostate cancer: active surveillance is preferred management Low-risk prostate cancer: all therapies are options	Active treatment; active surveillance for selected pts	PSA ≤ every 6 mo Biopsy ≤ annually	Consider MRI if aggressive cancer suspected or PSA increases with neg systematic bx	
NICE[30]	Active surveillance is preferred management	Radical treatment for disease progression	PSA every 3–4 mo, monitor kinetics; otherwise same as in Cancer Care Ontario guidelines	MRI on enrollment	

ASCO = American Society of Clinical Oncology; bx = biopsy; DRE = digital rectal examination; NCCN = National Comprehensive Cancer Network; neg = negative; NICE = National Institute for Health and Care Excellence; PSA = prostate-specific antigen; pts = patients.

Garisto and Klotz. Oncology 2017

Localized Prostate Cancer: XRT

- ADT added to radiation (EBXRT) improves survival for high risk or locally advanced patients[1]
  - 4-6 months (short course) for intermediate risk
  - Neoadjuv + concurrent + 2-3 years LHRH for hi risk[2,3]
  - 18 months may be acceptable[4]
- ADT needed even with dose escalation[5]
  - GETUG 14 – 377 pts tx 80 Gy, 5 yr RFS 84% w/ ADT vs 76% w/out (p=0.02)
- **Brachy boost** should be added when appropriate
- Doses <70 Gy inadequate
  - Unclear whether escalation >78 Gy beneficial



1. Pilepich MV et al. JCO 1997; 15:1013 (RTOG 8531)
2. Hanks GE et al. JCO 2003; 21:3972 (RTOG 9202)
3. Bolla M et al. Lancet 2002; 360:103 (EORTC)
4. Nabid A et al. Eur Urol 2018; 74:432-41.
5. Dubray M et al. ASCO 2016 (abstr 5021)

Localized Prostate Cancer: RRP

- ADT is not recommended prior to surgery
  - Neoadjuvant studies show some pCR with ADT + abi or ADT + apa
- Robotic (minimally invasive) is most common option
- Potency depends on nerve bundle preservation
  - Sacrifice of 1 side nerves ↓ chance of potency to 50%
- Adjuvant ADT for lymph node positive[1] and other high risk patients[2] "Investigational"
- **Adjuvant XRT** for +margins or T3 [3,4]

1. Messing EM et al. NEJM 1999; 341:1781
2. Dorff TB et al. JCO 2011;29:2040
3. Thompson IM et al. JAMA 2006; 296:2329 (S8794)
4. Bolla M et al. Lancet 2005; 366:13 (EORTC 22911)

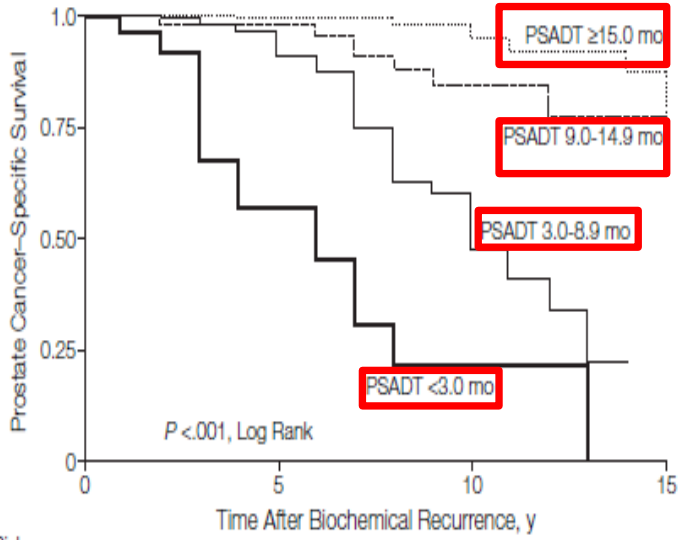
- **Definition**: PSA >0.2 after RRP, “nadir +2” after XRT
- ADT beneficial when giving salvage radiation for BCR
  - GETUG-AFU16[1] gave 6 months of goserelin with XRT 66 Gy or XRT alone; 5 year biochem RFS 80% vs 62% (HR 0.5)
  - RTOG 9601[2] gave bicalutamide 150 mg for 24 months with XRT 64.8 Gy or XRT alone; mets at 12 years 14% w/ bicalut vs 23% (p<0.001) and HR for OS 0.75 (2-sided p = 0.036).
  - SPPORT found 89% 5-year RFS for ADT + pelvic LN XRT compared to 83% w/out pelvic LN and 71% w/out ADT (i.e. prostate bed XRT only)
- BUT… minimal benefit of ADT when XRT started at PSA <0.8[4]

		Pre-RT PSA (ng/ml)		
Margin status	ISUP grade group (Gleason score)	0.1–0.5	0.6–1.0	>1.0
Negative	1 (6)	RT	RT	RT + STADT
	2, 3 (7)	RT	RT + STADT	RT + LTADT
	4, 5 (8–10)	RT [a]	RT + STADT	RT + LTADT
Positive	1 (6)	RT	RT + STADT	RT + LTADT
	2, 3 (7)	RT	RT + STADT	RT + LTADT
	4, 5 (8–10)	RT [a]	RT + LTADT	RT + LTADT

1. Carrie C. et al Lancet Oncol 2016; 17:747
2. Shipley WU et al. NEJM 2017; 376:417
3. Pollack A et al. J Urol 2019; supp (abstr MP72-01)
4. Spratt D et al. Eur Urol 2018; 73:156-65

Biochemical Recurrence (after salvage XRT): When (If) to Start ADT?

Figure 3. Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer–Specific Survival Curves by PSADT



No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Biochemical recurrence segregated by prostate-specific antigen doubling time among patients who experienced a biochemical recurrence. PSADT indicates prostate-specific antigen doubling time.

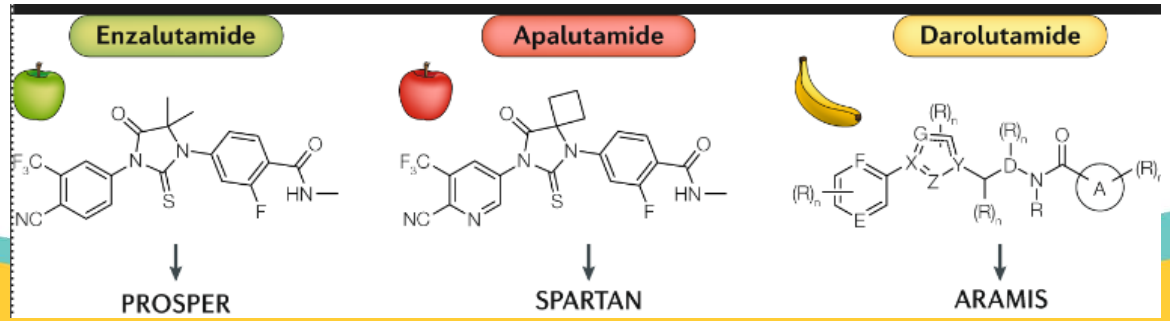
- PSA Doubling Time
- Time to Recurrence
- Gleason Grade
- COMORBIDITIES

HOW:

- Intermittent (4-12 months on)
- Degarelix vs Leuprolide/Goserelin

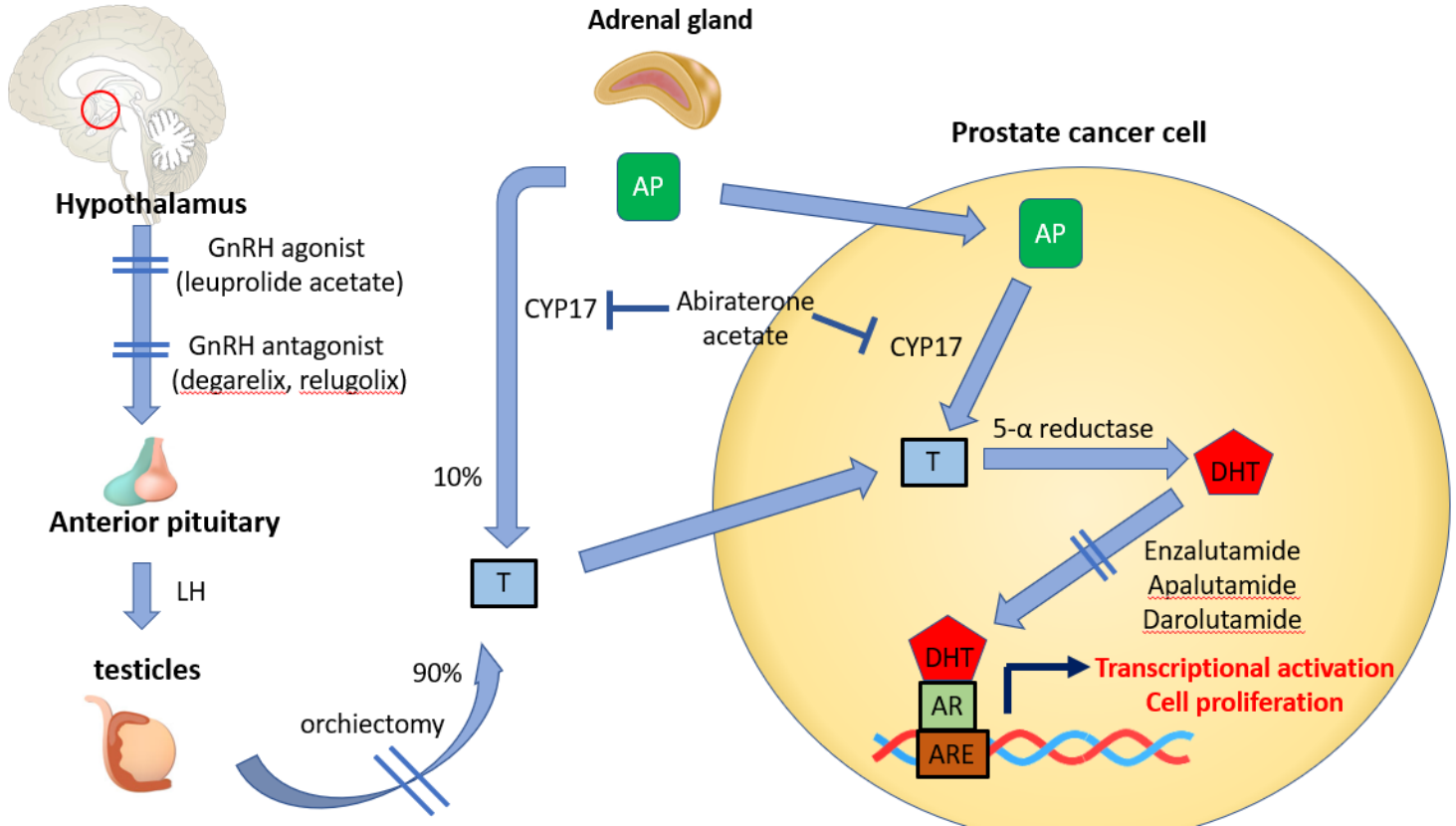
JAMA 2005; 294:433-439.

Agent	Apalutamide 240 mg daily	Darolutamide 600 mg BID	Enzalutamide 160 mg daily
Study name	SPARTAN	ARAMIS	PROSPER
Design	2:1 apa/placebo	2:1 daro/placebo	2:1 enza/placebo
Number of pts	1207	1509	1401
Inclusion:	PSA DT <10 mo Pelvic LN <2 cm OK	PSA DT ≤10 mo Pelvic LN <2cm OK bPSA ≥2	PSA DT ≤10 mo -- bPSA ≥2
Met Free Surv	40.5 mo vs 16.2 placebo (HR 0.29)	40.4 mo vs 18.4 placebo (HR 0.41)	36.6 mo vs 14.7 placebo (HR 0.07)
Discontinuation	10.7% apa, 6.3% placebo	8.9% daro, 8.7% placebo	10% enza, 8% placebo



Principles of treatment metastatic prostate cancer: Androgen Deprivation Therapy (ADT)

- **ADT is effective**
  - 60-70% will have PSA “normalization”
  - 30-50% will have >50% regression of measurable tumors
  - 60% will have palliation of symptoms
- **Castration**
  - **Surgical vs chemical**
  - Use AR antagonist (ex: bicalutamide) run-run-in to block flare
  - LHRH antagonist (degarelix) avoids flare



ADT: managing side effects

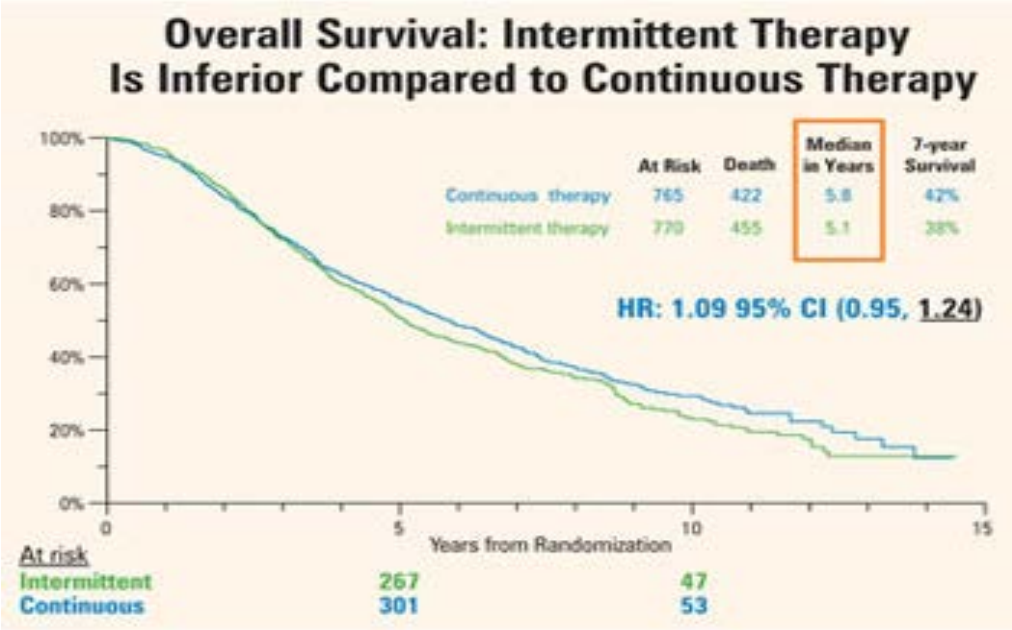
- Common: impotence, hot flashes, fatigue, gynecomastia, weight gain, muscle loss
- Metabolic: diabetes, lipids, **osteopenia**, cardiovascular disease
  - Check DEXA
  - Bisphosphonates if osteopenia or denosumab 60 mg SQ q6, which reduces vertebral fractures[1]
  - Resistance and Aerobic **Exercise** can improve muscle mass, physical function
  - **Vit D + Calcium**
  - LHRH antagonist may be safer than LHRH agonist[2]

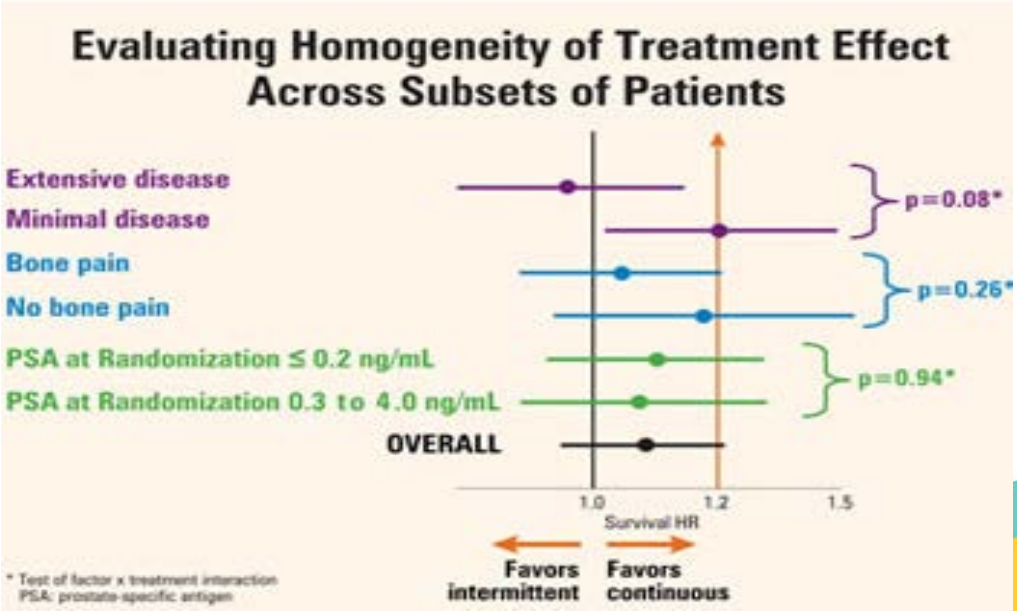
1. Smith MR et al. NEJM 2019; 361:745
2. Margel D et al. ASCO 2019; abstr 5015

mHSPC: Continuous ADT preferred over intermittent

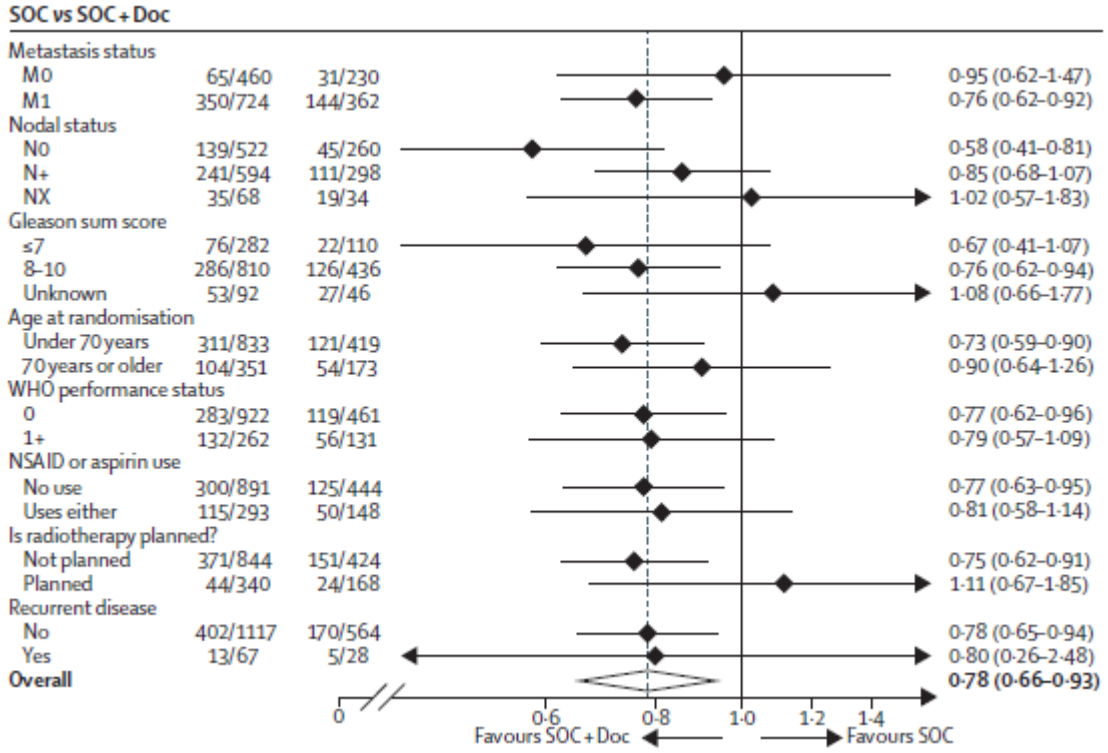
SWOG 9346

Hussain M et al,
NEJM 2013;
368:1314-25



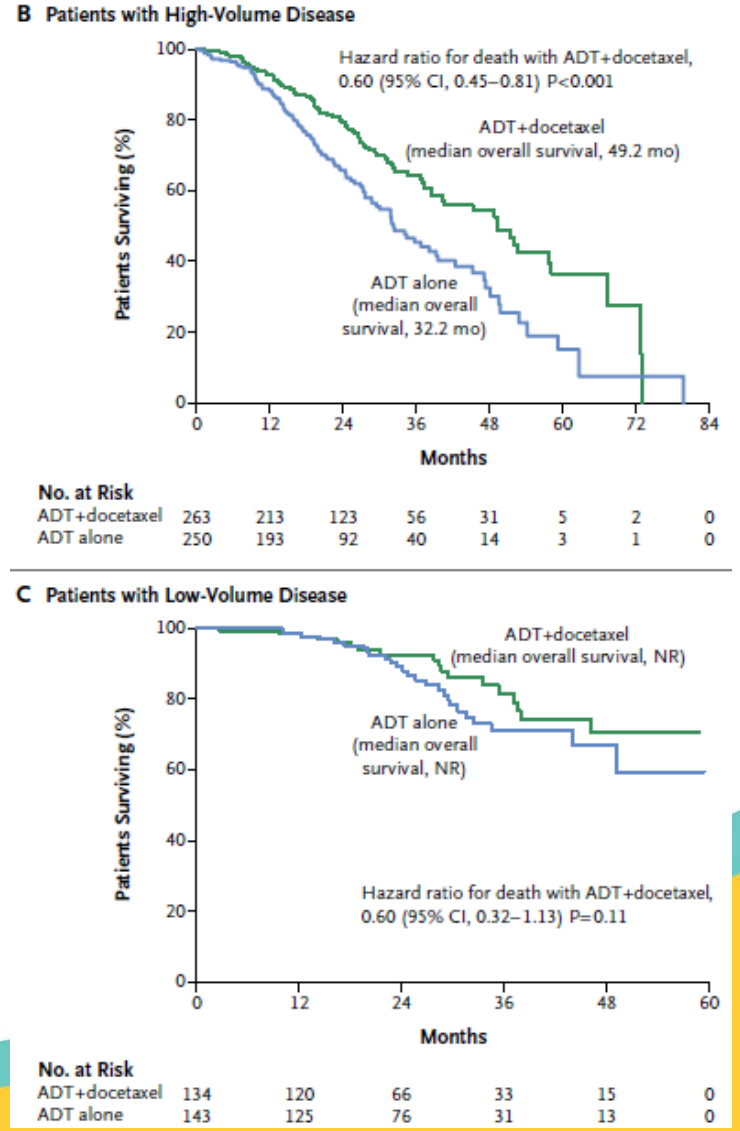


Early chemotherapy improved survival in metastatic hormone sensitive prostate cancer (HSPC)

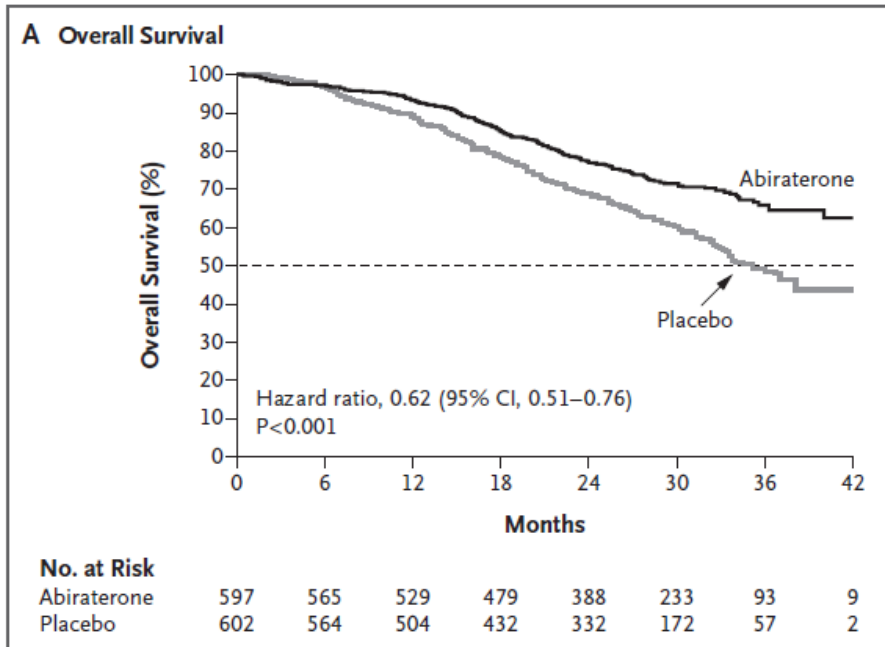


STAMPEDE (James et al, Lancet 2016; 387:1163-77)

CHAARTED (Sweeney CJ et al. NEJM 2015; 373:737-46)



Early abiraterone improves survival in mHSPC



LATITUDE 2 of 3 high risk features:

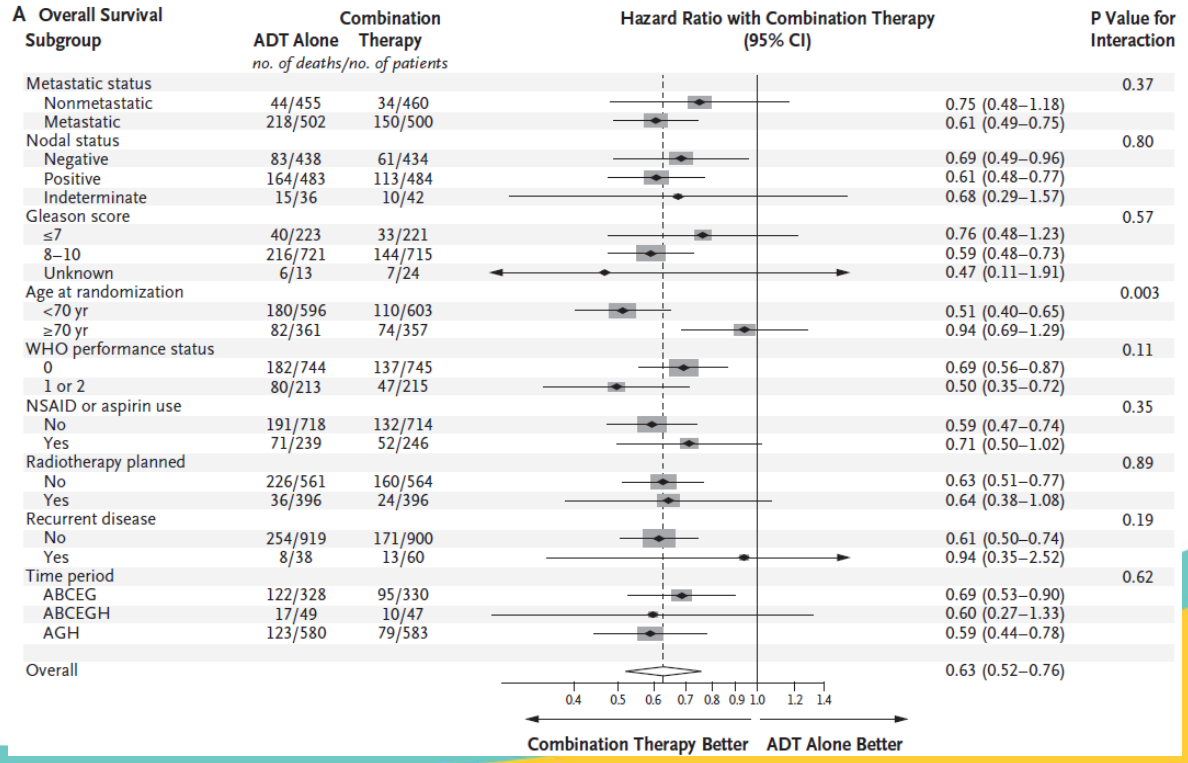
- Gleason 8-10
- 2+ bone metastases
- Visceral metastases

Fizazi K et al. NEJM 2017
DOI:10.1056/NEJMoa1704174

STAMPEDE:
Hi risk localized if 2/3:
Gleason 8-10 T3/T4 PSA >40

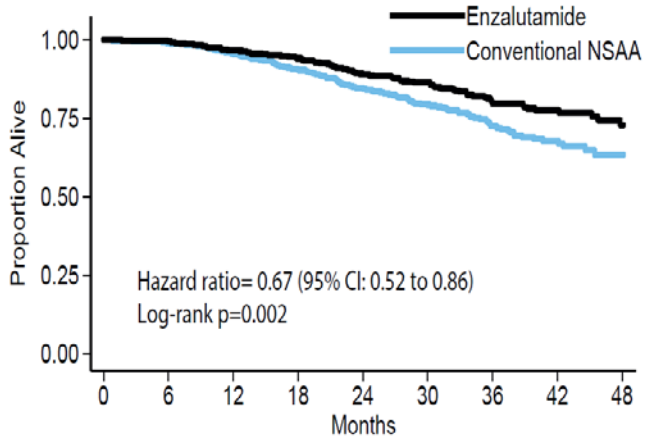
Biochemically recurrent if
PSA >4 and PSA DT <6 mo

James ND et al. NEJM 2017;
DOI: 10.1056/NEJMoa1702900

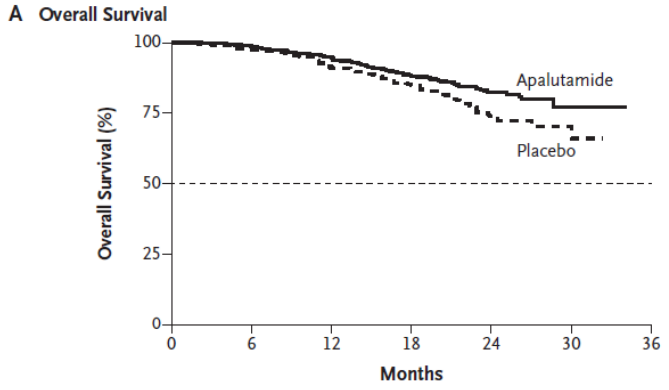


AR antagonists in mHSPC: ENZAMET and TITAN

- Up-front enzalutamide increased 3 year OS from 72% to 79% in ENZAMET[1], HR 0.67.
  - Bicalutamide allowed in control arm
  - No apparent advantage for enza after docetaxel; toxicity was noted
- TITAN[2] found improved OS at 24 months for apalutamide in mHSPC (82.4% vs 73.5%) compared to placebo



Number at risk									
Conventional NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45



No. at Risk							
Apalutamide	525	513	490	410	165	14	0
Placebo	527	509	473	387	142	16	0

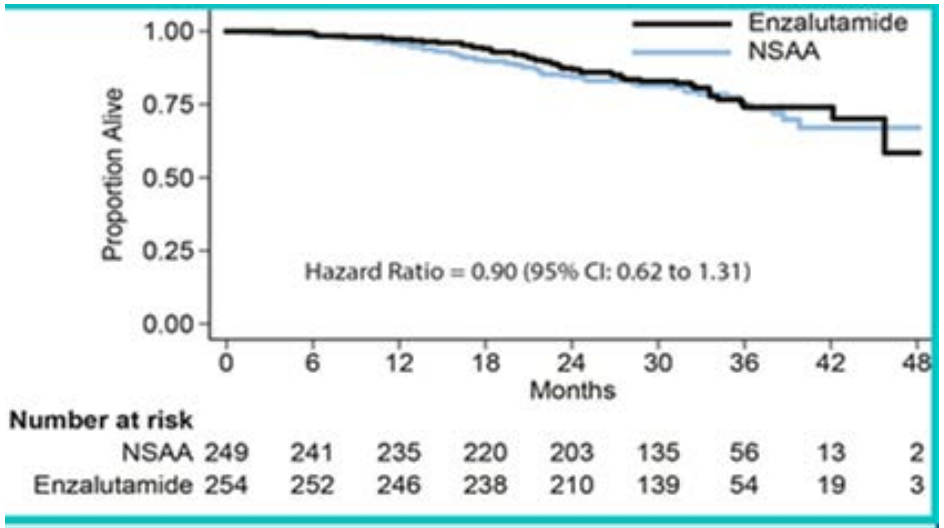
	No. of Patients	Median Overall Survival (95% CI)	Patients with Overall Survival at 24 Mo (95% CI)
		mo	%
Apalutamide	525	NE	82.4 (78.4–85.8)
Placebo	527	NE	73.5 (68.7–77.8)

Hazard ratio for death, 0.67 (95% CI, 0.51–0.89)
P=0.005

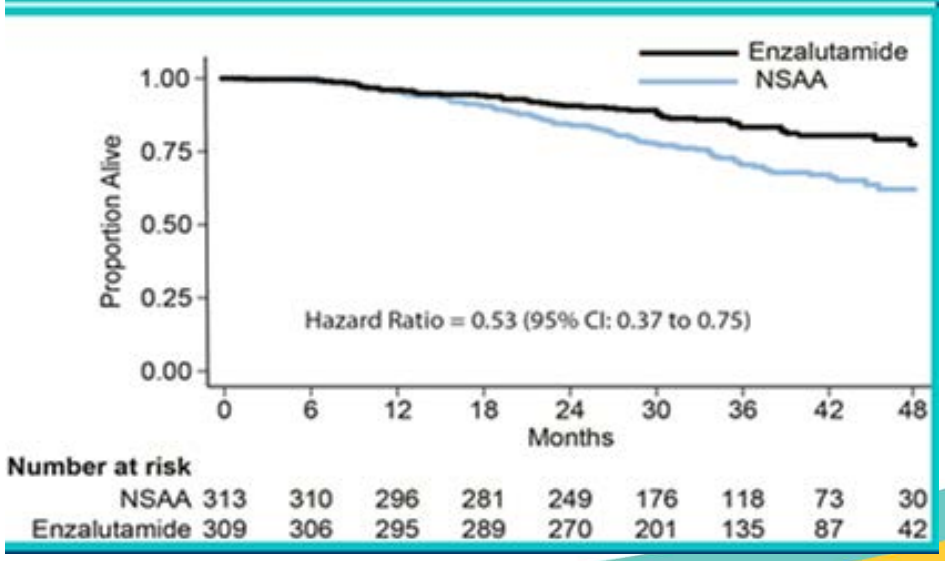
1. Davis ID et al. NEJM 2019; 381:121-31
2. Chi KN et al. NEJM 2019; 381:13-24

No apparent benefit for using both docetaxel and enza in ENZAMET

Testosterone Suppression + Docetaxel N=503 (71% High Volume)



Testosterone Suppression + No Docetaxel N=622 (37% High Volume)



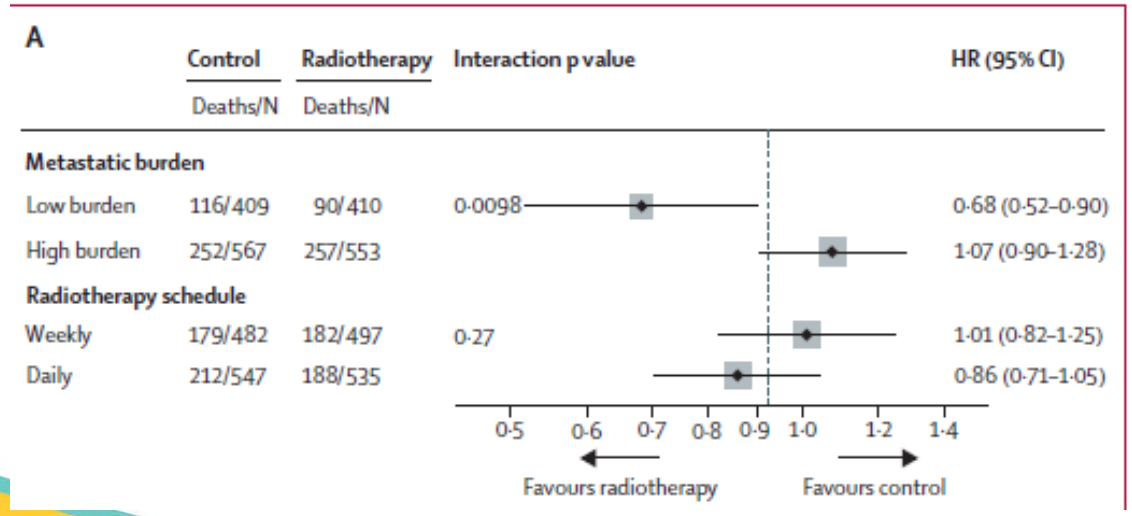
How will we choose between available agents?

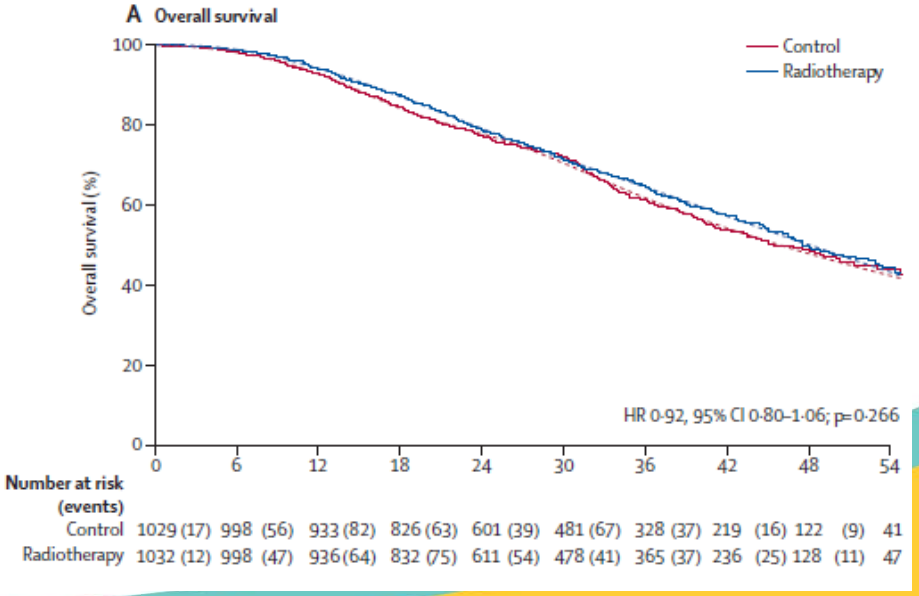
	DOCETAXEL	ABIRATERONE	ENZA/APA
Length of Treatment	**Short term** (approx 4.5 months)	Long term (approx 33 mo)	Long term (>36 months)
Financial	possible time off work	Prescription co-pays; **generic**	Prescription co-pays
Toxicities	Peripheral neuropathy, hair loss	Liver enzymes, electrolytes, HTN	CNS (seizures/ cognitive), falls
Corticosteroids	YES	YES	**NO**
Subsets	High-volume*	Any	Any

*≥4 bone mets with 1 outside axial skeleton OR visceral mets

- STAMPEDE: radiation to the prostate primary improves survival
  - only in low-volume subset

Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age (years)	Median (IQR) Range	68 (63–73) 37–86	68 (63–73) 45–87
PSA (ng/ml)	Median (IQR) Range	98 (30–316) 1–20590	97 (33–313) 1–11156
Metastatic burden	Low High Not classified	409 (42%) 567 (58%) 53	410 (43%) 553 (57%) 69
Site of metastases	Bone Liver Lung Distant lymph nodes Other	919 (89%) 23 (2%) 42 (4%) 294 (29%) 35 (3%)	917 (89%) 19 (2%) 48 (5%) 304 (29%) 33 (3%)
Docetaxel use	No Yes	845 (82%) 184 (18%)	849 (82%) 183 (18%)



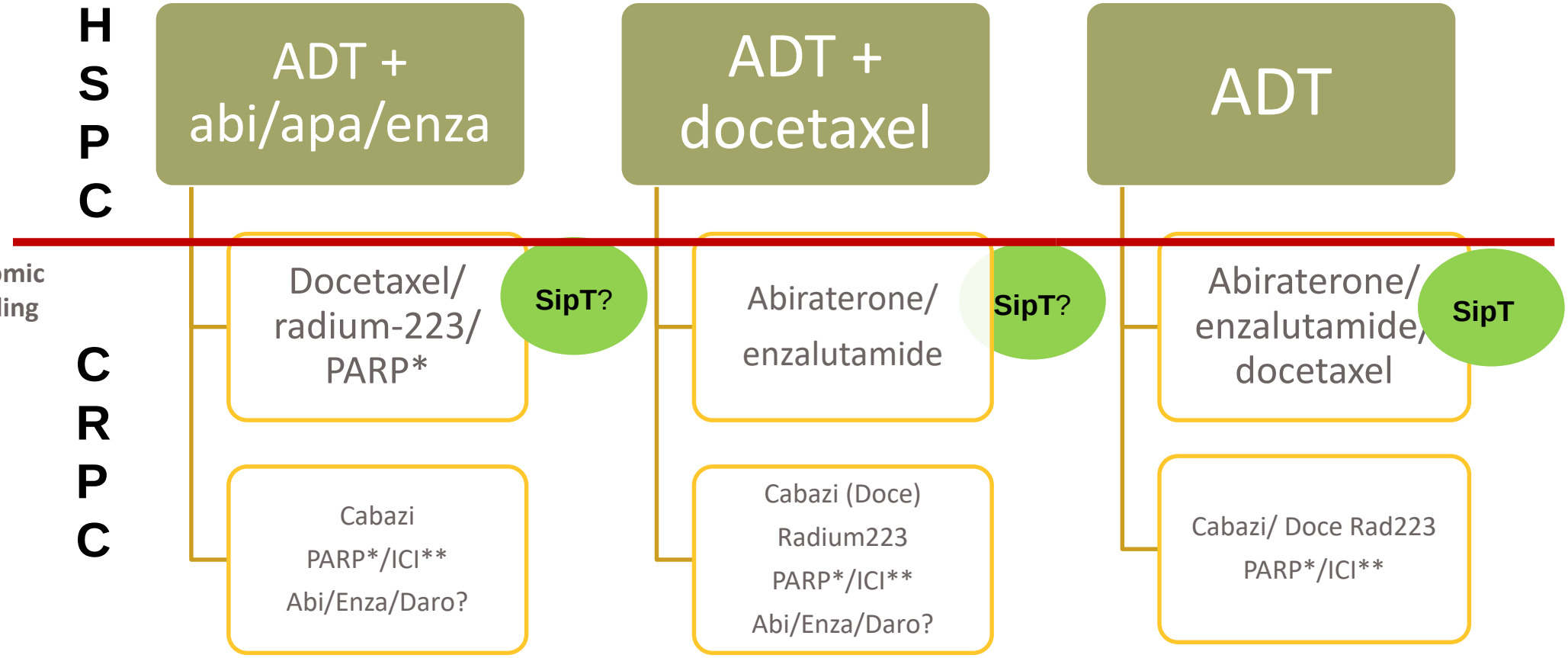


"Life Extending Therapies" for mCRPC

- **Abiraterone**
  - COU301: med OS 14.8 mo vs 10.9 mo for placebo (post TAX)[1]
  - COU 302: PFS 8.3 months → 16.5 months (pre TAX) [2]
- **Cabazitaxel**
  - Med OS 15.1 months vs 12.7 months mitoxantrone (post TAX)[3]
- **Docetaxel**
  - TAX327: med OS 18.9 months (16.5 mitoxantrone) [4]
- **Enzalutamide**
  - AFFIRM: med OS 18.4 months vs 13.6 for placebo [5] (post TAX)
  - PREVAIL: med OS 32.4 mo vs 30.2[6] pre TAX
    - (17 mo delay in chemo)
- **Radium223**
  - ALSYMPCA: med OS 14.9 months[7] (11.3 mo placebo)
- **Sipuleucel-T**
  - IMPACT: med OS 23.2 months[8] (18.9 placebo)

1. deBono J et al, NEJM 2011; 364:1995
2. Rahtkopf D et al, ASCO 2013; abstr 5
3. deBono JS et al, Lancet 2010; 376:1147
4. Tannock IF et al. NEJM 2004; 351:1502-12
5. Scher HI et al, NEJM 2012; 367:1187
6. Beer TM et al. Proc ASCO 2014
7. Parker C et al, ASCO 2013
8. Higano CS, et al. Cancer 2009; 115:3670

Current Paradigms for M1



- **Genomic Profiling**

AR = androgen receptor antagonist
PARP = *if DNA repair mutation identified
ICI = immune checkpoint inhib (**i.e pembrolizumab if MSI high)

There Is Not ONE Optimal Sequence…

- Clinical Factors may Impact Decision

Consider abiraterone first

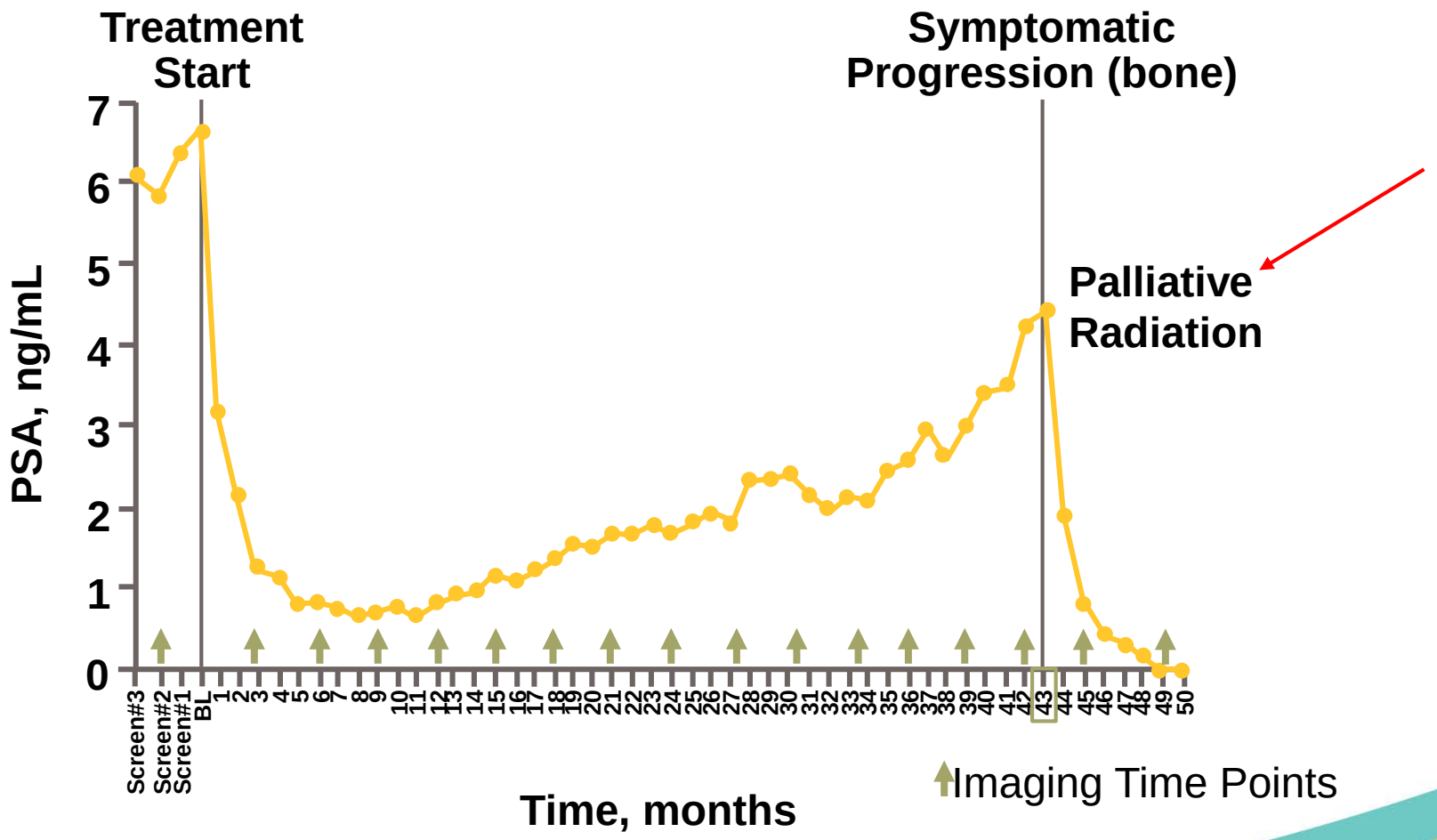
- Mild baseline pain; steroids may help
- Significant baseline fatigue
- Falls, gait, or neurological issues
- Older patients

Consider enzalutamide first

- Fragile diabetes
- Remote living
- Visceral metastases (pre TAX)
- Baseline edema

Keep in mind that the steroids with abiraterone are not supraphysiologic

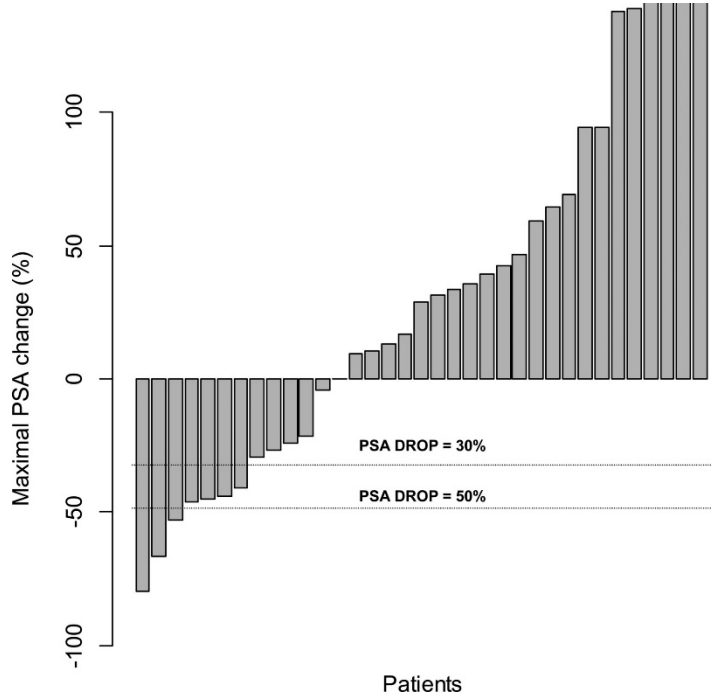
Optimizing use of existing therapies: Ensure Drug Is No Longer Working Before Stopping



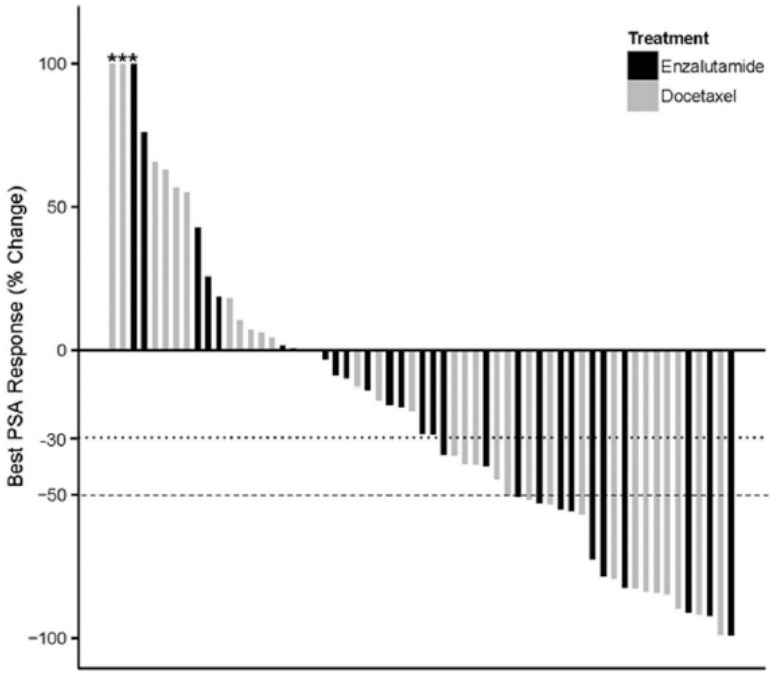
•Scher HI, et al. *J Clin Oncol*. 2011;29:3685-3704.

Sequencing: less effect of abi after enza, and enza after abi

Abiraterone response after prior treatment with enzalutamide[1]



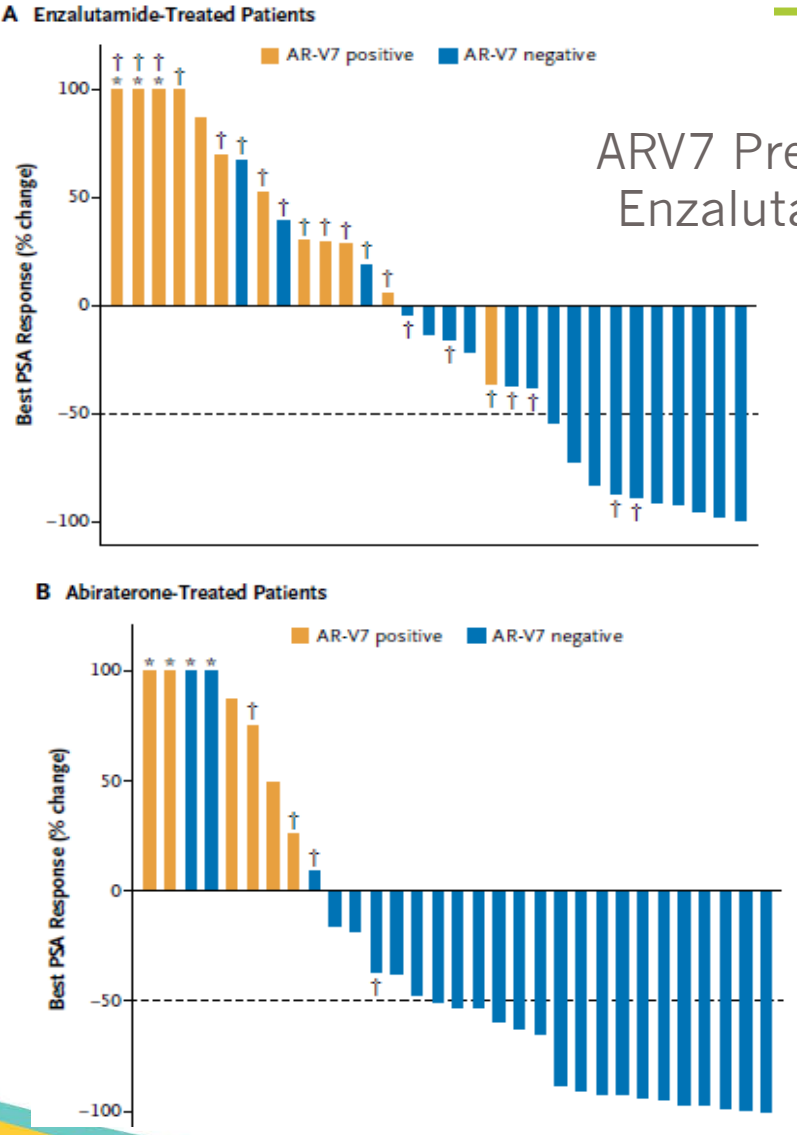
Enzalutamide versus docetaxel in men with CRPC progressing after abi[2]



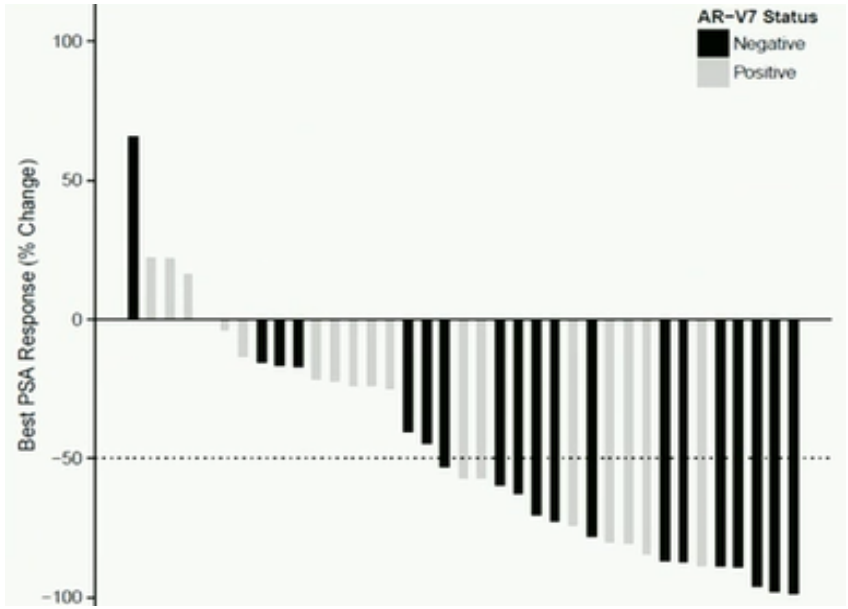
1. Loriot Y, et al. Ann Oncol 2013;24:1807-1812.
2. Suzman DL, et al. Prostate. 2014; 74:1278-1285.

Antonarakis et al, NEJM 2014.

ARV7 explains some cross-resistance



ARV7 Predicts Less Response to Enzalutamide and Abiraterone

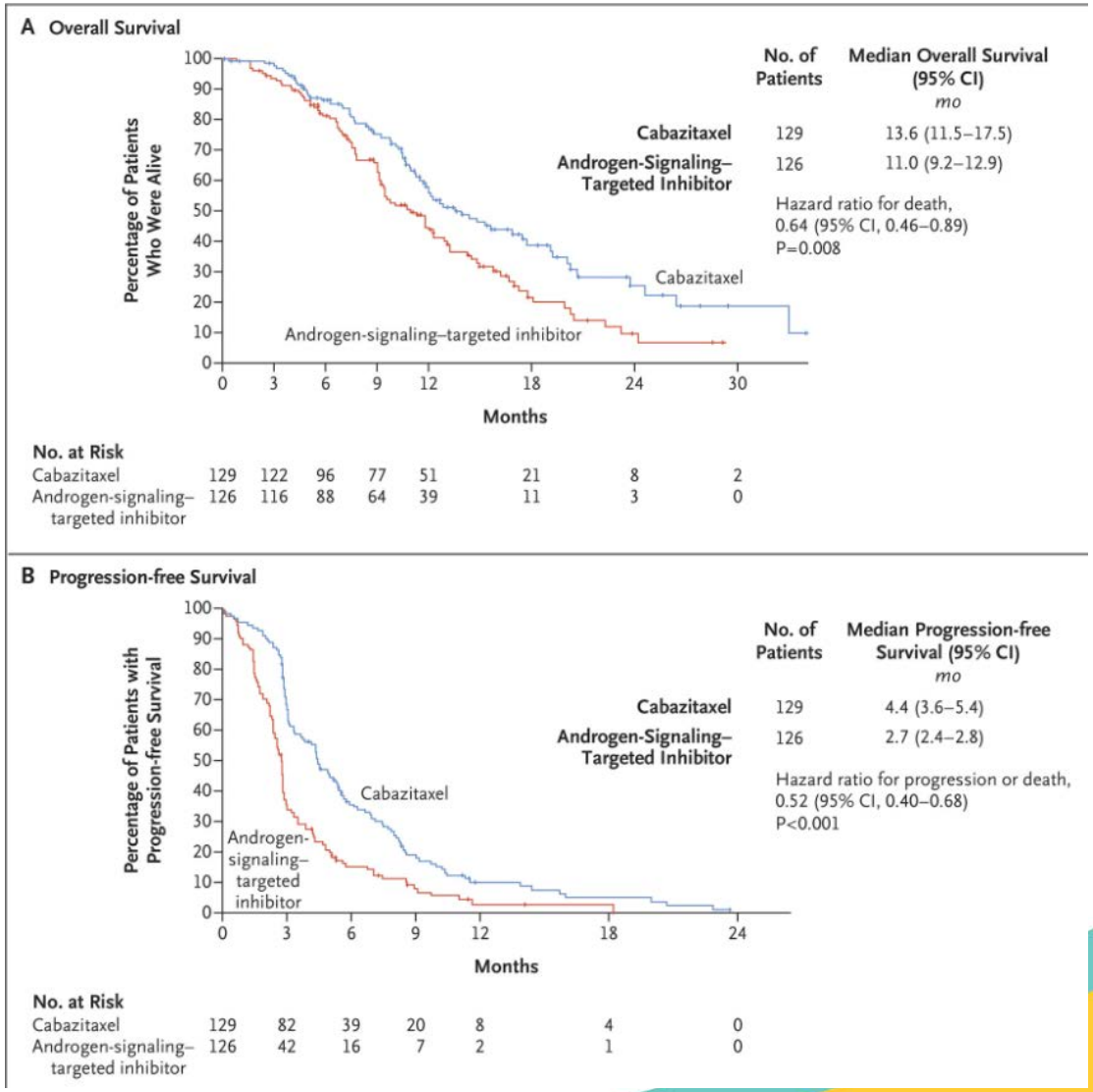


But response to Docetaxel is not impacted by ARv7

Antonarakis et al, 2015.

CARD: cabazitaxel more effective than abi/enza (ASTI) post abi/enza

- Men previously treated with both docetaxel and abi or enza
  - Median age 70 (46-85)
  - 70% had pain progression
- ORR 37% cabazi, 12% ASTI
- Grade ≥ 3 Adverse events in 56.3% with Cabazi, 52.4% with ASTI
  - 44.7% grade 3+ neutropenia- 3.2% febrile
  - Grade 3+ Cardiac disorders 4.8% with ASTI

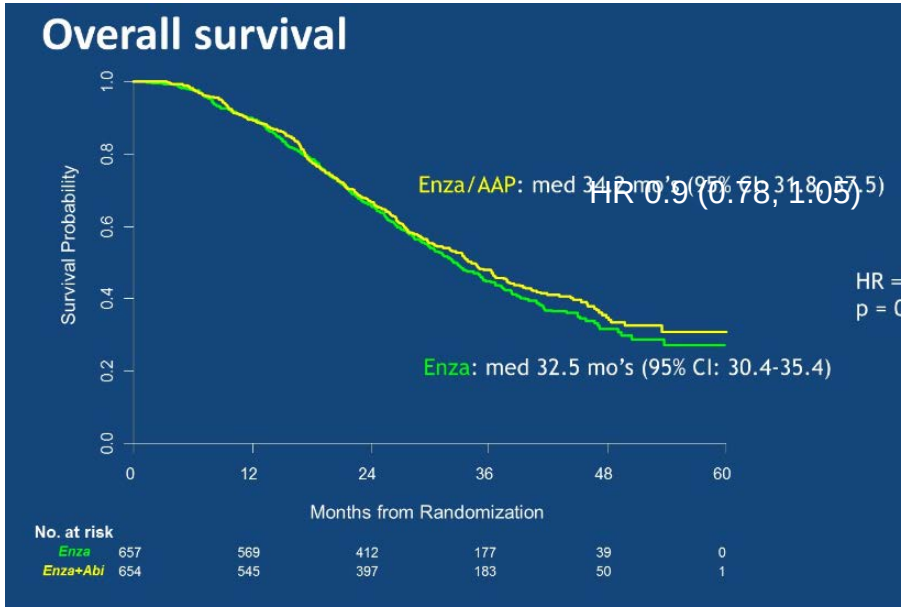


deWit R et al, NEJM 2019; 381:2506-18

Combinations have not been successful

- A031201 enza +/- abiraterone in mCRPC[1]
  - No diff in OS
  - Higher rate grade 3-5 Aes

- Neoadjuvant (ASCO 2020[2])
  - LHRH + Abi + Apa no better than LHRH + Abi (pathologic response)



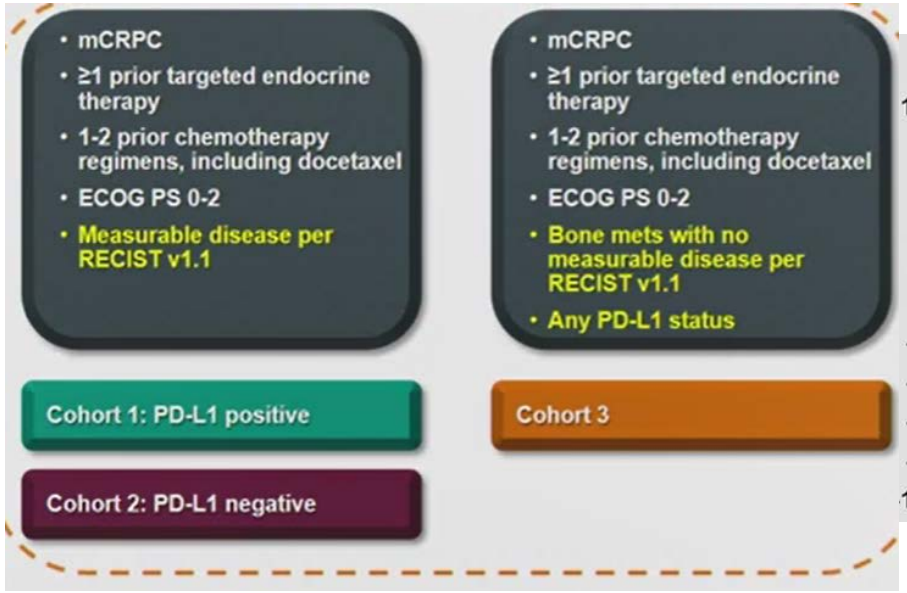
		APL (n=59)	APAL (n=55)
Pathologic Response	pCR	6 (10%)	7 (13%)
	MRD (≤5 mm)*	6 (10%)	5 (9%)
	pCR or MRD	12 (20%)	12 (22%)

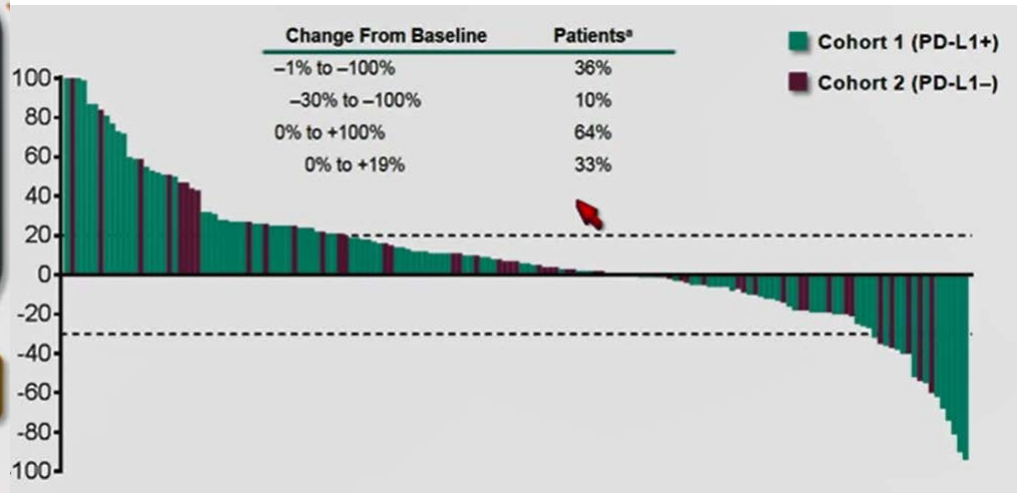
1. Morris MJ et al. ASCO 2019 abstr 5008 NCT01949337
2. McKay R et al. ASCO 2020 abstr 5503 NCT

- ERA223 identified increased fracture risk when abiraterone is used together with radium223[1]
- Shore et al (ASCO 2020) found this varied based on concurrent vs “layered” use[2]
  - bone support mitigated the risk
- EORTC 1333/ PEACE III[3]
  - Excess fractures for combination of enza + rad223
  - bone support eliminated the increased risk
  - Unclear yet whether advantage for enza w/rad223

1. Smith M et al, Lancet Oncol 2019; 20:408-19.
2. Shore N et al, ASCO 2020 abstr
3. Tombal BF et al. ASCO 2019 abstr 5007 NCT02194842

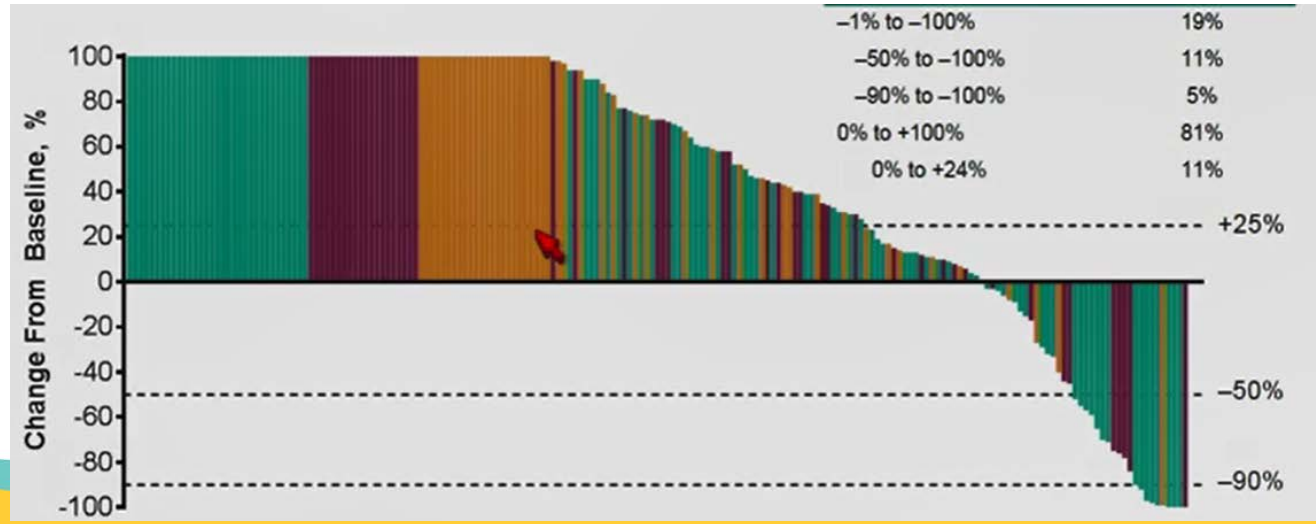
New agents: Pembrolizumab in mCRPC (KEYNOTE-199)



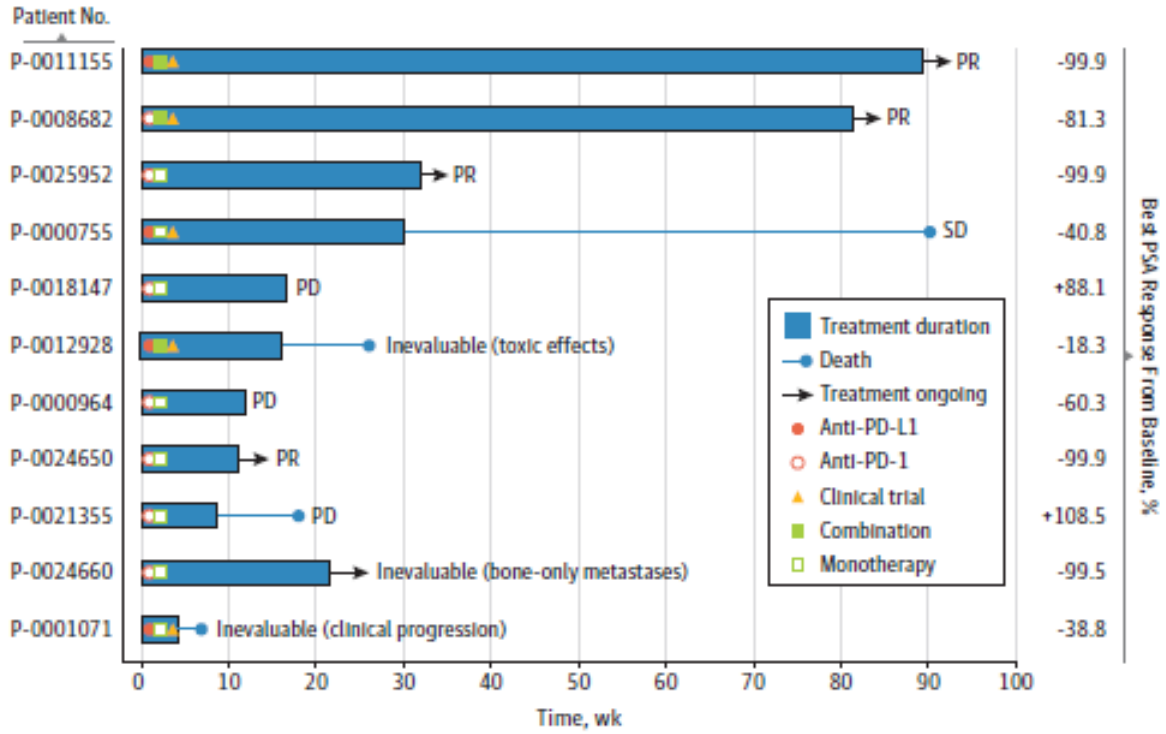


Top right: objective response
Bottom right: PSA changes

DeBono JS. ASCO 2018; oral present



- 32 of 1033 (3.1%) of prostate cancer patients tested with germline + somatic DNA sequencing had MSI-high or mismatch-repair status.
- 6 of 11 treated with PD-1/PD-L1 antibody therapy had >505 PSA decline and 4 of 11 had objective radiographic response.
- Duration of response up to 89 weeks

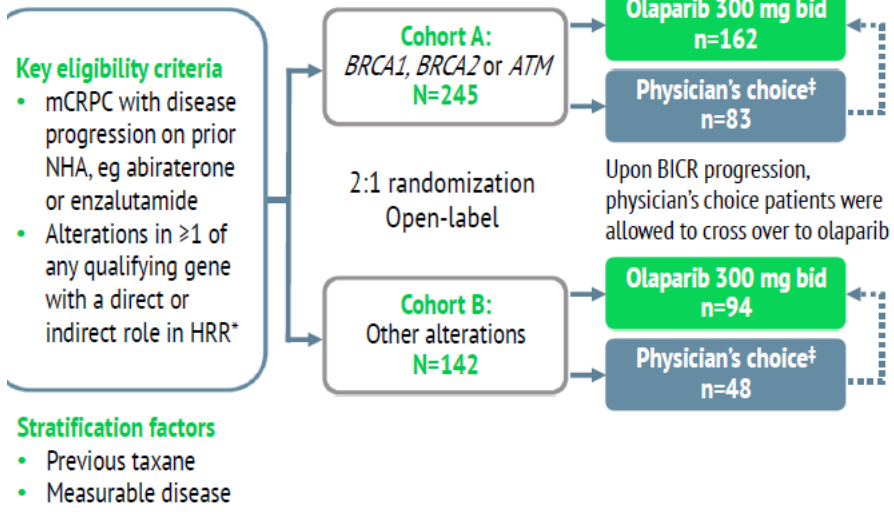


Abida W et al. JAMA oncol 2019; 5:471-8

- High response rate for olaparib in men with DNA repair deficiency
  - BRCA 1/2 , ATM, Fanconi, CHEK2
- TOPARP- B (ASCO 2019) olaparib 300 vs 400 BID
  - ORR 54% with **400 BID**. mPFS 5.4 months
  - Highest ORR BRCA 1/2 (80%), PALB2 (57%), ATM 37%, CDK12 25%, others 20%
- Rucaparib approved for BRCA1 and BRCA2
  - 54% PSA response and 47.5% objective response in BRCA patients[3]
  - Other mutations had limited benefit; 10.5% objective response in ATM, 0 with CDK12 and 11% with CHEK2[4]
- Awaiting data from additional agents (niraparib, talazoparib)

1. Mateo J et al. NEJM 2015; 373: 1697
2. Mateo J et al. ASCO 2019; abstr 5005
3. Abida W et al. Ann Oncol 2019; 30 (supp) abstr 846PD
4. Abida W et al. Clin Cancer Res 2020; 26:2487-96

PROFOUND: phase III data with PARP inhibitors



Primary endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key secondary endpoints

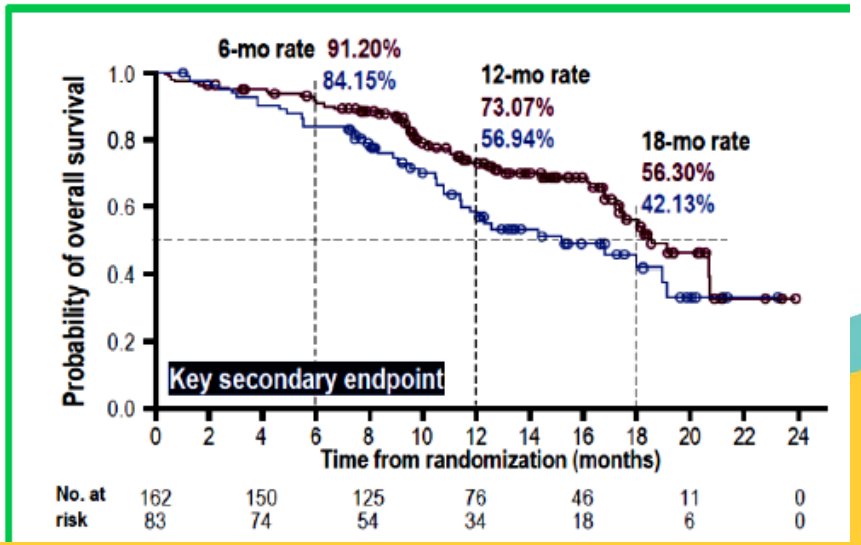
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in C
- O

rPFS 7.39 months vs 3.55 mo in cohort A

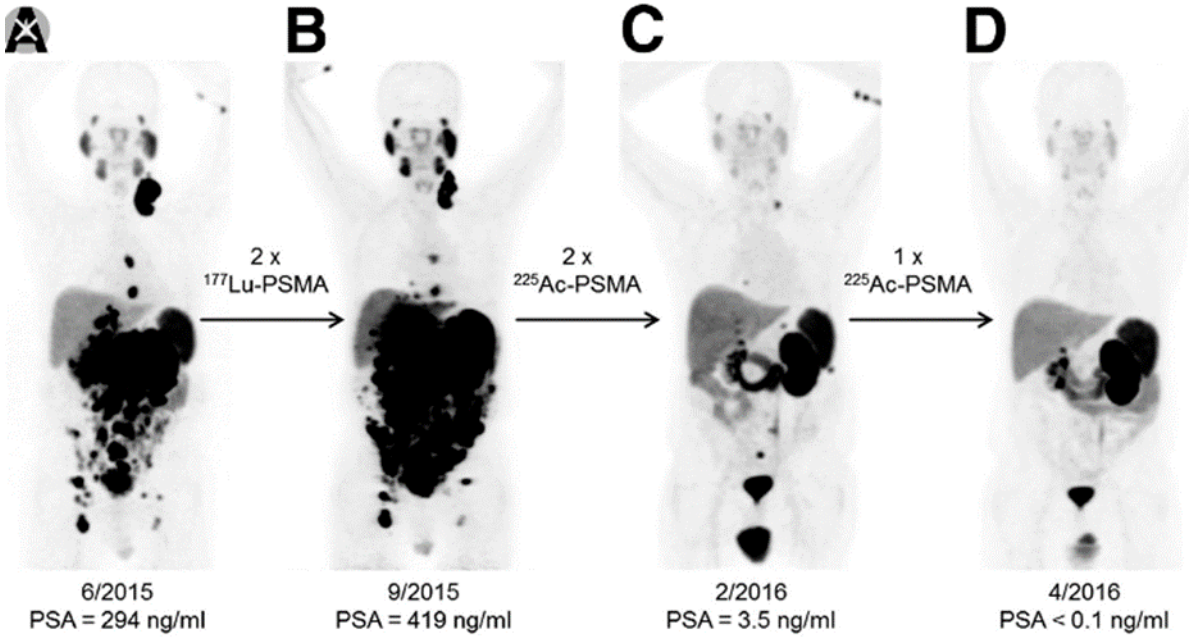
COHORT A	Olaparib (N=162)	Physician's choice (N=83)
Median OS (months)	18.50	15.11
Hazard ratio (95% CI)	0.64 (0.43-0.97) P=0.0173‡	

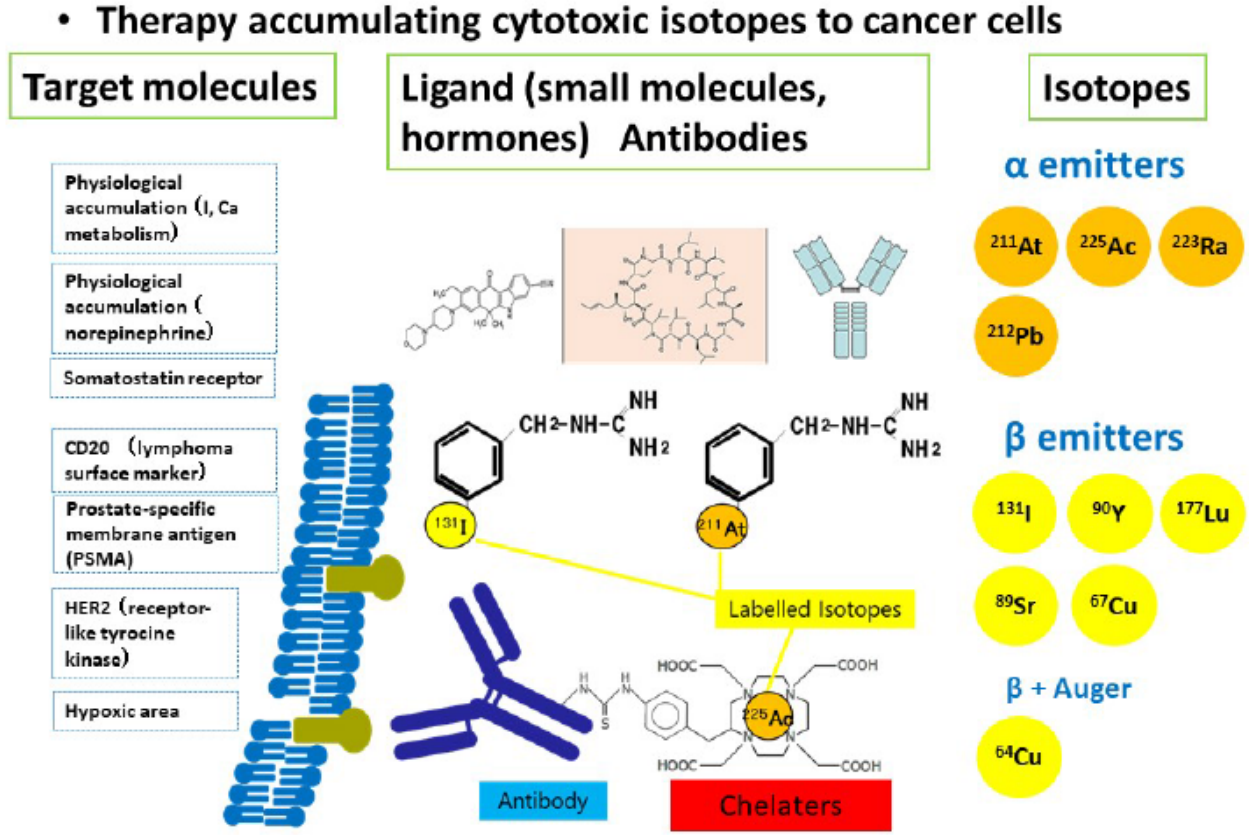
Hussain M, et al. Presented at ESMO 2019 Abstract #LBA12.

>80% crossover!



Radiopharmaceutical future: theranostics

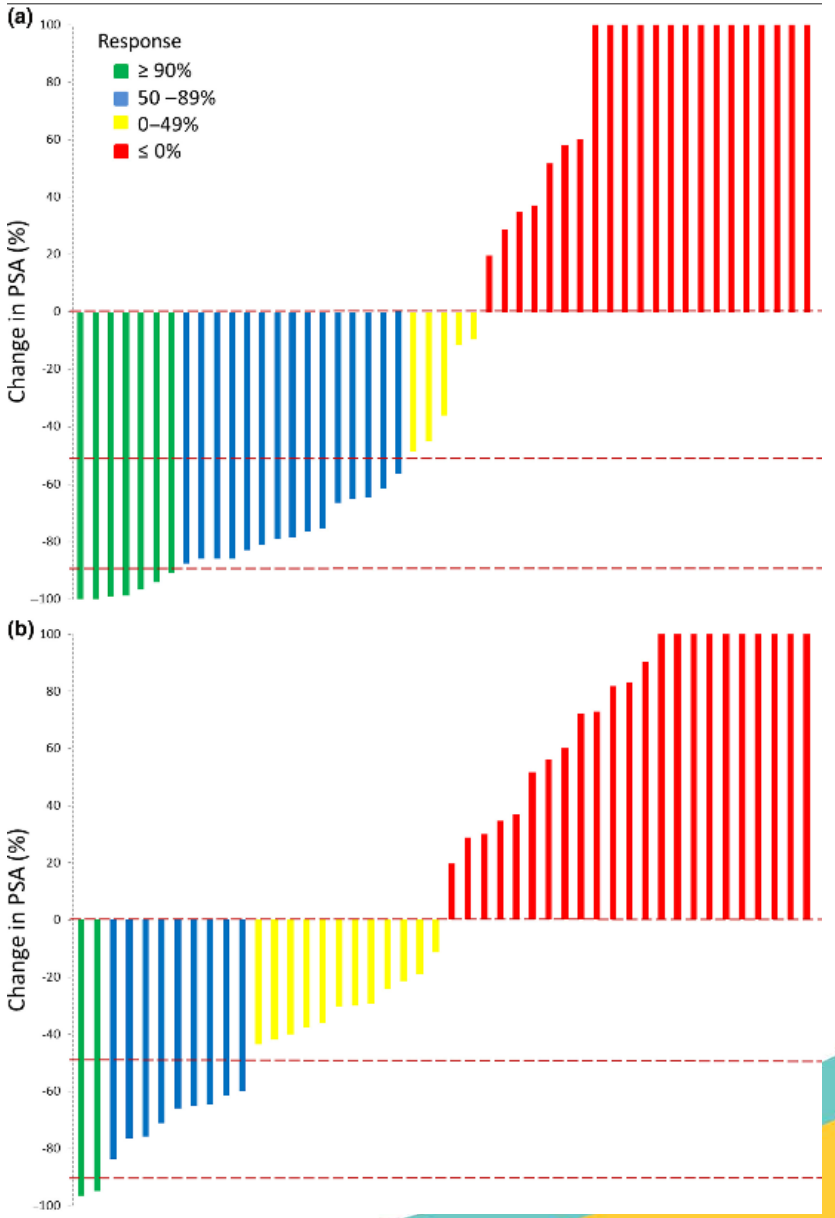




Limitations:

- Expression of the ligand (heterogeneity, downregulation)

- Australian experience[1]
  - 50 patients
  - Median 3 doses
  - 22 (45%) had PSA decline >50%
  - Main AEs: fatigue, nausea
- German experience[2]
  - 52 patients
  - 81% “any” PSA decline (44% >50%)
  - Med OS 60 weeks (i.e. 13.8 mo)
- VISION trial = randomized phase III
  - ongoing



1. McBean R et al.J Med Imag Rad Onc 2019; 63:538
2. Ahmadzadehfar H et al. Eur J Nucl Med Mol Imag 2017; 44:1448

- Other abiraterone dosing schedules
  - 500 mg w/ or w/out food - microparticle (YONSA)
  - 250 mg w/low-fat food (ZYTIGA)
  - Prednisone 5 mg daily mHSPC, 5 mg BID mCRPC
- Cabazitaxel dosing
  - 25 mg/m2 original approval, need GCSF
  - 20 mg/m2 similar efficacy in PROSELICA, ?need GCSF
- Side effects/ monitoring
  - Abiraterone: LFTs, electrolytes, blood pressure
  - Apalutamide: thyroid, rash
  - Radium223: CBC prior to each dose
- Oligomets SBRT: not prime-time yet, not likely on boards

- Localized
- Staging (imaging) only for high risk
- Increased emphasis on genetic and molecular testing
- Biochemical recurrence
  - add ADT to salvage XRT
  - Individualize based on PSA and margins
- metastatic prostate cancer (mHSPC)
  - Abiraterone, Docetaxel, Enza/Apalutamide… most men should get more than just LHRH
  - Consider XRT to prostate (STAMPEDE)
  - No benefit yet for combining or “switch maintenance” with doce followed by ARTI
- non-metastatic CRPC (m0CRPC or nmCRPC)
  - Apalutamide, Darolutamide, Enzalutamide
  - PSA DT <10 months
- Adding enza + abi doesn’t give benefit
- Sequencing abi → enza or enza → abi with limited benefit
- Individualized therapy
  - Pembro only in MSI high (?addl mutations)
  - PARP inhibitors with genomic selection
  - Lu177-PSMA ? with PET selection