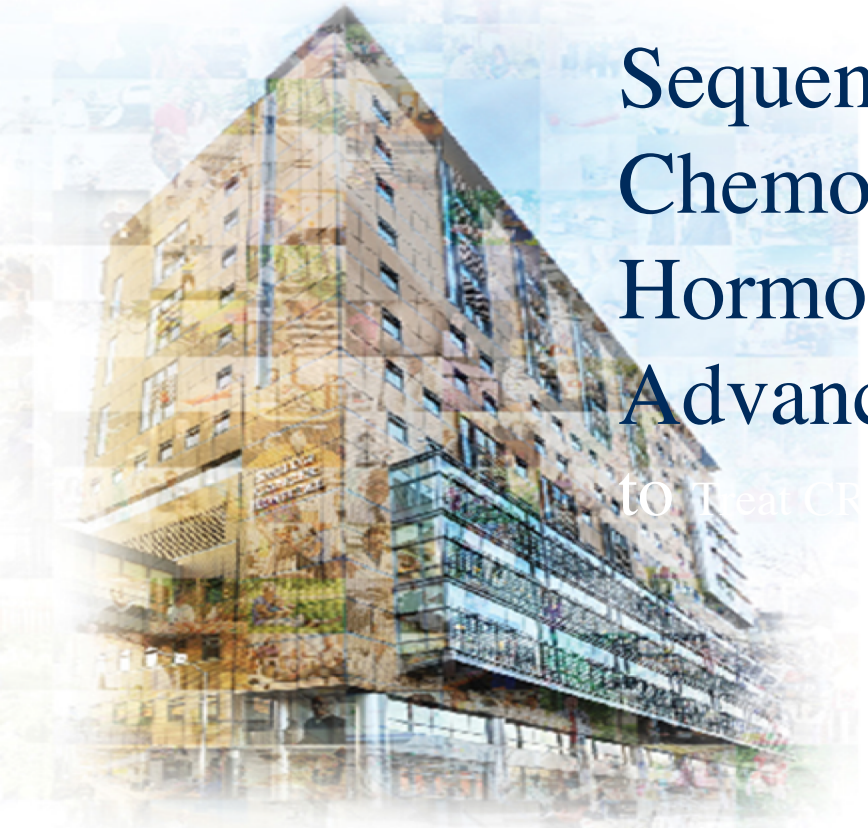

Sequencing of Chemotherapy and Hormonal Therapy in Advanced Prostate Cancer

to Treat CR

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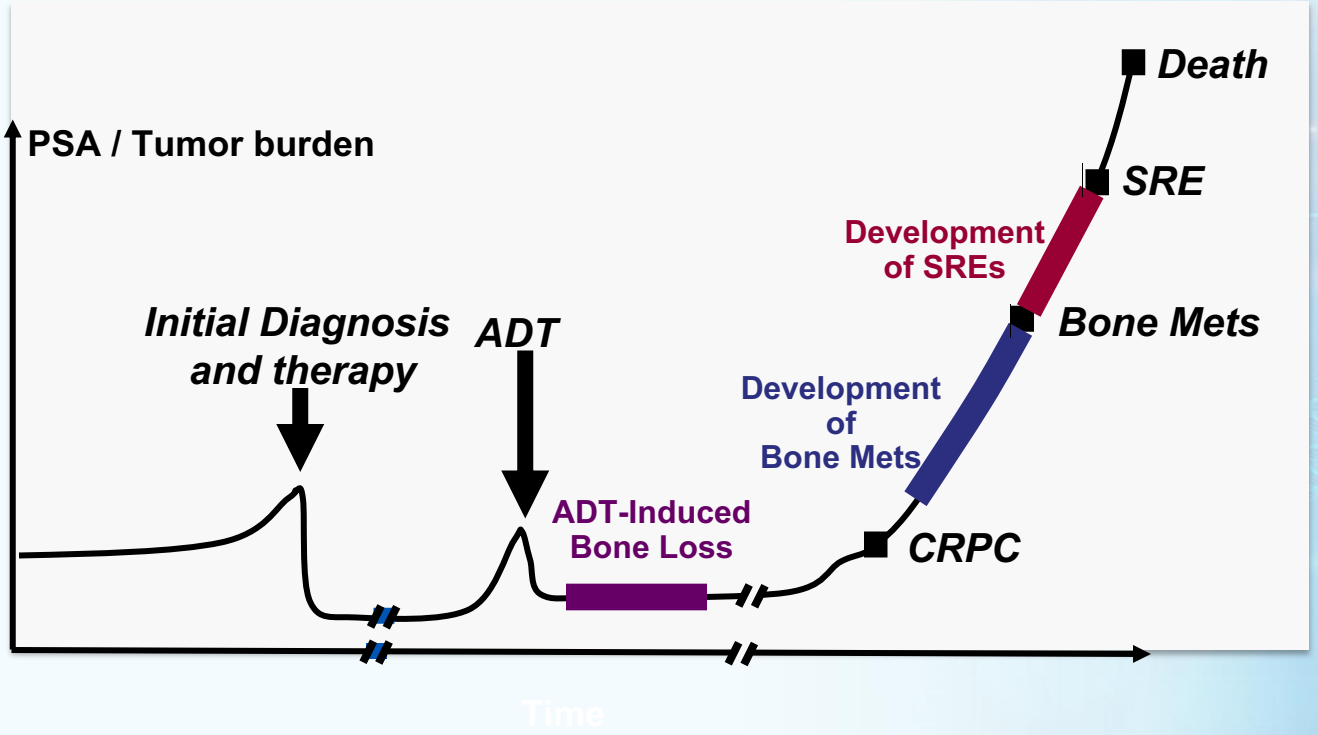
Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

Yale SCHOOL OF MEDICINE

DART

Natural History of Prostate Cancer



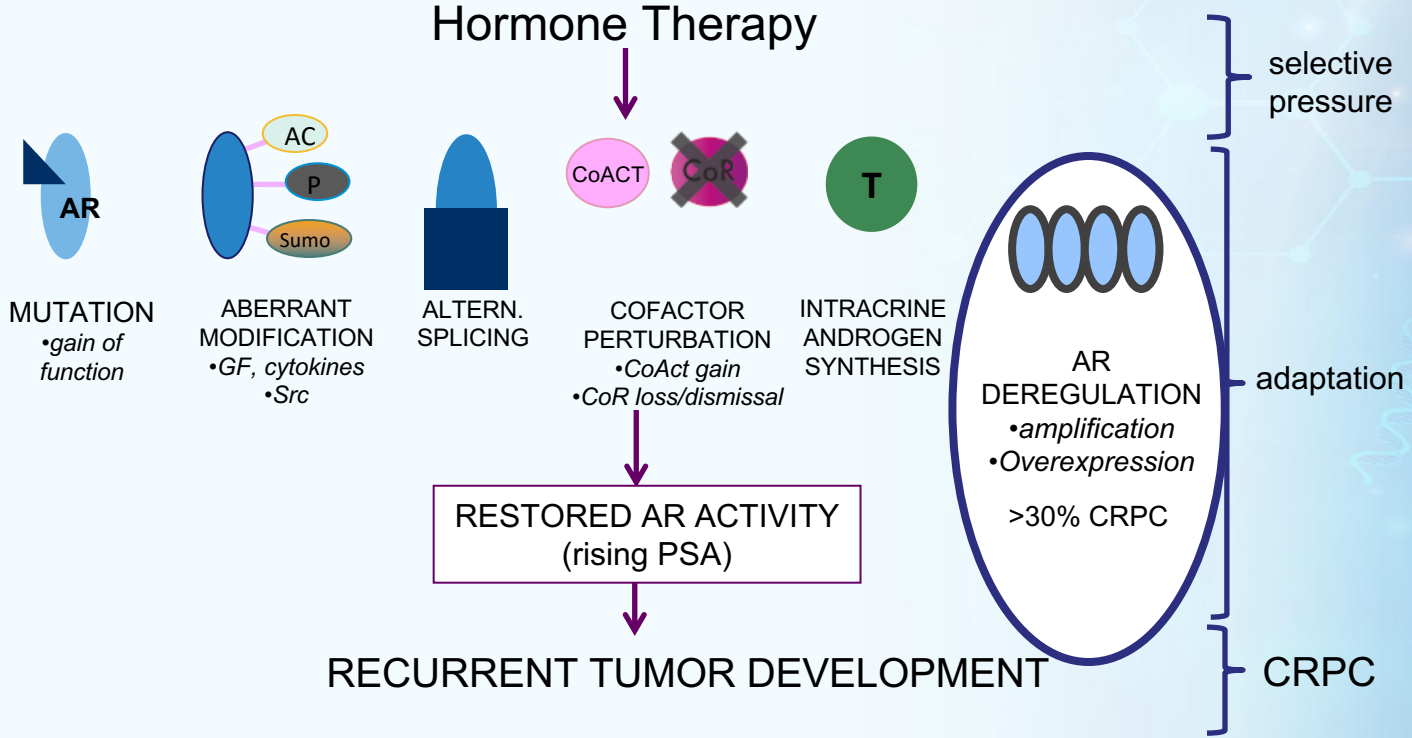
CRPC = Castrate resistant Prostate Cancer; SRE = Skeletal Related Event

Definition of CRPC

- Castrate level of serum testosterone
  - Currently, T < 50 ng/dL is most accepted
- Increasing PSAs or progressive disease on imaging
- Historical (but not accurate) terminology
  - Hormone refractory
  - Androgen independent

Scher HI, et al. J Clin Oncol. 2008;26:1148-1159.

Development of Castrate-Resistant Prostate Cancer



Penning and Knudsen. *Trends Endocrinol Metab*. 2010;21(5):315-24.

Understanding the Biology of CRPC: Driver Pathways of Dependency of PC

	Primary	Mets
Androgen Receptor (AR)	**55%**	**100%**
PTEN loss	**25%**	**80%**
PI3K/Akt, Ras/Raf, RB	**42%**	**100%**
TMPRSS2-ETS fusion	**50%**	**33%**

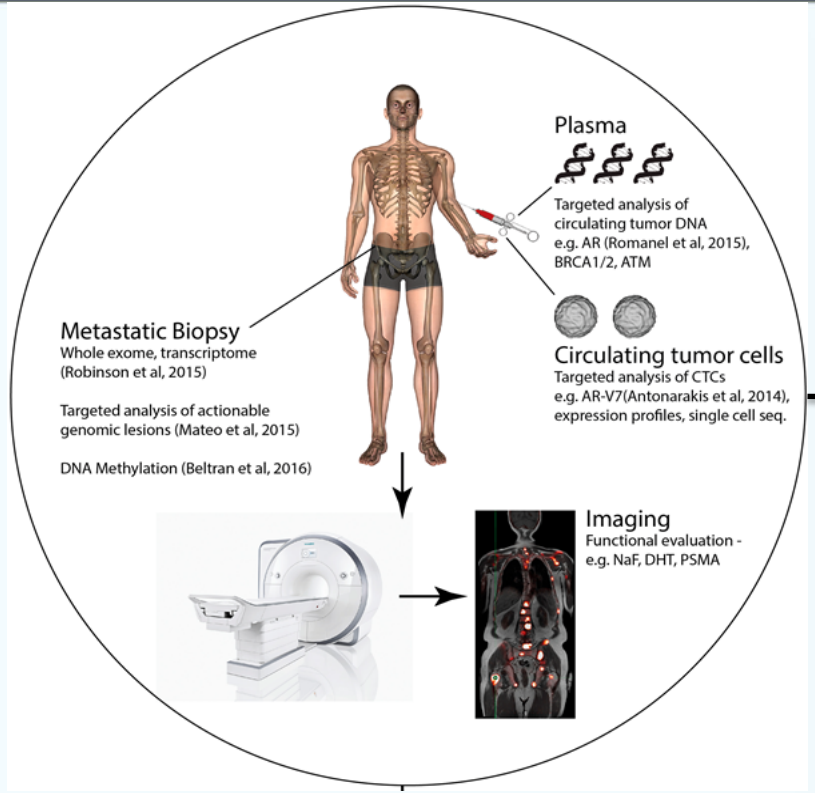
Tomlins SA, et al. *Eur Urol.* 2009; 56(2):275-86.
Taylor B, et al, *Cancer Cell.* 2010;18(1):11-22.
Jenkins RB, et al. *Cancer Res* 1997;57(3):524-31.
Khor LY, et al. *Clin Cancer Res.* 2007; 13(12): 3585–3590.

Common Genomic Alterations in CRPC

- *EGR* gene fusion (40%-50%)
- *AR* gene point mutation or amplifications (50%-60%)
- *TP53* mutation or deletion (40%-50%)
- *PTEN* deletion (40%-50%)
- *RB1* deletion (20%)
- DNA repair genes (20%-30%) —*BRCA1/2, ATM*

Bertran, et al. 2016 ASCO Educational Book. Presented June 4, 2016. Hosoya, et al. Cancer Sci. 2014;105:370-88.

Molecular Biomarkers Under Investigation: Improving Clinical Decision Making for Patients with Advanced Prostate Cancer



Treatment Decision

Image from Bertran, et al. 2016 ASCO Educational Book. Presented June 4, 2016.

Emerging Biomarkers

- Circulating tumor cell (CTC) DNA analyses in patients with CRPC—potential to track changes in response and resistance during treatment
- AR-V7 in CTCs in men with mCRPC
  - Associated with resistance to abiraterone and enzalutamide therapy
  - Potential to identify men at higher risk for progression while on abiraterone or enzalutamide who may be better suited for early taxane-based chemotherapy
  - Prospective AR-V7 biomarker-driven trials are underway
  - Development of a standardized, certified AR-V7 assay is underway
- Testing men with metastatic prostate cancer for DNA-repair gene mutations could assist in predicting the results of therapeutic options
  - Bi-allelic loss of DNA repair genes associated with clinical response to PARP inhibitor olaparib
  - PARP inhibition has durable antitumor activity in men with mCRPC and germline *BRCA2* mutations

Antonarakis ES, et al. *J Clin Oncol*. 2017 Apr 6:JCO2016701961.
Bertran, et al. 2016 ASCO Educational Book. Presented June 4, 2016. Hosoya, et al. Cancer Sci. 2014;105:370-88

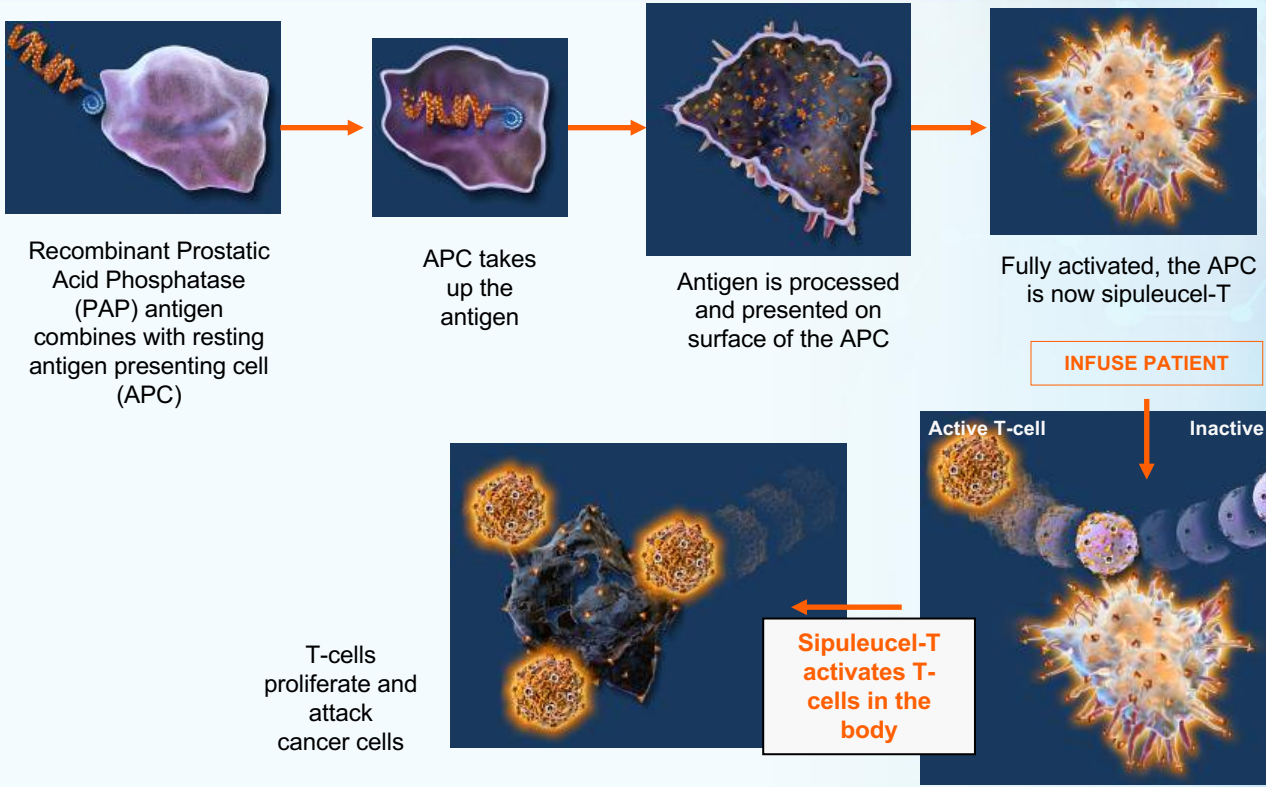
Classes of Agents for CRPC Treatment

- Immunotherapeutic
  - Sipuleucel -T
- Hormonal
  - Abiraterone, Enzalutamide, Docetaxel
- Cytotoxic
  - Docetaxel, Cabazitaxel
- DNA Damage
  - Rad 223
  - Olaparib

How Do We Sequence These Agents?

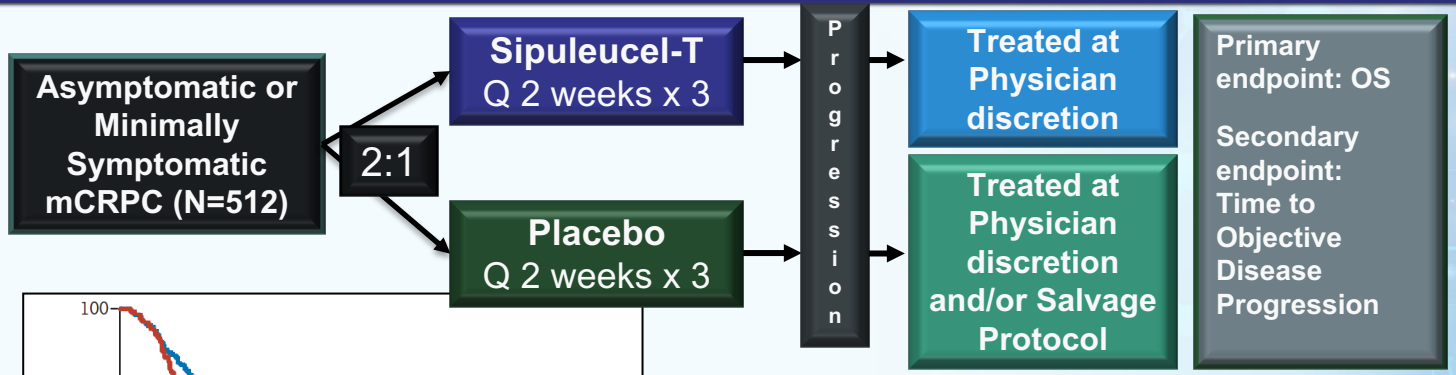
- Clinical Characteristics
  - Symptomatic vs Asymptomatic
  - Visceral vs Non Visceral
  - Pre vs Post Docetaxel
  - Classes of drugs

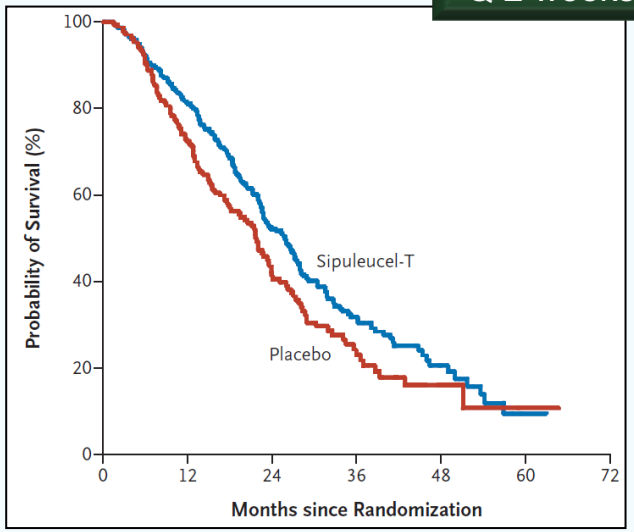
Sipuleucel-T: Autologous APC Cultured With Pap-cytokine Fusion Protein



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

Survival Benefit with Sipuleucel-T in *Asymptomatic/Minimally Symptomatic* mCRPC (IMPACT)





- **4.1 month survival benefit with Sipuleucel-T**
- **Reduction in risk of death: 22.5%**
  (HR = .775; 95% CI, .614-.979; *P* = .032)

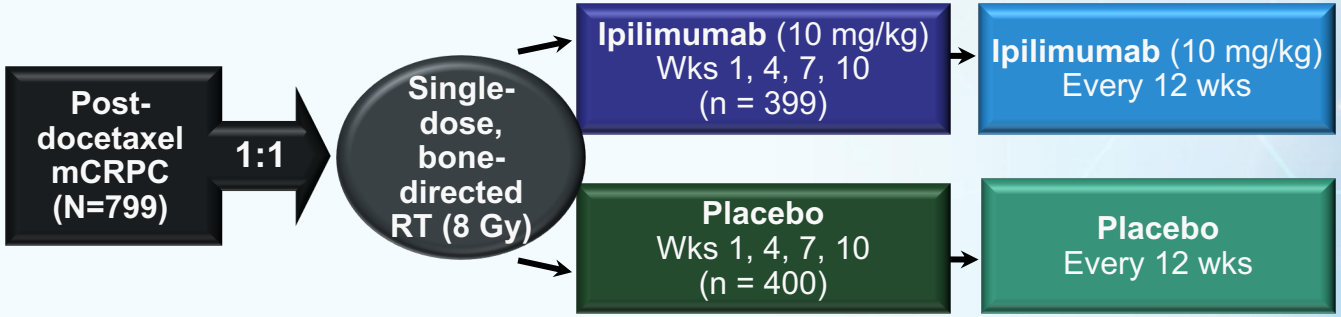
Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422 .

Sipuleucel-T: Lower Baseline PSA is Associated with a Greater Overall Survival Benefit (IMPACT)

	Baseline PSA, ng/mL			
	≤ 22.1 (n = 128)	22.1 – 50.1 (n = 128)	50.1 – 134.1 (n = 128)	134.1 (n = 128)
Median OS, months				
Sipuleucel-T	41.2	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
HR (95% CI)	0.51 (0.31-0.85)	0.74 (0.47-1.17)	0.81 (0.52 -1.24)	0.84 (0.55-1.29)

Schellhammer, PF, et al. *Urology.* 2013;81:1297-1302

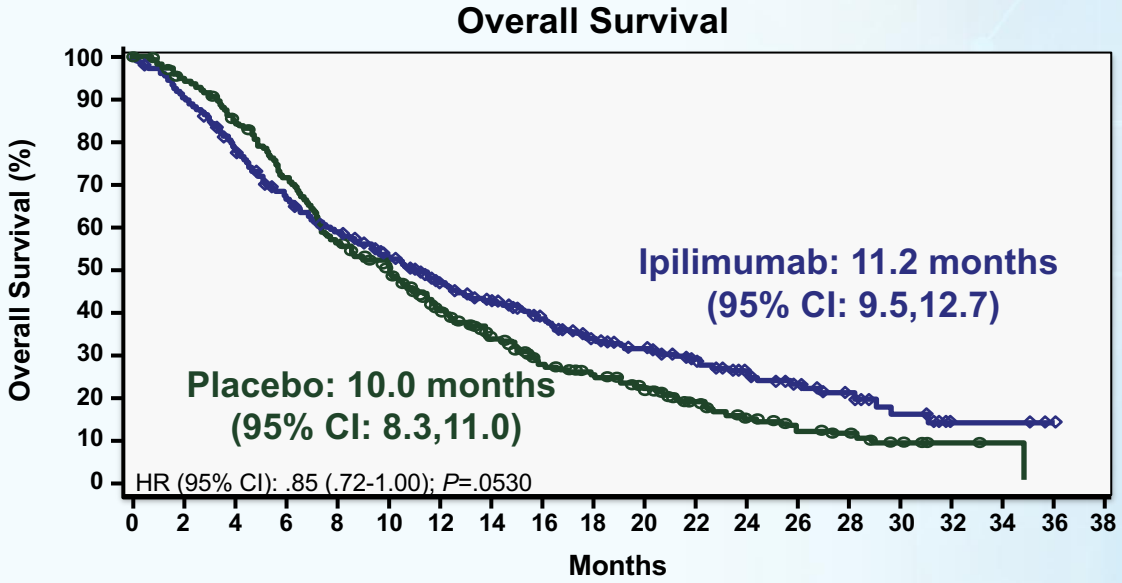
Phase 3 Study of Ipilimumab in *Post-Docetaxel* mCRPC (CA184-043): Study Design



- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival (PFS), safety
- Exploratory endpoint: prostate-specific antigen (PSA) response rate

*ClinicalTrials.gov Identifier: NCT00861614.
ALP=alkaline phosphatase; ECOG=Eastern Cooperative Oncology Group; RT=radiotherapy.
1. Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

Phase 3 Study of Ipilimumab in *Post-Docetaxel* mCRPC (CA184-043)



Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab*
  - The most frequent severe immune-related AEs were diarrhea and colitis

*See poster presentation at this meeting: Beer et al. Abstract ID: 52.

[1]Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

PDL-1 Expression in Prostate Cancer

- Hormone sensitive radical prostatectomy specimens express high levels of PDL-1 in 52.2% of cases[1]
- Patients progressing on enzalutamide have significantly increased PDL-1/2 dendritic cells in blood compared to those progressing on treatment[2]
- Nivolumab treatment in men with CRPC demonstrated no objective responses in 17 patients; 2 patients who had tissue stained for PDL-1 demonstrated no immunoreactivity[3]
- 3/20 samples (15%) had focal areas of PD-L1 positivity, although in only two of the three positive samples was plasma membrane staining clearly observed on malignant epithelial cell[4]

1. Gevensleben, et al. *Clin Cancer Res.* 2016;22:1969-1977.
2. Bishop, et al. *Oncotarget*. 2016;6:234-242.
3. Topalian, et al. *N Engl J Med.* 2012;366:2443-2454.
4. Martin, et al. *Prostate Cancer Prostatic Dis*. 2015;18:325-332.

Pembrolizumab Added to Enzalutamide Progressors

- 5 of 27 (19%) patients had a confirmed PSA response
- 4 of 19 (21%) patients had stable disease >6 months (range 34-64 weeks)
- Median followup 19 weeks (range 3-67 weeks)
- Immune mediated grade ≥3 toxicity: 2 colitis, 1 myositis, 2 hypothyroidism

Responder	Cycle 1	PSA (ng/ml) every 3-weeks and nadir	Measurable Disease at Baseline	Best Radiologic Response	MSI
1	April 2015	70.65 → 11.11 → 1.18 → 0.11 → 0.08	Yes (lymph)	PR	present
2	October 2015	46.09 → 41.22 → 12.99 → 9.89 → 0.02	No	n/a	n/a
3	January 2016	2502.75 → 1.26 → 0.07 →0.01 → <0.01	Yes (liver)	PR	absent
4	March 2016	82.43 → 17.34 → 0.3 → 0.01	No	n/a	n/a
5	June 2016	250 → 88.69 → 5.1 → 0.43 → 0.18*	Yes (liver)	PR	pending

To date, none of the responders have relapsed

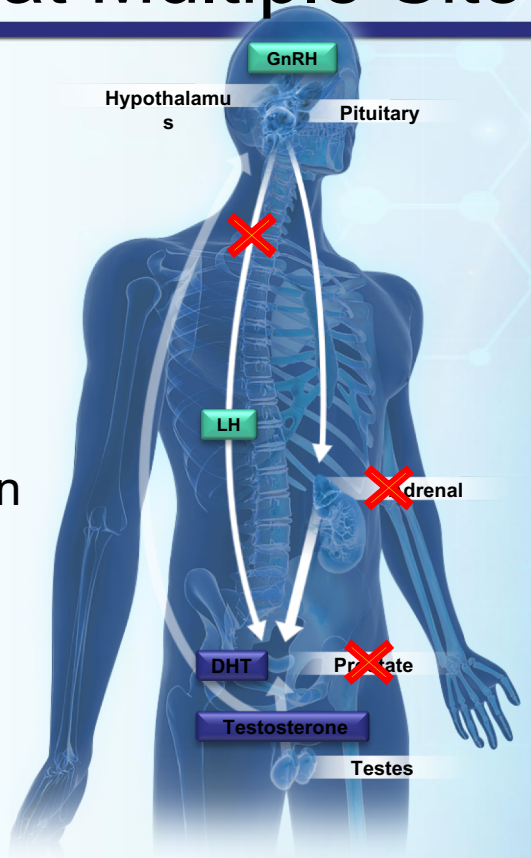
Graff JN et al. *Oncotarget.* 2016; 7:52810-52817. Graff JN et al. *EMSO.* 2016; Abstract 719O.

How Do We Make Immunotherapy Work Better For The Prostate Cancer “Non-inflamed Phenotype?”

- “Non-inflamed” phenotype is very common in prostate cancer
- Immune priming strategies may be necessary to generate tumor antigen-specific T cells
- Chemotherapy or radiation to release neoantigens for dendritic cell priming
- Identification of oncogenic pathways that result in T-cell exclusion
- May need to perform combination therapy

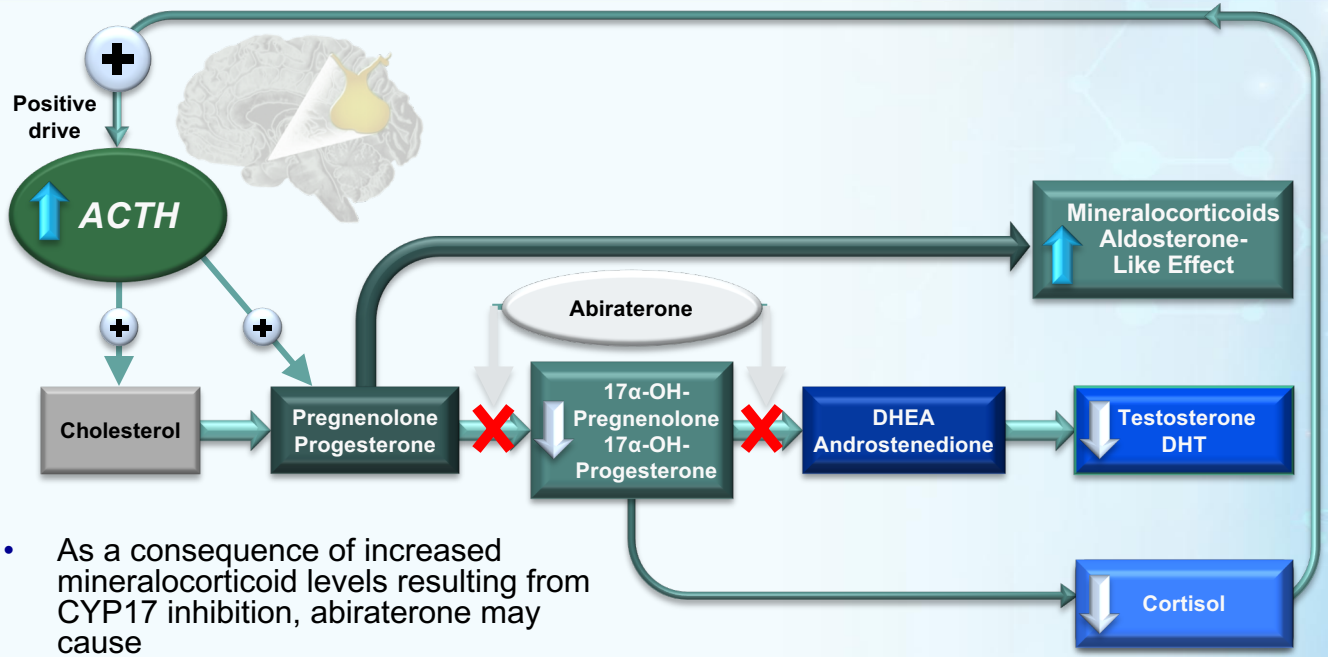
Abiraterone Acetate Inhibits Androgen Production at Multiple Sites

- Abiraterone acetate inhibits the CYP17 enzyme required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissue
- ADTs, such as treatment with GnRH analogs or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in prostatic tumor tissue



Attard G, et al. *J Clin Oncol*. 2008;26:4563-4571.

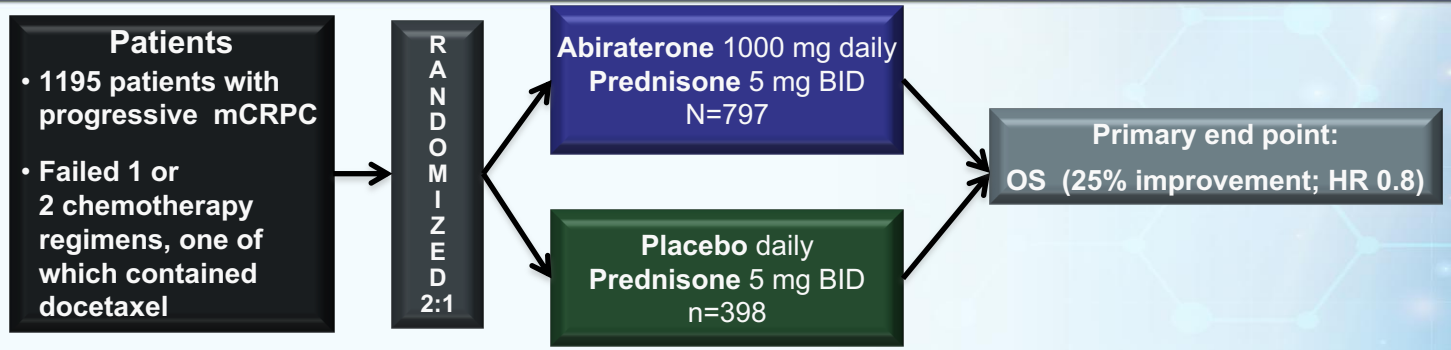
Abiraterone Acetate Mineralocorticoid Effects

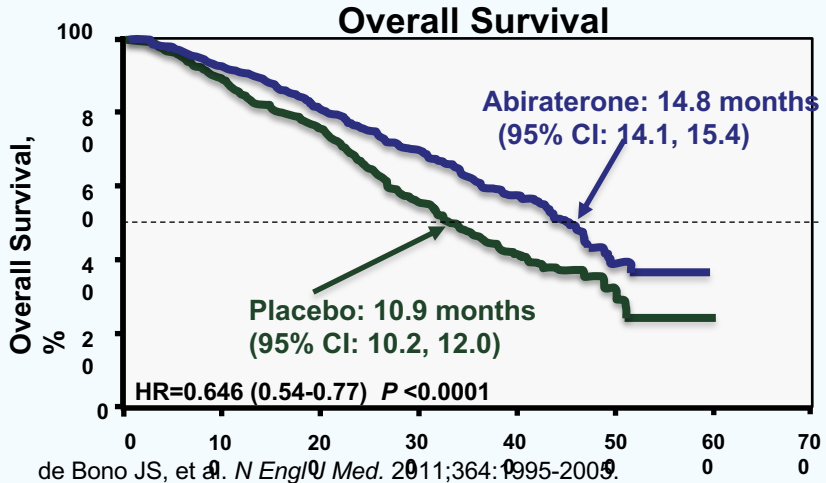


- As a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition, abiraterone may cause
  - **Hypokalemia**
  - **Hypertension**
  - **Fluid retention**

Attard G, et al. *J Clin Oncol*. 2008;26:4563.

Abiraterone Improves OS in *Post-Docetaxel* mCRPC (COU-AA-301)





- **1 Prior Chemo OS: 14.0 mos AA vs 10.3 mos placebo**
- **2 Prior Chemo OS: 15.4 mos AA vs 11.5 mos placebo**

de Bono JS, et al. *N Engl J Med.* 2011;364:1995-2005.

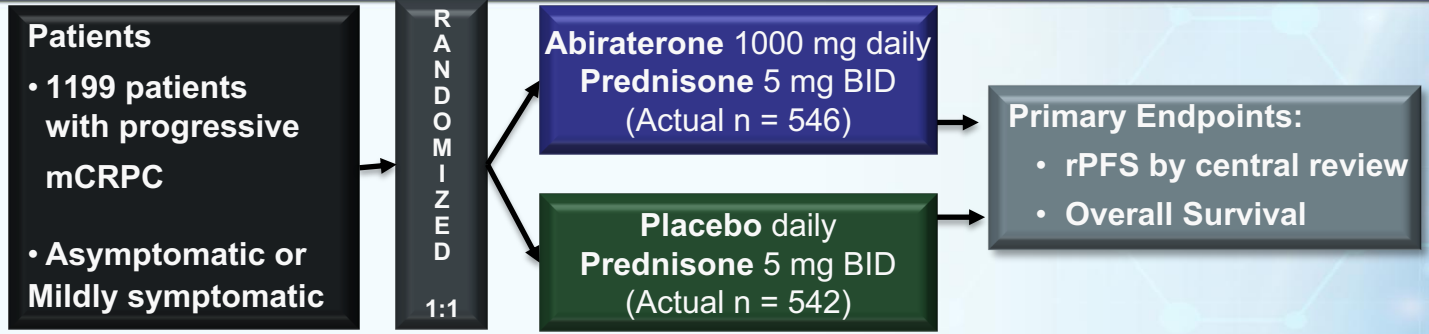
Abiraterone in *Post-Docetaxel* mCRPC (COU-AA-301): AEs of Interest

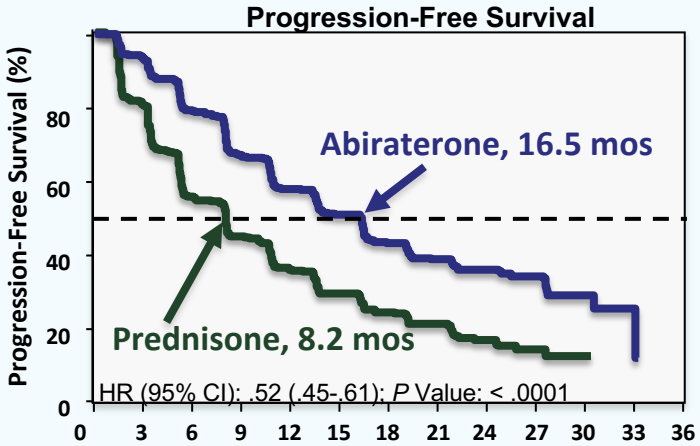
	Abiraterone Acetate + Prednisone (n=791)			Placebo + Prednisone (n=394)		
Adverse Event, no. patients (%)	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Fluid retention and edema	241 (31)	16 (2)	2 (<1)	88 (22)	4 (1)	0
Hypokalemia	135 (17)	27 (3)	3 (<1)	33 (8)	3 (1)	0
Cardiac disorders	106 (13)	26 (3)	7 (1)	42 (11)	7 (2)	2 (<1)
LFT abnormalities	82 (10)	25 (3)	2 (<1)	32 (8)	10 (3)	2 (<1)
Hypertension	77 (10)	10 (1)	0	31 (8)	1 (<1)	0

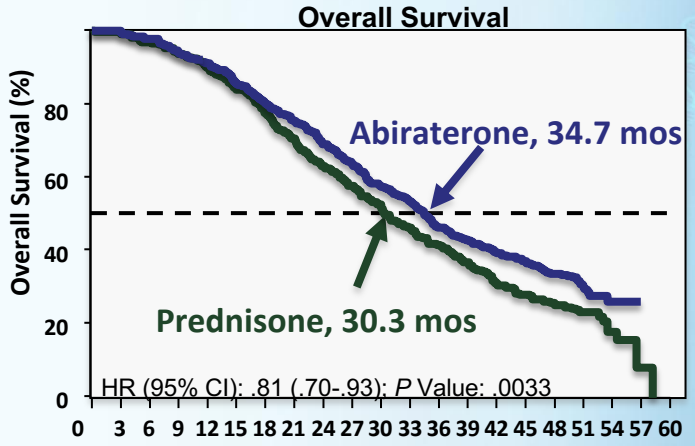
- Adverse events associated with elevated mineralocorticoid levels, cardiac events, and LFT abnormalities were deemed of special interest
- These events were more common in the abiraterone acetate group (55% vs 43%; *P*<.001) but were largely mitigated by the use of low-dose prednisone

de Bono JS, et al. *N Engl J Med.* 2011;364:1995-2005.

Abiraterone Doubled Time to rPFS and Improves OS in *Chemo-naïve m*CRPC (COU-AA-302)

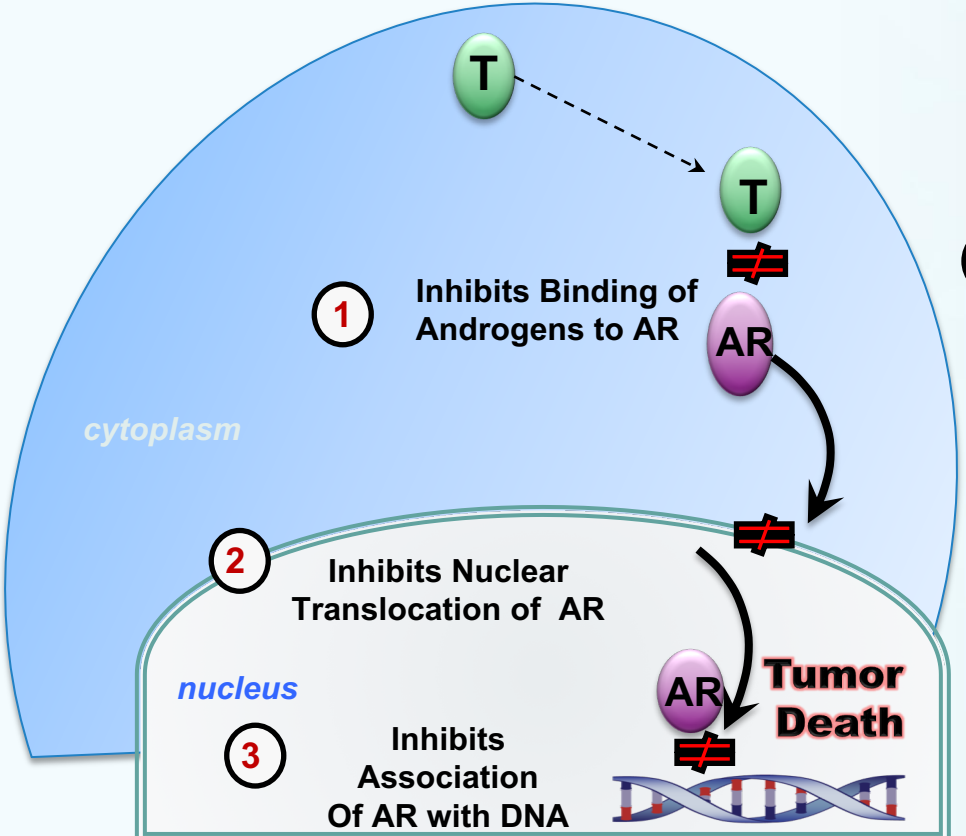






Ryan et al. *N Engl J Med*. 2013;368(2):138-48. Ryan et al. Reported at ESMO 2014 Congress. Abstract 753O.

Enzalutamide Inhibits Androgen Binding

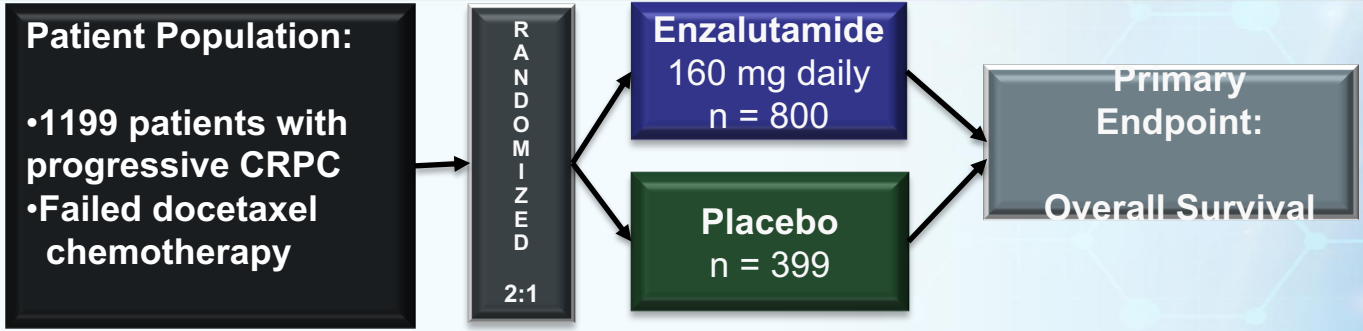


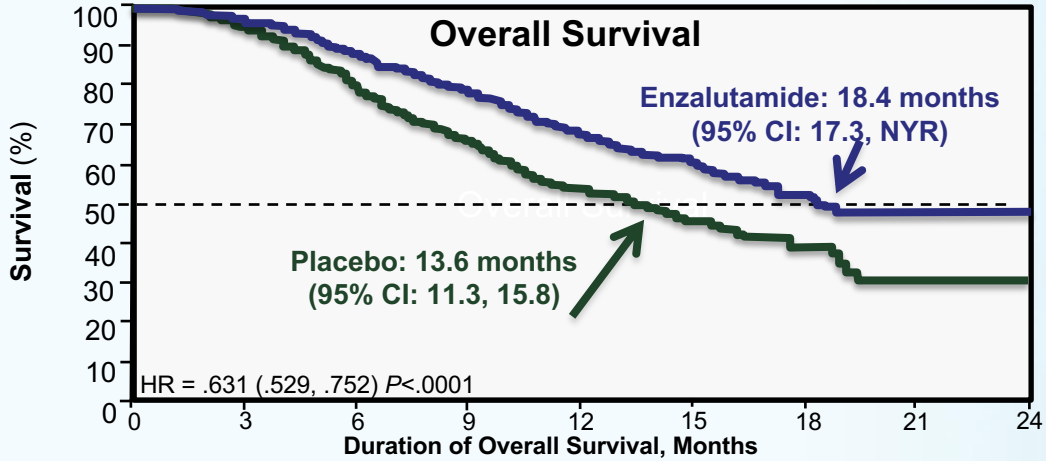
1. Enzalutamide inhibits AR–testosterone binding

2. Enzalutamide receptor inhibition blocks the activational change induced by AR–testosterone binding

3. Enzalutamide inhibits AR–testosterone nuclear translocation and DNA transcription

Enzalutamide Significantly Prolonged Survival in *Post-Docetaxel* CRPC (AFFIRM)





Enzalutamide Prolonged Median Survival by 4.8 Months vs Placebo

Scher HI, et al. *N Engl J Med*. 2012 ;367:1187-1197

Enzalutamide Prolonged rPFS and Reduced Risk of Death in *Chemo-naïve* CRPC (PREVAIL)

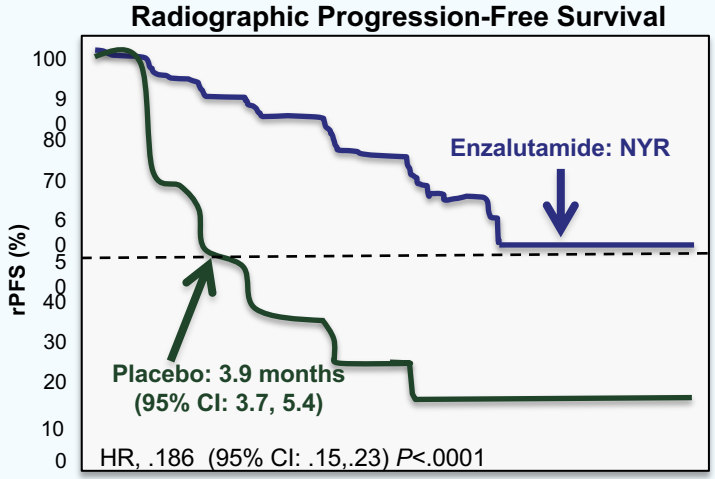
Patients
- 1717 men with progressive mCRPC
- Asymptomatic/mildly symptomatic
- Chemotherapy naïve
- Steroids allowed, but not required

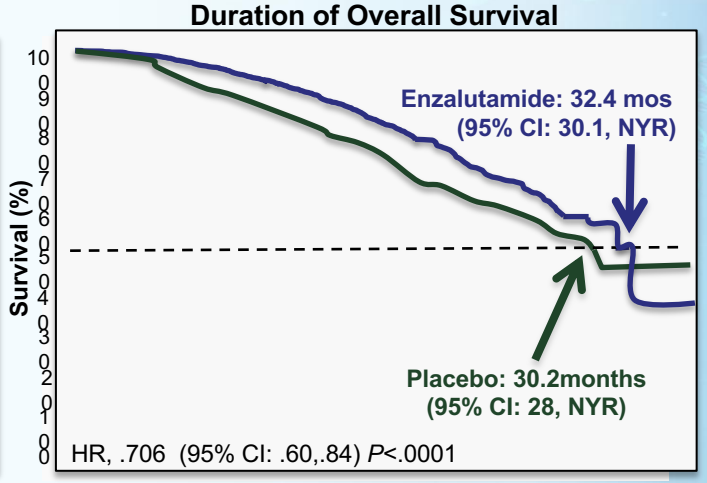
RANDOMIZED 1:1

Enzalutamide
160 mg daily (capsules)
n=872

Placebo
n=845

Primary Endpoints:
- Overall Survival
- Radiographic progression-free survival





Beers T et al. 2014 ASCO Genitourinary Cancers Symposium; San Francisco, CA

Enzalutamide Adverse Events

- Seizures occurred in:
  - **0.9%** of patients receiving enzalutamide who previously received docetaxel (**AFFIRM**)
  - **0.1%** of patients who were chemotherapy-naïve (**PREVAIL**)

Adverse Reactions (≥ 10%) in the Enzalutamide-treated Patients (≥ 2% over placebo)	
• Asthenia/fatigue	• Back pain
• Decreased appetite	• Constipation
• Arthralgia	• Diarrhea
• Hot flush	• Upper respiratory tract infection
• Dyspnea	• Headache
• Peripheral edema	• Musculoskeletal pain
• Decreased weight	• Hypertension
• Dizziness/vertigo	

Beers T et a

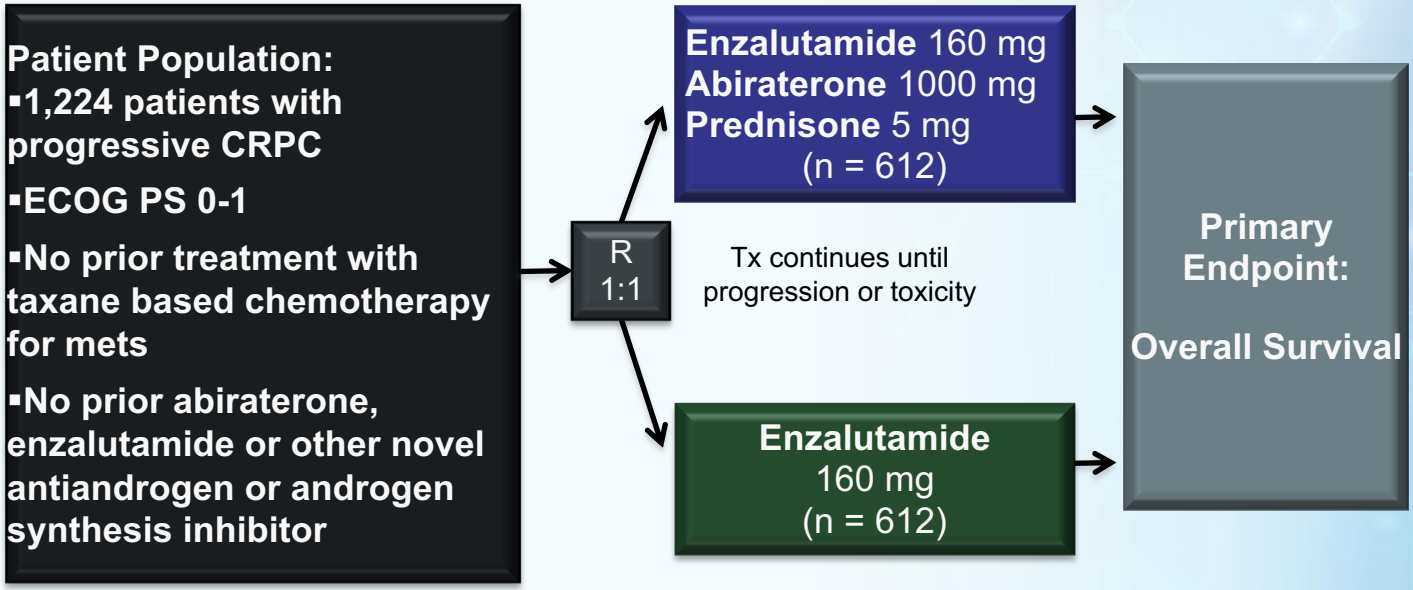
Sequencing of Abiraterone and Enzalutamide

	Prior Docetaxel	N	PSA Decline ≥30%, %	PSA Decline ≥50%, %	Median TTP, mo	Median PFS, mo
Abiraterone after enzalutamide						
Noonan[1]	Y	27	11	4	NR	3.5
Loriot[2]	Y	38	18	8	NR	2.7
Enzalutamide after abiraterone						
Schrader[3]	Y	35	37	29	4.0[a]	–
Bianchini[4]	Y	39	41	13	2.2	2.8
Badrising[5]	Y	61	46	21	4.0	2.8
Cheng[6]	Y	122	39	26	–	–
Azad[7]	Y	68	-	22	4.6	–
Cheng[6]	N	28	40	36	–	–
Azad[7]	N	47	-	26	6.6	–

[a] Responders.

1. Noonan KL et al. *Ann Oncol*. 2013;24:1802-1807. 2. Loriot Y et al. *Ann Oncol*. 2013;24:1807-1812. 3. Schrader AJ et al. *Eur Urol*. 2014;65:30-36. 4. Bianchini D et al. *Eur J Cancer*. 2014;50:78-84. 5. Badrising S et al. *Cancer*. 2014;12:968-975. 6. Cheng et al. *J Clin Oncol*. 2014;32(suppl 4):Abstract 18. 7. Azad et al. *Eur Urol*. 2015; 67:23-29.

Phase 3 Study of Enzalutamide vs Enzalutamide/Abiraterone/Prednisone in *Chemo-naïve* mCRPC (ALLIANCE [A031201]): Study Design



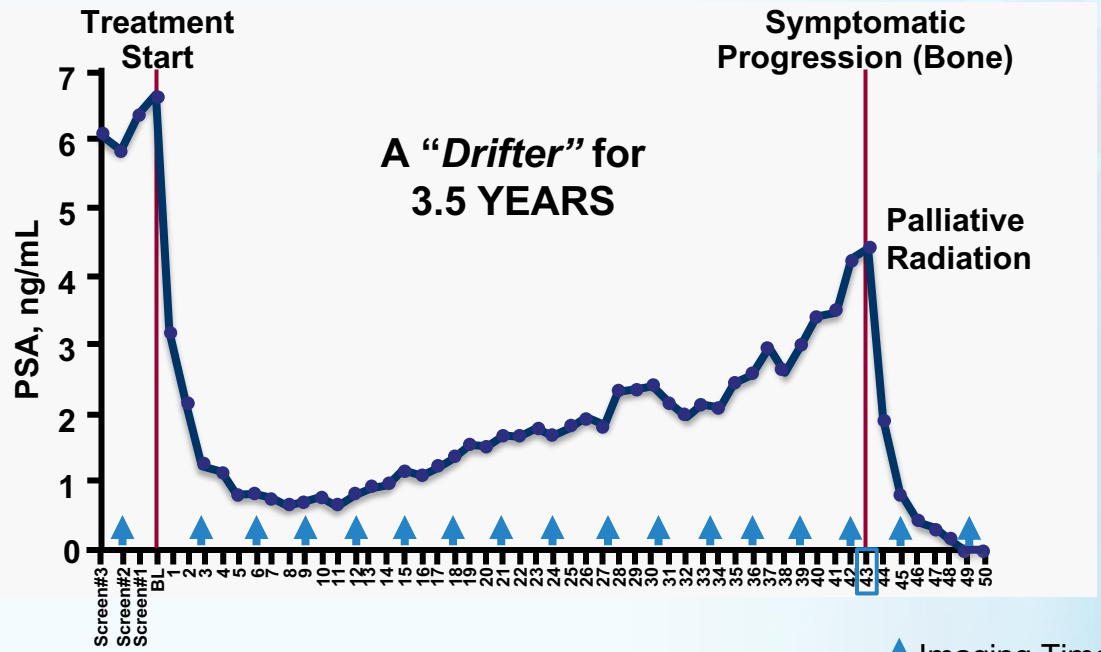
ClinicalTrials.gov Identifier: NCT01949337

Next Generation AR-targeting Agents: Lessons Learned

- Optimal timing to initiate therapy remains undefined
  - Need for clinical judgment in terms of disease biology, level of patient comfort/discomfort, realities of pharmacoeconomics
- When is the appropriate time to discontinue treatment with abiraterone/enzalutamide
  - Biochemical vs clinical/radiographic progression
- Phase III trials of abiraterone and enzalutamide permitted patients to remain on therapy at time of PSA progression until overt radiographic or clinical progression if there was evidence of ongoing clinical benefit

Emerging Resistance May or May Not Require a Change in Therapy

Ensure drug is no longer working before stopping: Treat through rises in PSA in the absence of other signs of progression

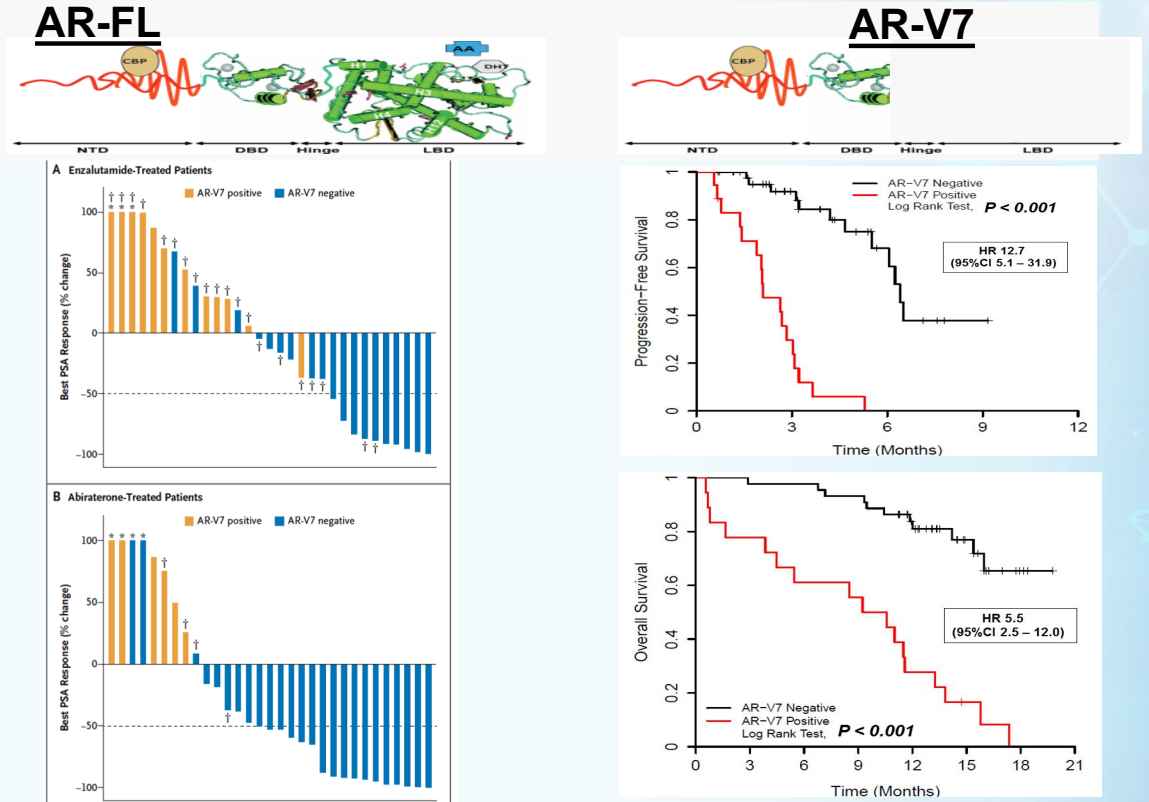


Scher HI et al. *J Clin Oncol*. 2011;29:3685-3704.

Next Generation AR-targeting Agents: Lessons Learned

- Clinical evidence of cross resistance
  - Retrospective studies suggest a much lower response rate and response duration to use of alternative agent (i.e. enzalutamide) in patients progressing on abiraterone and vice versa
  - Some suggestion of impact on docetaxel response rates
- Potential mechanisms of cross resistance to next generation AR pathway agents
  - Glucocorticoid activation of AR
    - Arora, VK et al. *Cell*. 2013;155: 1309–1322
  - Gain of function mutation in DHT
    - Chang, HS et al. *Cell.* 2013;154:1074–1084
  - Androgen Receptor Splice Variants

AR-V7 and Resistance to Abiraterone/Enzalutamide



Antonarakis ES et al. *N Engl J Med.* 2014;371:1028-38

Improved OS with Cabazitaxel in *Post-Docetaxel* mCRPC (TROPIC)

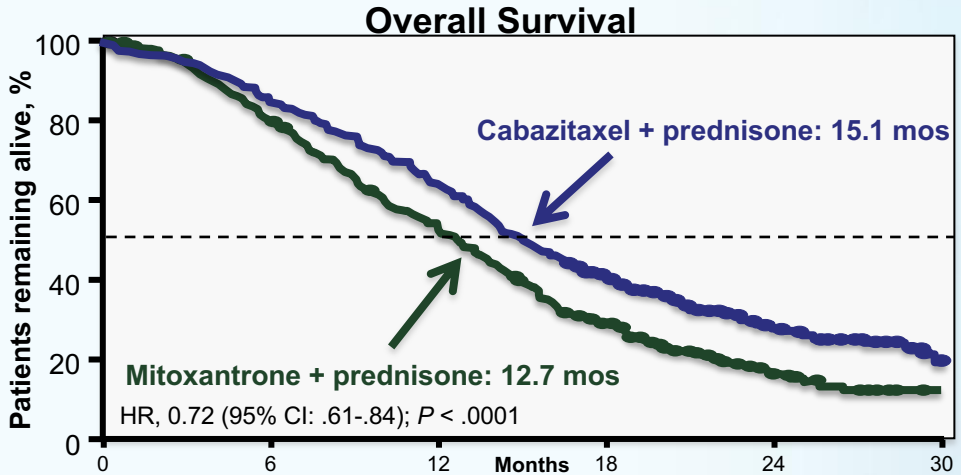
- **mCRPC patients** who progressed during and after treatment with a docetaxel-based regimen (N=755)
- **Stratification**
  - ECOG PS (0,1,vs 2)
  - Measurable vs Non-measurable disease

Cabazitaxel 25 mg/m² q 3 wk **+ prednisone*** for 10 cycles (n=378)

Mitoxantrone 12 mg/m² q 3 wk **+ prednisone*** for 10 cycles (n=377)

Primary endpoint: OS

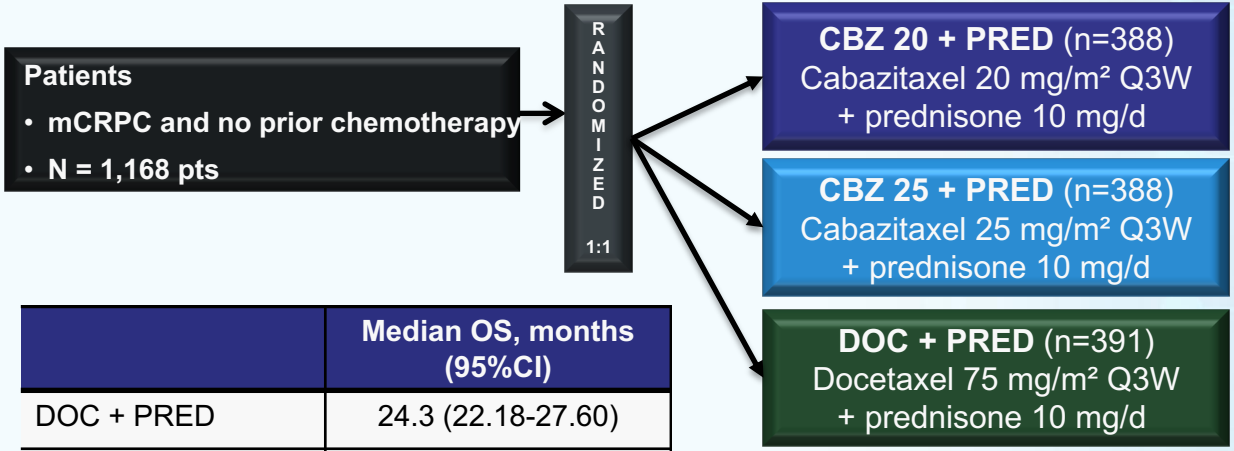
Secondary endpoints: PFS, response rate, and safety



de Bono JS, et al. *Lancet*. 2010;376:1147-1154.

*Oral prednisone/prednisolone: 10 mg daily.

Cabazitaxel No Better Than Docetaxel in *Chemo-naïve* mCRPC (FIRSTANA)



	Median OS, months (95%CI)
DOC + PRED	24.3 (22.18-27.60)
CBZ 20 + PRED	24.5 (21.75-27.20)
CBZ 25 + PRED	25.2 (22.90-29.67)

	HR (95% CI)	*P* Value
CBZ 20 vs DOC	1.009 (.85-1.197)	.9967
CBZ 25 vs DOC	.97 (.819-1.16)	.7574

- Did not demonstrate superiority in OS of CBZ 20 or CBZ 25 vs DOC
- PFS did not differ significantly across treatment arms
- Response rates were similar; tumor response per RECIST 1.1 was significantly higher for CBZ 25

Sartor, et al. *J Clin Oncol.* 2016;34(suppl; abstract 5006).

Summary of Therapies with Survival Benefit for mCRPC

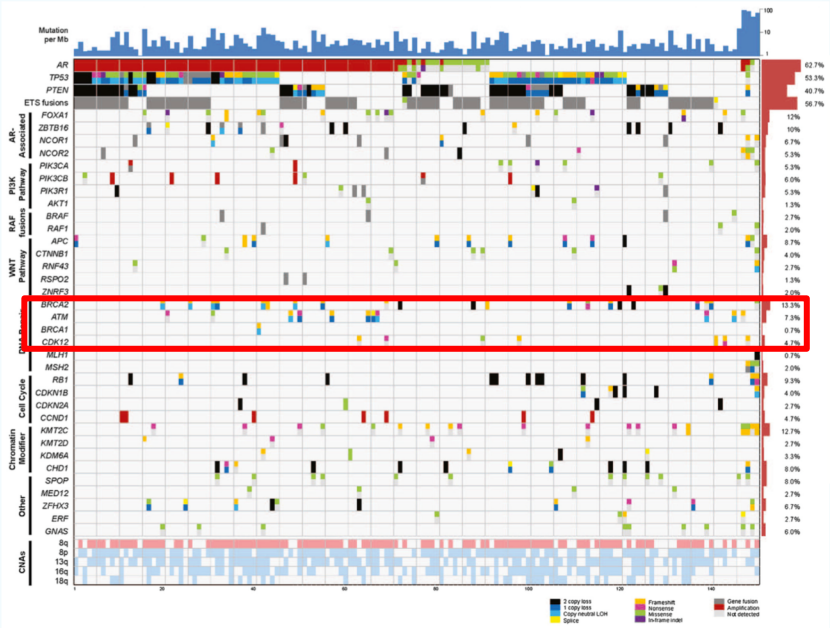
Agent	Indication	Route Schedule	Corticosteroids	Symptoms	Contra-indications	PSA Response	Median OS Benefit, Mos
Sipuleucel-T	Pre/post docetaxel	IV every 2 wk x 3	no	asymptomatic, minimally sx	narcotics for pain, liver mets	No	4.1
Abiraterone	Pre/post docetaxel	oral, empty stomach	yes*	not specified	severe liver dysfx, low K, heart failure	Yes	Post-doc: 4.6 Pre-doc: 4.4
Enzalutamide	Pre/post docetaxel	oral	no	not specified	seizures	Yes	Post-doc: 4.8 Pre-doc: 4.0
Docetaxel	mCRPC	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	Yes	2.4
Cabazitaxel	Post docetaxel	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	Yes	2.4
Radium-223	Post docetaxel or not fit for doc	IV, every 4 wks for 6 doses	not required	symptomatic bone metastases	visceral mets	NR	3.6

* In clinical trials and on FDA label.

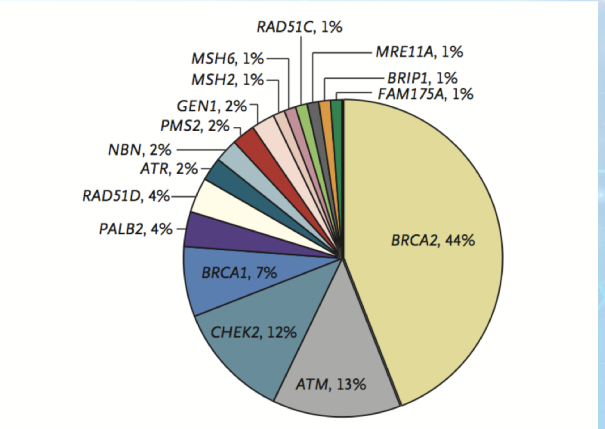
Novel Approaches for Prostate Cancer: DNA Repair and Cancer

- Gene mutations cause DNA repair to be less effective than normal
- Faulty repair can lead to gene mutations
  - Allows mutated cells to survive and replicate - tumor development/growth
- Targeted therapies showing positive pre-clinical and clinical results
- Importance of targeted therapies will increase with improved genetic testing

DNA Repair Gene Alterations are Common in Metastatic Prostate Cancer



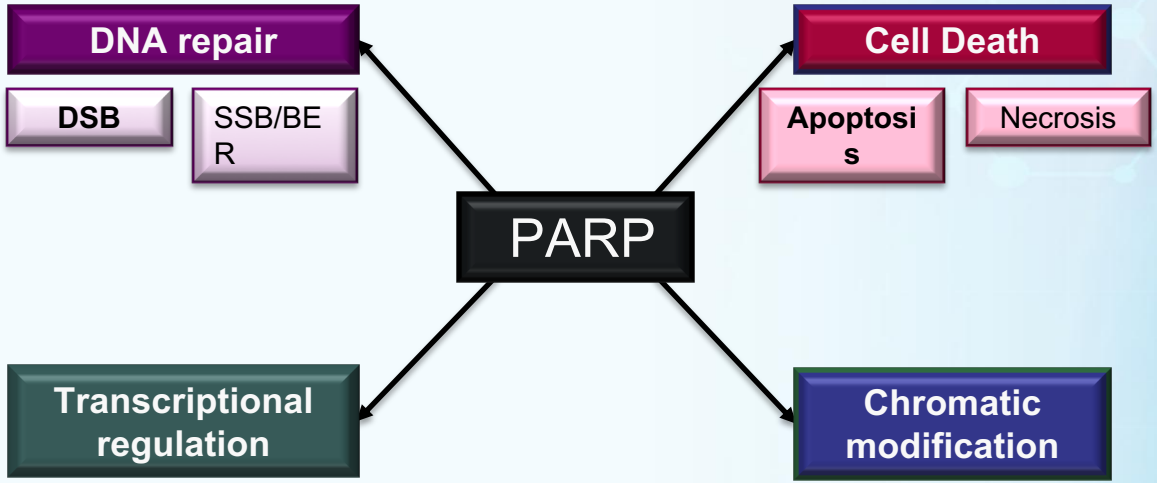
- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations increases with disease progression



- 11.8% of men with metastatic prostate cancer have a germline alteration in 16 DNA damage repair genes
- Age and family history did not affect mutation frequency

Robinson D, et al. *Cell* 2015; 161:1215-28. Pritchard CC, et al. *N Engl J Med.* 2016; 375(5):443-53.

PARP
(Poly-(ADP-ribose) Polymerase)



PARP Inhibitors

- PARP is involved in multiple aspects of DNA repair
- PARP inhibition has durable antitumor activity in men with mCRPC with germline *BRCA2* mutations
- Currently, there are at least five different PARP inhibitors in phase III clinical trials: **olaparib**, **rucaparib**, **niraparib**, **velaparib**, and **talazoparib**
  - Treatment of ovarian, breast, gastric, pancreatic, prostate, lung adenocarcinoma, glioblastoma cancers

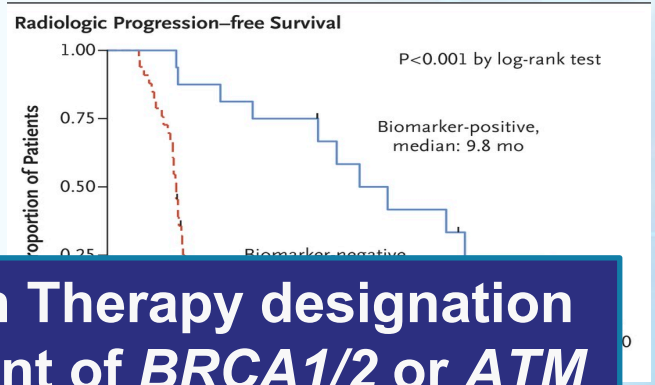
Dhawan, et al. *Oncologist.* 2016 Jun 17. pii: theoncologist.2016-0135

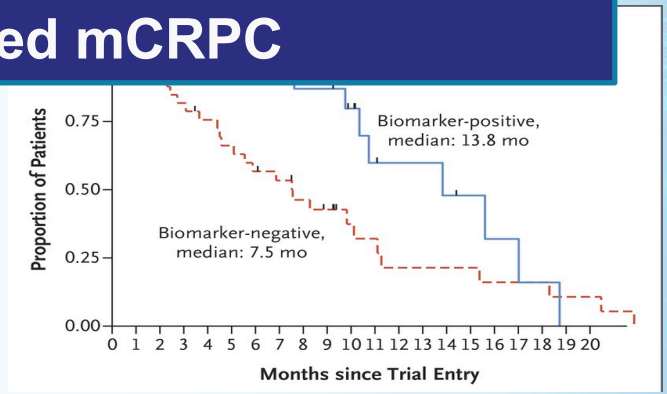
Phase 2 Study of Olaparib in mCRPC (TOPARP-A)

- Mutations
  - 14/16 (88%) of patients **with** a DNA repair alteration had a response
  - 2/33 (6%) of patients **without** a DNA repair alteration had a response

Granted Breakthrough Therapy designation by US FDA for treatment of *BRCA1/2* or *ATM* gene mutated mCRPC

M	
M	
ORR (partial or complete)	32.7%
Duration of response	9 months
Reduction of PSA ≥50%	22% (14/49)
Confirmed reduction in CTC < 5 cells/7.5 mL	29% (14/49)





Mateo, et al. *N Engl J Med.* 2015; 373:1697-1708.

Conclusions

- Rapid development and FDA approval of multiple agents over the last 5 years has outpaced our ability to understand/study optimal integration/combination/sequences in the management of patients with mCRPC
- Clinically apparent cross resistance to next generation AR pathway inhibitors will require both clinical and translational studies to determine optimal utilization of these agents
- Genomic profiling is expanding our options for targeted and personalized medicine