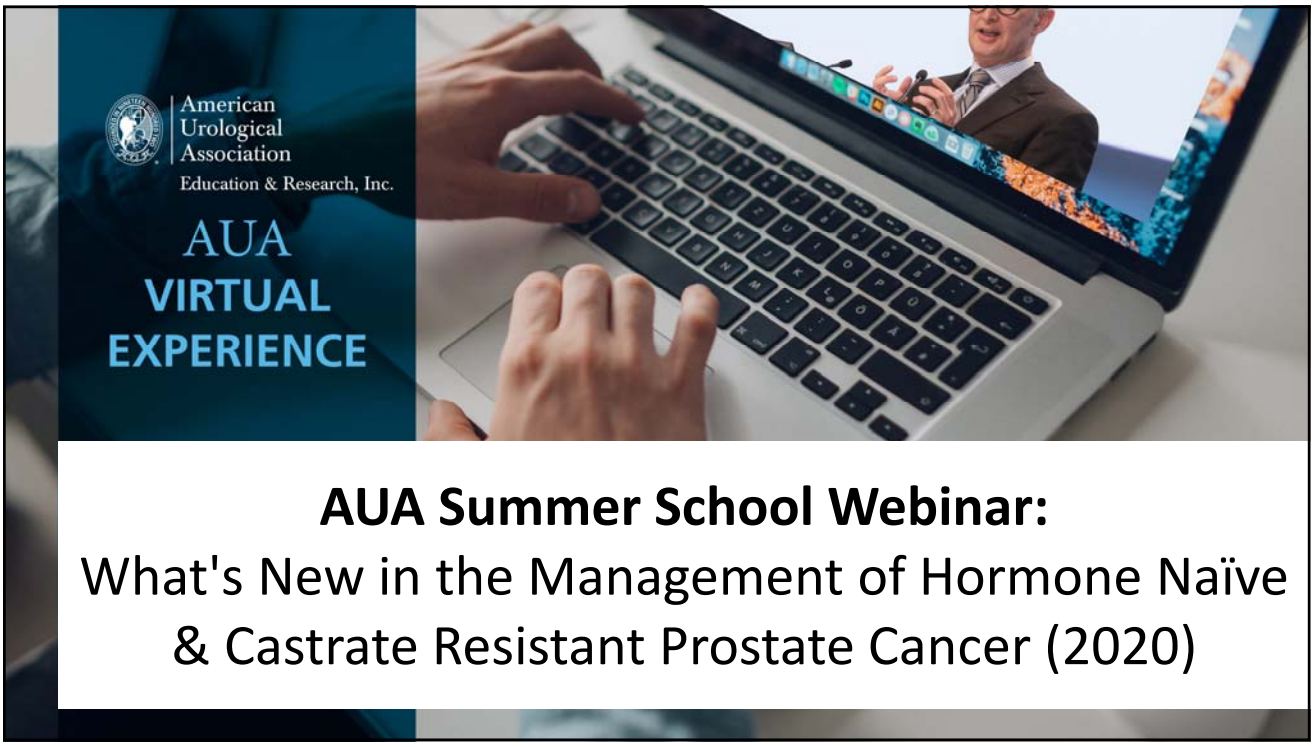

AUA Summer School Webinar:

What's New in the Management of Hormone Naïve & Castrate Resistant Prostate Cancer (2020)

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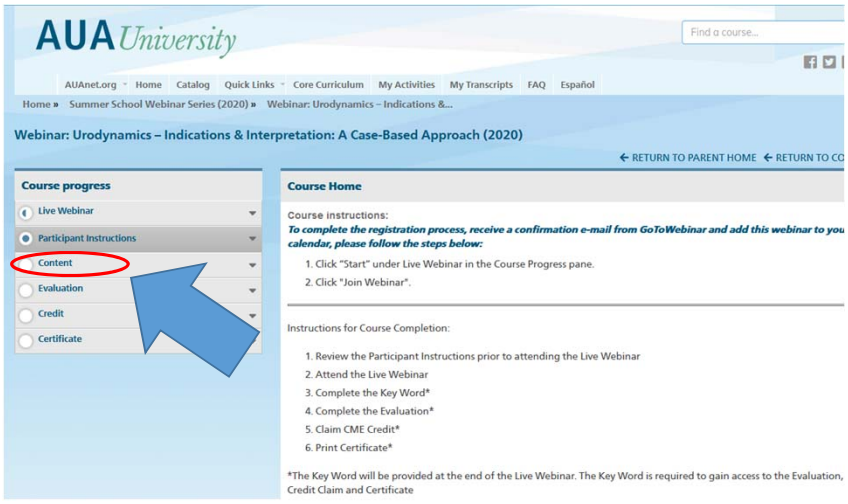

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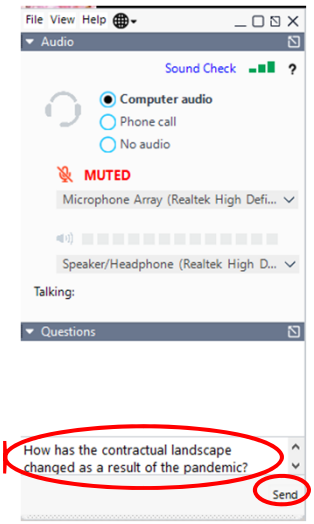

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Acknowledgements

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Course Director

Judd W. Moul, MD, FACS

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Knowledge Assessment

Question 1

According to the 2020 AUA guidelines for advanced prostate cancer, which of the following statements is **NOT** true regarding treatment options for men with newly diagnosed metastatic hormone sensitive prostate cancer?

A) In addition to androgen deprivation therapy, treatment intensification should be considered with enzalutamide, apalutamide, docetaxel, or abiraterone/prednisone.
(Guideline #15)

B) 6 cycles of Docetaxel and ADT should be considered in high or low volume de novo disease based on the interim and final analysis of the CHAARTED clinical trial. (Guideline #10 - see discussion)

C) ADT and first-generation antiandrogens (bicalutamide,flutamide,nilutamide) are no longer considered the standard of care for this disease state. (Guideline #17)

D) ADT and Abiraterone/ prednisone demonstrated significant improvement in overall survival and progression free survival in the interim analysis as well as the final analysis of the LATITUDE clinical trial. (Guideline #15)

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Question 2

A 71 –year-old pediatric surgeon who retired to a home in the mountains, fell off a ladder and fractured his wrist and ankle. Was not intoxicated but admits to 4 oz, ETOH per day. Never had a seizure. Moderate voiding dysfunction. Imaging demonstrated 3 osteoblastic lesions at T7, L2, and L5 .PSA 113. CT scan C/A/P negative for visceral or soft tissue disease. T7 bone biopsy positive for metastatic CaP. Liver enzymes slightly elevated but bilirubin negative. Germline testing positive for BRCA1.
You diagnose low volume mHSPC. In addition to ADT you would treat him with:

A) Enzalutamide or apalutamide
B) Abiraterone/prednisone and prostate RT
C) 6 cycles docetaxel
D) Olaparib or rucaparib

Question 3

A fit 68 yo M with bone mCRPC who received abiraterone acetate progressed by PSA after 8 months, then receives docetaxel X6 with a transient response in pain symptoms and PSA before both the PSA begins to rise again and his pain symptoms recur. His restaging bone and CT scans reveal no visceral lesions but multiple new bone metastases and multiple 3-5 cm enlarged pelvic and retroperitoneal lymph nodes. What is the best treatment choice for this patient?

A) Enzalutamide
B) Radium-223
C) Sipuleucel-T
D) Cabazitaxel

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Question 4

A 53 yo M with mCRPC has previously received abiraterone acetate, docetaxel, radium-223 and cabazitaxel. His disease is progressing and his most recent restaging imaging reveals multiple new 1-3 cm liver metastases. His ECOG performance status is 1, and he tells you he would like to try more therapy. You perform a metastatic biopsy of a liver metastasis and you find a MSH2 alteration with accompanying microsatellite instability. This opens the door for which of the following treatment options?

A) Sipuleucel-T
B) Atezolizumab
C) Pembrolizumab
D) Olaparib

Question 5

M0 CRPC is defined by which true criteria?

A) PET scan with no detectable metastatic disease
B) Serum Testosterone less than 20 while on continuous ADT
C) Rising PSA while on continuous ADT
D) Nodal disease outside the true pelvis

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Faculty

Lawrence I. Karsh, MD, FACS
Evan Y. Yu, MD

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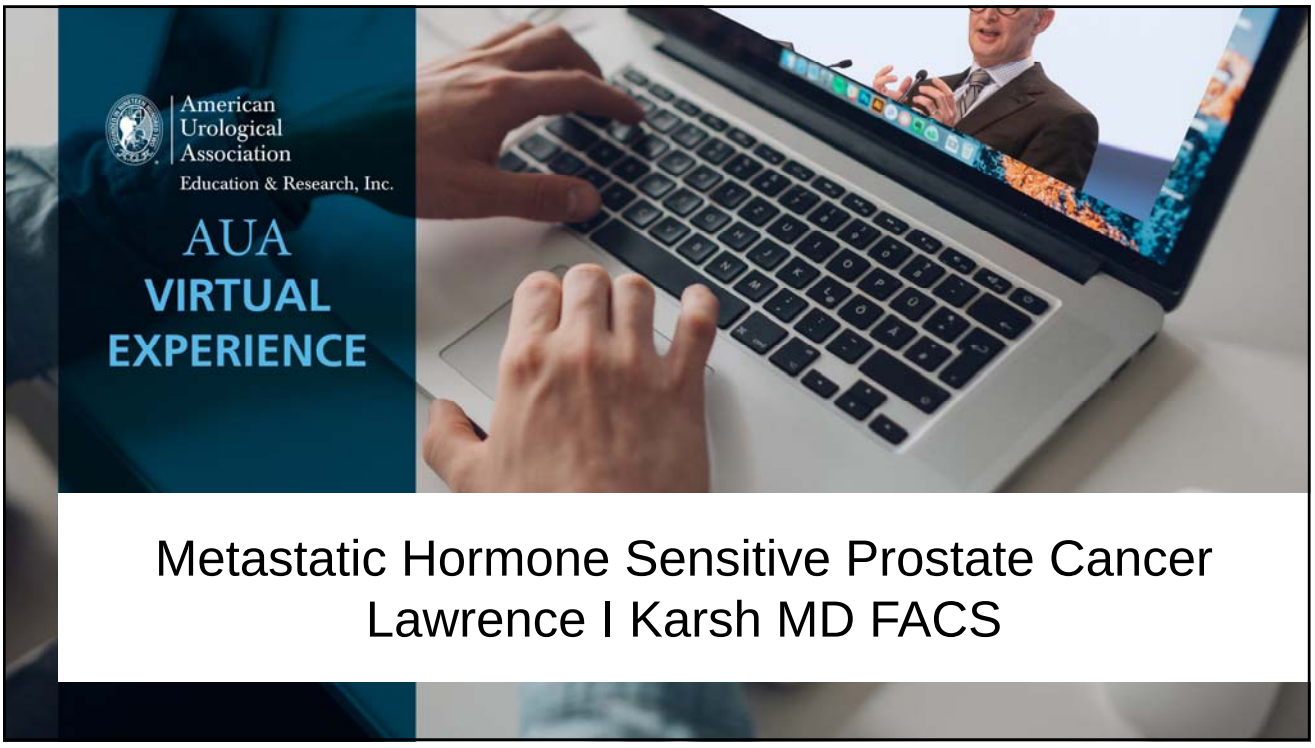
Learning Objectives

After participating in this course, attendees will be able to:

1. List the three main advanced prostate cancer disease states (HSMPC); M0 CRPC and M1 CRPC) and be able to identify these patients in urologic practice.
2. Identify FDA-hormonal and non-hormonal therapies for use in each of these three disease states: HSMPC, M0 CRPC, M1 CRPC.
3. Demonstrate the safe use and unique mechanism of action and side effects of new and existing agents.
4. Explain the sequencing of novel therapies and be able to identify patient progression of disease by PSA, imaging and signs and symptoms.
5. Work in team care including urologists, advanced practice providers, oncology nursing, oncology pharmacy, medical oncology and radiation oncology and their support staffs.



Disclosures

Consultant

- Astellas, Aurora Oncology Inc. Bayer, Dendreon ,Ferring/Fergene,Genentech, Genomic Health, Janssen, Merck, Pfizer, Urogen,UROGPO,Vaxiion,3D Biopsy,

Speaker

- Astellas, Astra Zeneca, Bayer, Clovis Oncology, Janssen, Pfizer

PI Clinical Trials

- Allergan, Astellas, Astra Zeneca, Bayer, BMS, Dendreon, Exact Science, Epizyme, FKD Therapies, Ferring, Genome DX Biosciences, Genomic Health, Hinova, Janssen, Merck, Myovant, Nucleix, Pfizer, Precision Biopsy, Precision Med, Roche-Genetech, Siemens, Urogen

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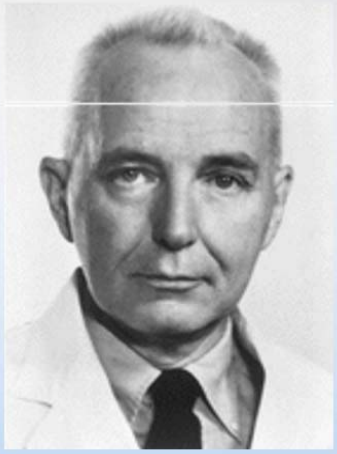

STUDIES ON PROSTATIC CANCER

II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND

CHARLES HUGGINS, M.D.
R. E. STEVENS JR., M.D.
AND
CLARENCE V. HODGES, M.D.
CHICAGO

Huggins C, et al. Arch Surg. 1941;43:209-215.

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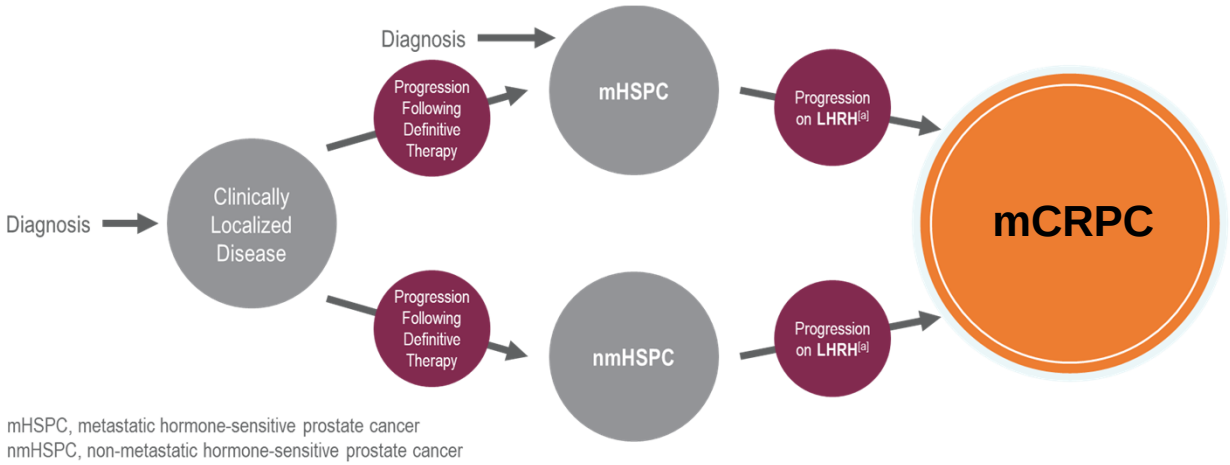
The Continuum of Prostate Cancer Progression[1, 2, 3]



mHSPC, metastatic hormone-sensitive prostate cancer
nmHSPC, non-metastatic hormone-sensitive prostate cancer

[a] Or after bilateral orchiectomy.[3]

1. Scher HI et al. J Clin Oncol 2016;34(12):1402-18. 2. Scher HI et al. PLoS One 2015;10(10):e0139440. 3. American Urological Association. Castration-resistant prostate cancer: AUA guideline (2018). www.auanet.org/guidelines/prostate-cancer-castration-resistant-(2013-amended-2018).

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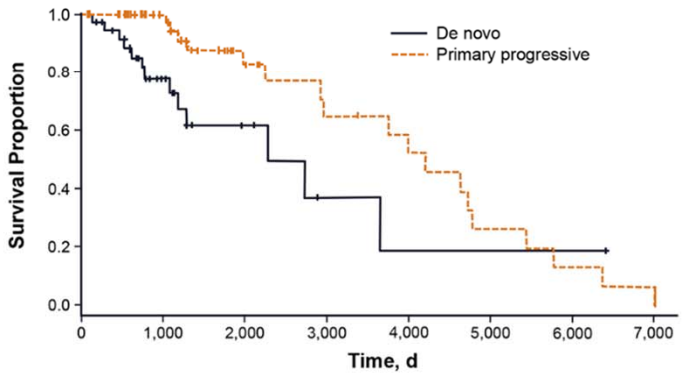
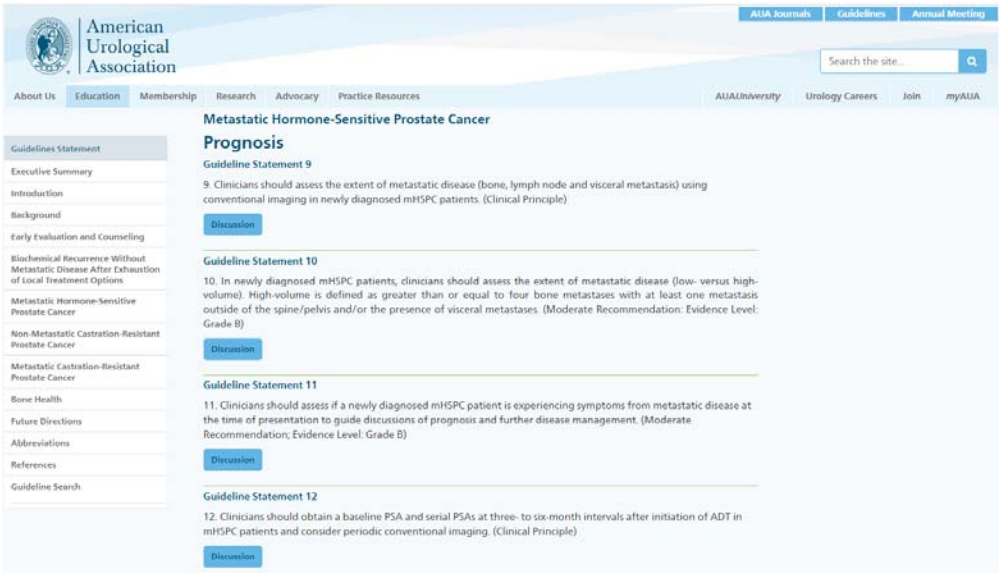
Differences Between De Novo vs Progressive Metastatic Prostate Cancer[1]

OS for De Novo vs Primary Progressive Disease From Time of Metastases



1. Finianos A et al. *Clin Genitourin Cancer*. 2017. pii:S1558-7673(17)30247-1. [Epub ahead of print].



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Metastatic Hormone-Sensitive Prostate Cancer

Prognosis

Guideline Statement 9

9. Clinicians should assess the extent of metastatic disease (bone, lymph node and visceral metastasis) using conventional imaging in newly diagnosed mHSPC patients. (Clinical Principle)

Discussion

Guideline Statement 10

10. In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (low- versus high-volume). High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases. (Moderate Recommendation: Evidence Level: Grade B)

Discussion

Guideline Statement 11

11. Clinicians should assess if a newly diagnosed mHSPC patient is experiencing symptoms from metastatic disease at the time of presentation to guide discussions of prognosis and further disease management. (Moderate Recommendation; Evidence Level: Grade B)

Discussion

Guideline Statement 12

12. Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic conventional imaging. (Clinical Principle)

Discussion

- Guidelines Statement
- Executive Summary
- Introduction
- Background
- Early Evaluation and Counseling
- Biochemical Recurrence Without Metastatic Disease After Exhaustion of Local Treatment Options
- Metastatic Hormone-Sensitive Prostate Cancer
- Non-Metastatic Castration-Resistant Prostate Cancer
- Metastatic Castration-Resistant Prostate Cancer
- Bone Health
- Future Directions
- Abbreviations
- References
- Guideline Search

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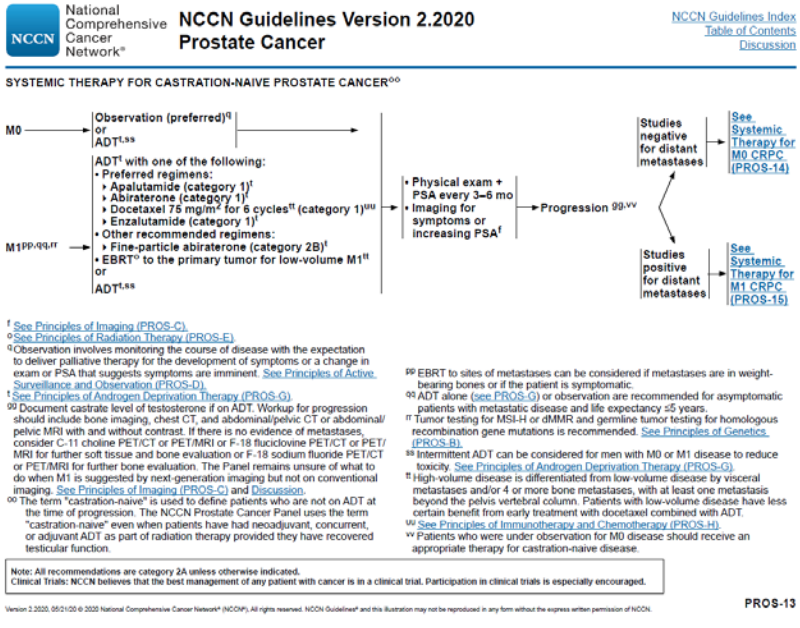

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR CASTRATION-NAIVE PROSTATE CANCER[oo]

M0 → Observation (preferred)[q] or ADT[t,ss]

M1[pp,qq,rr] → ADT[t] with one of the following:
- Preferred regimens:
  - Apalutamide (category 1)[t]
  - Abiraterone (category 1)[t]
  - Docetaxel 75 mg/m² for 6 cycles[tt] (category 1)[uu]
  - Enzalutamide (category 1)[t]
- Other recommended regimens:
  - Fine-particle abiraterone (category 2B)[t]
- EBRT[o] to the primary tumor for low-volume M1[tt] or ADT[t,ss]

→ Physical exam + PSA every 3–6 mo
→ Imaging for symptoms or increasing PSA[f]
→ Progression [pp,vv]

Studies negative for distant metastases → See Systemic Therapy for M0 CRPC (PROS-14)

Studies positive for distant metastases → See Systemic Therapy for M1 CRPC (PROS-15)

[f] See Principles of Imaging (PROS-C).
[o] See Principles of Radiation Therapy (PROS-E).
[q] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-D).
[t] See Principles of Androgen Deprivation Therapy (PROS-G).
[pp] Document castrate level of testosterone if on ADT. Workup for progression should include bone imaging, chest CT, and abdominal/pelvic CT or abdominal/pelvic MRI with and without contrast. If there is no evidence of metastases, consider C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI for further soft tissue and bone evaluation or F-18 sodium fluoride PET/CT or PET/MRI for further bone evaluation. The Panel remains unsure of what to do when M1 is suggested by next-generation imaging but not on conventional imaging. See Principles of Imaging (PROS-C) and Discussion.
[oo] The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.
[qq] EBRT to sites of metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[rr] ADT alone (see PROS-G) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.
[tt] Tumor testing for MSI-H or dMMR and germline tumor testing for homologous recombination gene mutations is recommended. See Principles of Genetics (PROS-B).
[ss] Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G).
[tt] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
[uu] See Principles of Immunotherapy and Chemotherapy (PROS-H).
[vv] Patients who were under observation for M0 disease should receive an appropriate therapy for castration-naive disease.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PROS-13

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Metastatic disease + Have not progressed on ADT OR have not started ADT = mCSPC

Other terms used to describe metastatic castration-sensitive prostate cancer (mCSPC) in medical literature include the following[1]:

- **Metastatic hormone-sensitive prostate cancer (mHSPC)[2]**
- Metastatic hormone-naïve prostate cancer[3]
- Metastatic castration-naïve prostate cancer[4]
- Metastatic non-castrate prostate cancer[3]

Regardless of which term is used, these patients have metastatic prostate cancer and have not yet developed castration resistance*[1-3]

*Castration resistance is defined as a serum testosterone level ≤50 ng/dL with biochemical progression (PSA increase ≥25% and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later) or radiographic progression (the appearance of new lesions).[5,6]

1. Hahn AW, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:363-371. **2.** Kyriakopoulos CE, et al. *J Clin Oncol*. 2018;36(11):1080-1087. **3.** Morris MJ, et al. *J Clin Oncol*. 2018;36(15):1521-1539. **4.** Chi KN, et al. *Lancet Oncol*. 2018;19(2):194-206. **5.** Scher HI, et al. *J Clin Oncol*. 2016;34(12):1402-1418. **6.** Cornford P, et al. *Eur Urol*. 2017;71(4):630-642.

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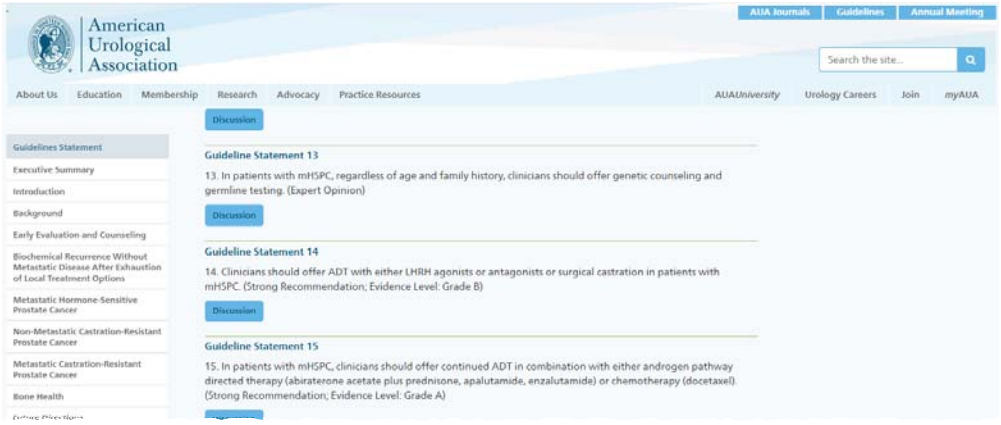

Guideline Statement 13

13. In patients with mHSPC, regardless of age and family history, clinicians should offer genetic counseling and germline testing. (Expert Opinion)

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Guideline Statement 15

15. In patients with mHSPC, clinicians should offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (Strong Recommendation; Evidence Level: Grade A)

Approved Agents for mCSPC

	HR (95% CI) for OS	Trial
Docetaxel	0.72 (0.59-0.89) *P* = .0018	CHAARTED[1]
Docetaxel	0.78 (0.66-0.93) *P* = .006	STAMPEDE[2]
Abiraterone	0.66 (0.56-0.78) *P* <.0001	LATITUDE[3]
Abiraterone	0.63 (0.52-0.76) *P* <.001	STAMPEDE[4]
Enzalutamide	0.67 (0.52-0.86) *P* = .002	ARCHES[5]
Apalutamide	0.67 (0.51-0.89) *P* = .0053	TITAN[6]

1. Kyriakopoulos CE et al. *J Clin Oncol*. 2018;36:1080-1087. 2. James ND et al. *Lancet*. 2016;387:1163-1177.
3. Fizazi K et al. *N Engl J Med*. 2017;377:352-360. 4. James ND et al. *N Engl J Med*. 2017;377:338-351.
5. Armstrong et al. Journal of Clinical Urology 37, no32 2974-2986
6.Smith

Characteristics of Enrolled Patients: CHAARTED/LATITUDE/STAMPEDE

CHAARTED
- High volume: presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis
- Low volume

LATITUDE
- Required to have at least 2 high-risk prognostic features
- Gleason score ≥8, ≥3 bone lesions, measurable visceral metastasis
- Similar to high volume group of CHAARTED

STAMPEDE
- Newly diagnosed metastatic, node-positive, or high-risk locally advanced with at least two: T3/T4, Gleason score of 8 to 10, and/or PSA level ≥40 ng/mL

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Intensified up-front Therapy for Prostate Cancer

Is Earlier Better?

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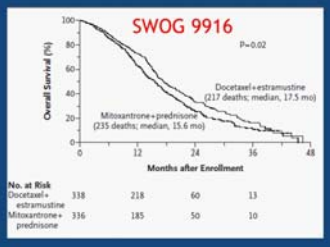
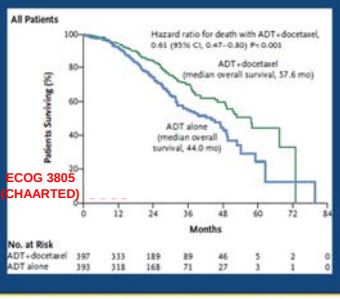
The Revolution in Prostate Cancer Therapy Begins 2015

- Before CHAARTED we "saved arrows in our quiver"
  - SWOG 9916[1] and TAX 327[2] found docetaxel prlonged median survival ~ 2 months in mCRPC
- In ECOG 3805 (CHAARTED)[3], up-front docetaxel increased median overall survival by **13.6 months**
  - **Confirmed simultaneously by STAMPEDE[4]**

HITTING PROSTATE CANCER HARD, EARLY IS CRITICAL TO LONG-TERM CONTROL





ECOG 3805 (CHAARTED)

1. Petrylak et al NEJM 2004; 351:1513 2. Tannock et al NEJM 2004; 351:1502
3. Sweeney et al NEJM 2015; 373:737 4. James et al Lancet 2016; 387:1163

Presented by Tanya B. Dorff MD ASCO 2019

2

CHAARTED: Randomized Trial Assessing Addition of Docetaxel to ADT[1]

N = 790
Median age 63 y

Stratification
- Extent of metastasis: High vs low
- Age: ≥70 vs <70 y
- ECOG PS: 0-1 vs 2
- CAB >30 days: yes vs no
- SRE prevention: yes vs no
- Prior adjuvant ADT: ≤12 mo vs >12 mo

R

Arm A
ADT + docetaxel 75 mg/m² Q21D for maximum of 6 cycles

Evaluate Q3W while receiving docetaxel and at week 24 then Q12W

Arm B
ADT alone

Evaluate Q12W

Follow for time to progression and OS

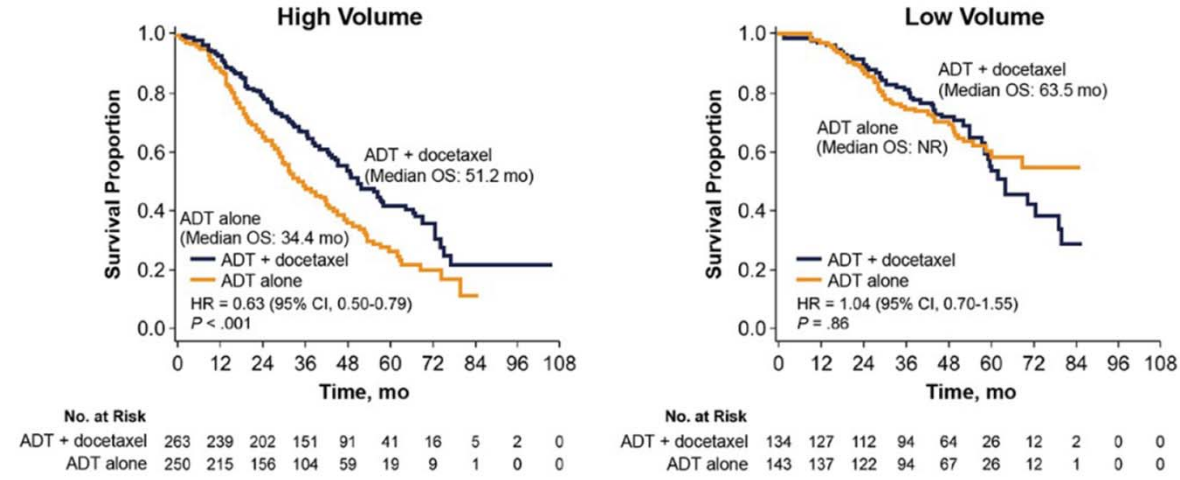
Chemotherapy at investigator's discretion at progression

- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone
- High volume defined as visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis
- **Primary endpoint:** OS

1. Sweeney CJ et al. *N Engl J Med*. 2015;373:737-746.

Chemohormonal Therapy in mHSPC: CHAARTED[1] (Cont'd)

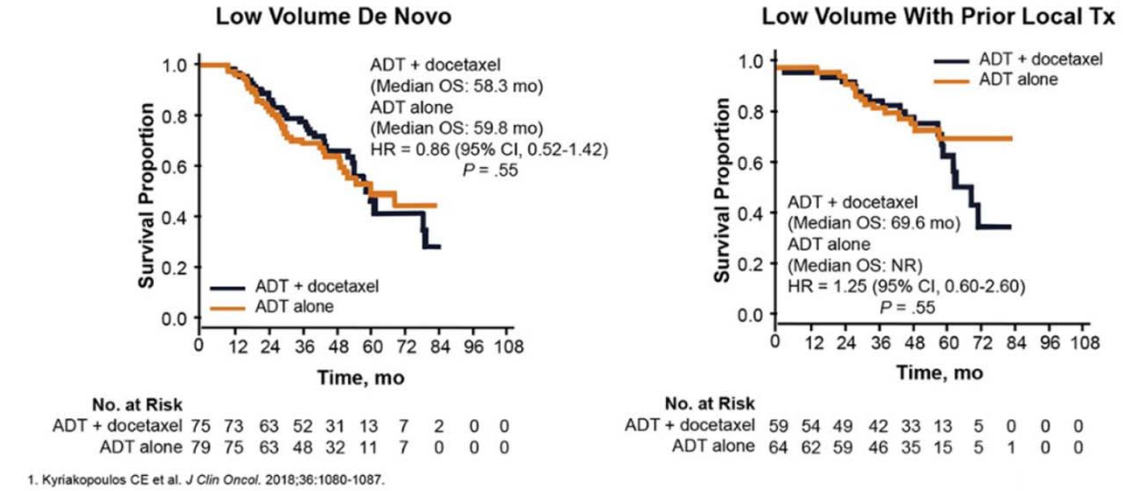
Long-Term Survival Analysis of the Randomized Phase 3 E3805 CHAARTED Trial



1. Kyriakopoulos CE et al. *J Clin Oncol.* 2018;36:1080-1087.

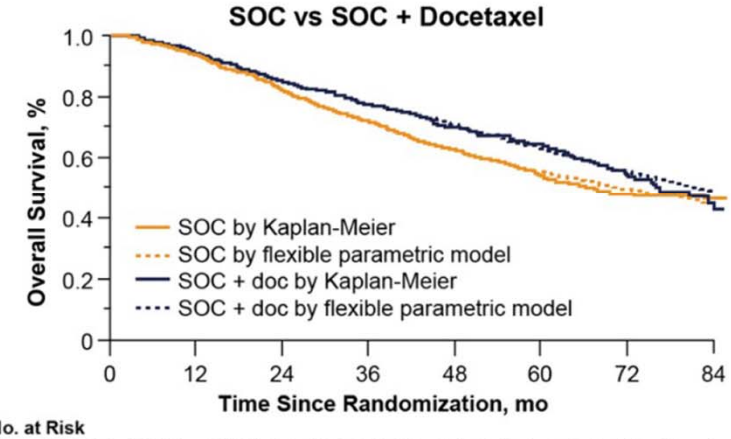
Chemohormonal Therapy in mHSPC: CHAARTED[1] (Cont'd)

Long-Term Survival Analysis of the Randomized Phase 3 E3805 CHAARTED Trial



1. Kyriakopoulos CE et al. *J Clin Oncol.* 2018;36:1080-1087.

STAMPEDE: Chemohormonal Therapy in mHSPC—Survival[1]



No. at Risk

SOC	1,184	(73)	1,093	(134)	876	(92)	538	(60)	322	(35)	166	(17)	87	(2)	43
SOC + doc	592	(33)	545	(52)	447	(35)	290	(22)	181	(12)	93	(13)	51	(6)	20

SOC: 415 deaths
SOC + docetaxel: 175 deaths
HR = 0.78 (95% CI, 0.66-0.93)
P = .006

Median OS (5-y rate)
SOC: 71 mo (55%)
SOC + docetaxel: 81 mo (63%)

1. James ND et al. *Lancet*. 2016;387:1163-1177.

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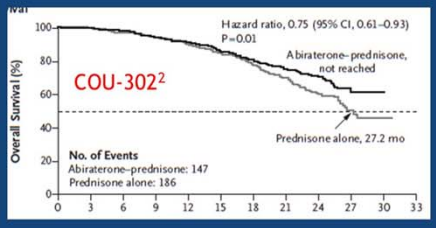
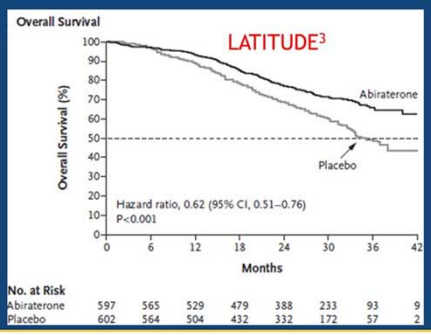
The Revolution Continues with up-front Abiraterone in 2017

- Abiraterone acetate + prednisone in mCRPC prolonged survival with HR 0.65 post-docetaxel (COU-301)[1], 0.75 pre-docetaxel (COU-302)[2].
- Up-front abiraterone increased median OS with HR 0.62 in LATITUDE[3], and improved 3-year survival from 76% to 83% (HR 0.63) in STAMPEDE[4].





No. at Risk

Abiraterone	597	565	529	479	388	233	93	9
Placebo	602	564	504	432	332	172	57	2

1. deBono et al NEJM 2011; 364:1995 2. Ryan et al. NEJM 2013; 368:138
Presented by Tanya B. Dorff MD ASCO 2019 3. Fizazi et al NEJM 2017; 377:352 4. James et al. NEJM 2017; 377:338 - STAMPEDE

LATITUDE: Phase 3 Trial of Abiraterone in Patients With Newly Diagnosed Metastatic Prostate Cancer[1]

Patients
- Newly diagnosed adult men with high-risk mHNPC

High-risk defined as meeting at least 2 of 3 following criteria:
- Gleason score of ≥8
- Presence of ≥3 lesions on bone scan
- Presence of measurable visceral lesion

Stratification factors
- Presence of visceral disease (yes/no)
- ECOG PS (0-1 vs 2)

RANDOMIZED 1:1

- ADT + abiraterone acetate (AA) 1,000 mg QD + prednisone (P) 5 mg QD (n = 597)
- ADT + placebo (n = 602)

Efficacy endpoints

Co-primary
- OS
- rPFS

Secondary

Time to:
- Pain progression
- PSA progression
- Next symptomatic skeletal event
- Chemotherapy
- Subsequent prostate cancer therapy

- Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada
- Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results

1. Fizazi K et al. *N Engl J Med.* 2017;377:352-360.

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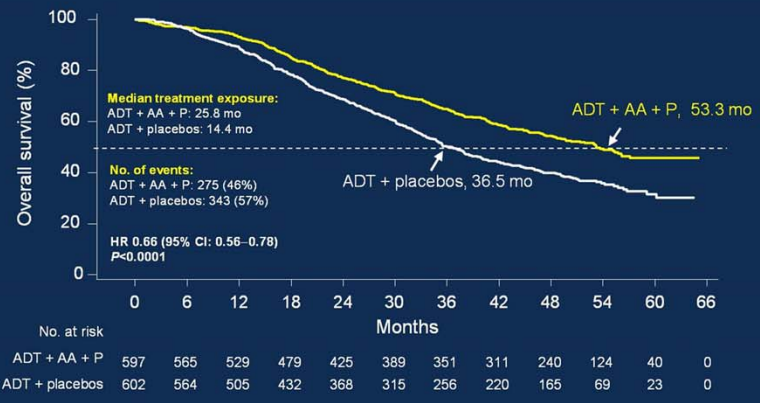
Final Analysis: Overall Survival



- **Median OS for patients receiving ADT + AA+P reached 4.5 years, 16.8 months longer than ADT+ placebos**

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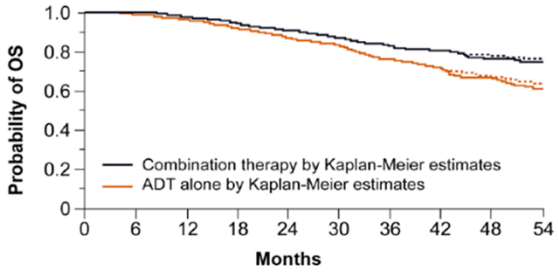
STAMPEDE: Overall Survival With Abiraterone[1]



Deaths
ADT + ABI + prednisolone (P): 184
ADT: 262

HR = 0.63
95% CI, 0.52-0.76
P < .001

No. of Patients (deaths)

Combination therapy	960	(26)	917	(63)	840	(67)	541	(25)	161
ADT alone	957	(37)	909	(88)	806	(92)	491	(36)	123

1. James ND et al. *N Engl J Med.* 2017;377:338-351.

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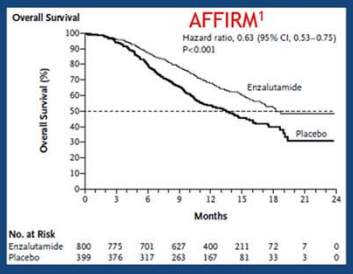
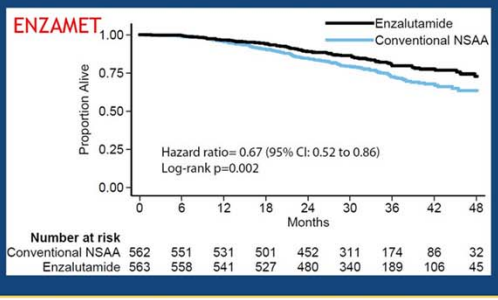
The Revolution is Validated: ENZAMET

- Enzalutamide improved survival in mCRPC, HR 0.63 post-docetaxel (AFFIRM)[1], HR 0.71 pre-docetaxel (PREVAIL)[2]
  - Enzalutamide delayed metastasis by median 22 months in non-metastatic CRPC (PROSPER)[3].
- Up-front enzalutamide increased 3 year OS from 72% to 79% in ENZAMET, HR 0.67.





1. Scher et al NEJM 2012; 367:1187 (AFFIRM)
2. Beer et al. NEJM 2014; 371:424 (PREVAIL)
3. Hussain et al. NEJM 2018; 378:2465 (PROSPER)

Presented by Tanya B. Dorff MD ASCO 2019

ENZAMET: SOC ± Enzalutamide in mCSPC[1]

Stratification Factors
- Volume of metastasis[a]: High vs low
- Planned early docetaxel: Yes vs no
- ECOG PS: 0-1 vs 2
- Antiresorptive therapy: Yes vs no
- Comorbidities (ACE-27): 0-1 vs 2-3
- Study site

R

Arm A Testosterone suppression + Standard NSAA → Evaluate every 12 weeks

Arm B Testosterone suppression + ENZA 160 mg/d → Evaluate every 12 weeks

CRPC therapy at investigator's discretion at progression

Follow for time to progression and OS

- Prior to randomization, testosterone suppression up to 12 weeks and 2 cycles of docetaxel was allowed
- Intermittent ADT and cyproterone were not allowed
- NSAA: bicalutamide, nilutamide, flutamide

[a] High volume = visceral metastases and/or ≥4 bone metastases (≥1 beyond pelvis and vertebral column).

1. Davis ID et al. *N Engl J Med*. 2019;381:121-131.

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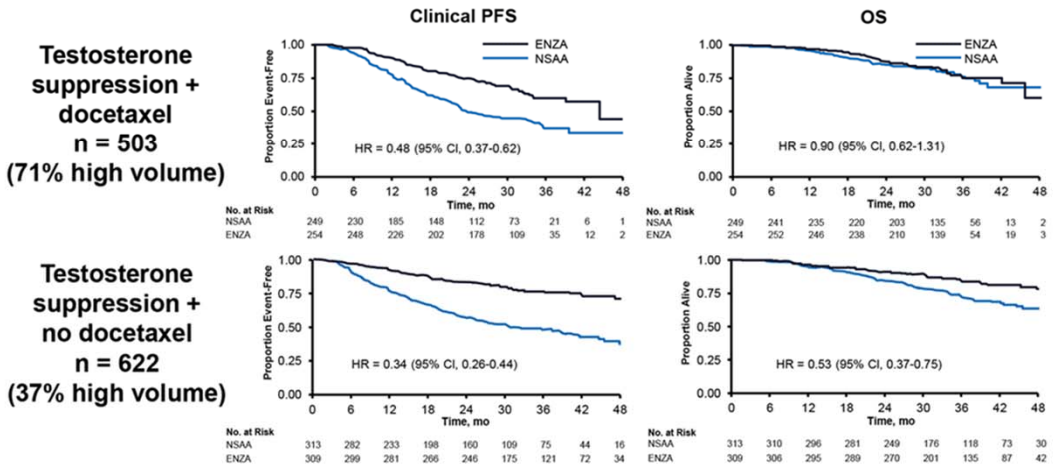
Concurrent Docetaxel: Prespecified Subgroup of Interest (Biology and Treatment Implications)[1]



1. Davis ID et al. *N Engl J Med*. 2019;381:121-131.

New 2019 Treatment Options for mHSPC

Apalutamide

- 3rd generation AR signaling inhibitor
- Has activity at 3 places
  - Blocks binding of androgen to AR
  - Prevents AR from entering cell nucleus
  - Inhibits AR binding to DNA
- Less likely to cross blood brain barrier
- Approved 2018 for nmCRPC, based on the SPARTAN trial with PSADT <10 mo
- Approved 2019 for mHSPC based on the TITAN trial
- Dose: 240 mg QD w/ADT

Enzalutamide

- 3rd generation AR signaling inhibitor
- Has activity at 3 places
  - Blocks binding of androgen to AR
  - Prevents AR from entering cell nucleus
  - Inhibits AR binding to DNA
- Approved in 2012 and 2014 for mCRPC
- Approved in 2018 for nmCRPC based on PROSPER trial with PSADT <10 mo
- Approved 2019 for mHSPC based on ARCHES trial
- Dose: 160 mg QD w/ADT

Smith, et al. *N Engl J Med.* 2018; 378:1408-1418. Chi, KN, et al. *N Engl J Med.* 2019; 381:13.
Hussain M et al. *N Engl J Med*. 2018;378:2465-2474. Armstrong, et al. *J Clin Oncol*. 2019 Nov 10;37(32):2974-2986.

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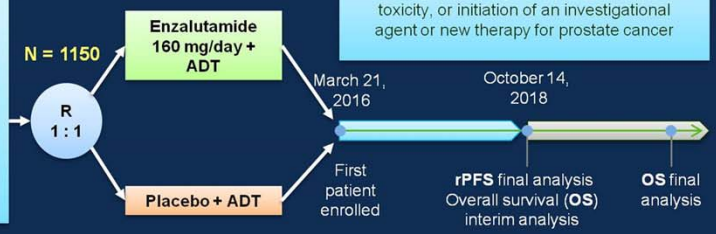
ARCHES study design

Key eligibility criteria

- mHSPC (confirmed by bone scan, CT, or MRI), histologically confirmed adenocarcinoma
- ECOG Performance Status 0 to 1
- Current ADT duration ≤3 months unless prior docetaxel, then ≤6 months

Stratification factors

- Volume of disease (low vs. high*)
- Prior docetaxel therapy for mHSPC (none, 1–5, or 6 cycles)



Key discontinuation criteria

Radiographic progression, unacceptable toxicity, or initiation of an investigational agent or new therapy for prostate cancer

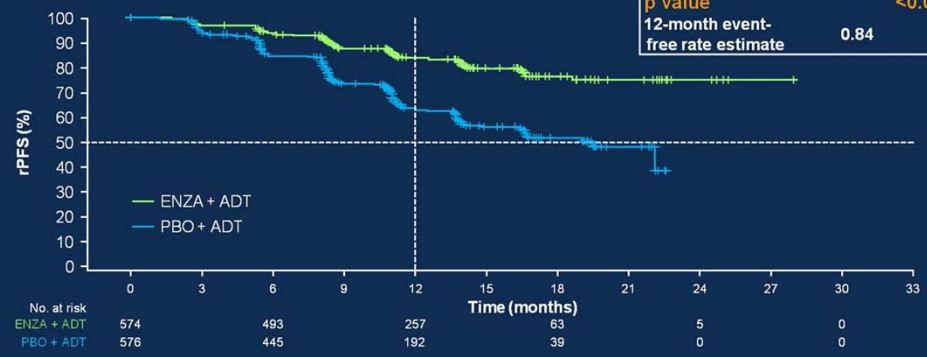
Primary endpoint

- rPFS: time from randomization to first objective evidence of radiographic progression assessed centrally, or death from any cause within 24 weeks of treatment discontinuation, whichever occurs first

*Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥4 bone lesions, ≥1 of which must be in a bony structure beyond the vertebral column and pelvic bone

Primary endpoint: rPFS

	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, month (95% CI)	NR (NR, NR)	19.45 (16.59, NR)
HR (95% CI)	0.39 (0.30, 0.50)	
p value	<0.0001	
12-month event-free rate estimate	0.84	0.64



- As of October 14, 2018 (cut-off date), 769 patients were still on treatment, 437 (76%) for enzalutamide + ADT and 332 (58%) for placebo + ADT

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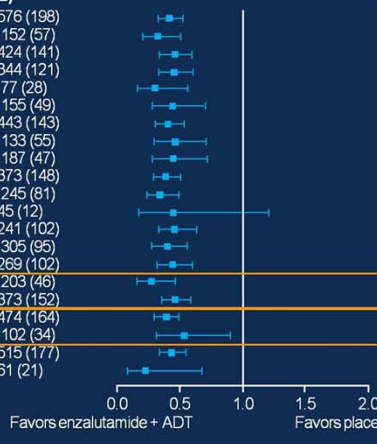
Subgroup analysis of rPFS

Subgroup	Enzalutamide + ADT / placebo + ADT N (E)	Hazard ratio (95% CI)
All patients	574 (89) / 576 (198)	0.39 (0.30, 0.50)
Age <65 years	149 (21) / 152 (57)	0.30 (0.18, 0.49)
Age ≥65 years	426 (68) / 424 (141)	0.43 (0.32, 0.58)
Geographic region – Europe	341 (55) / 344 (121)	0.43 (0.31, 0.59)
Geographic region – North America	86 (12) / 77 (28)	0.27 (0.14, 0.54)
Geographic region – rest of the world	147 (22) / 155 (49)	0.41 (0.25, 0.68)
ECOG status 0 at baseline	448 (65) / 443 (143)	0.38 (0.28, 0.51)
ECOG status 1 at baseline	125 (24) / 133 (55)	0.43 (0.27, 0.70)
Gleason score at initial diagnosis <8	171 (21) / 187 (47)	0.42 (0.25, 0.70)
Gleason score at initial diagnosis ≥8	386 (63) / 373 (148)	0.36 (0.27, 0.48)
Disease localization at baseline – bone only	268 (33) / 245 (81)	0.31 (0.21, 0.47)
Disease localization at baseline – soft tissue only	51 (5) / 45 (12)	0.42 (0.15, 1.20)
Disease localization at baseline – bone and soft tissue	217 (50) / 241 (102)	0.44 (0.31, 0.61)
Baseline PSA value at or below overall median	293 (40) / 305 (95)	0.37 (0.26, 0.54)
Baseline PSA value above overall median	279 (49) / 269 (102)	0.41 (0.29, 0.58)
Low volume of disease	220 (13) / 203 (46)	0.24 (0.13, 0.45)
High volume of disease	354 (76) / 373 (152)	0.44 (0.33, 0.57)
No prior docetaxel therapy	471 (68) / 474 (164)	0.36 (0.27, 0.48)
Prior docetaxel therapy	103 (21) / 102 (34)	0.53 (0.31, 0.92)
Previous use of ADT or orchiectomy	535 (86) / 515 (177)	0.41 (0.31, 0.52)
No previous use of ADT or orchiectomy	39 (3) / 61 (21)	0.20 (0.06, 0.66)



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Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial in Patients with mCSPC

TITAN

Patient Population* (N=1052)
- Patients with mCSPC
  - Up to 6 cycles of prior docetaxel use are allowed
  - ECOG PS ≤1
  - ≥1 bone lesion with or without visceral metastases
  - With both high- and low-volume disease were eligible†

Stratification factors:
- Gleason score at diagnosis (≤7 vs >7)
- Region (North America and European Union)
- Prior docetaxel use (yes vs no)

Randomized[1] 1:1

- **Apalutamide 240 mg once daily + ADT (n=525)**
- **Placebo + ADT (n=527)**

Dual Primary Endpoints
- OS
- rPFS

Secondary Endpoints
- Time to initiation of cytotoxic chemotherapy

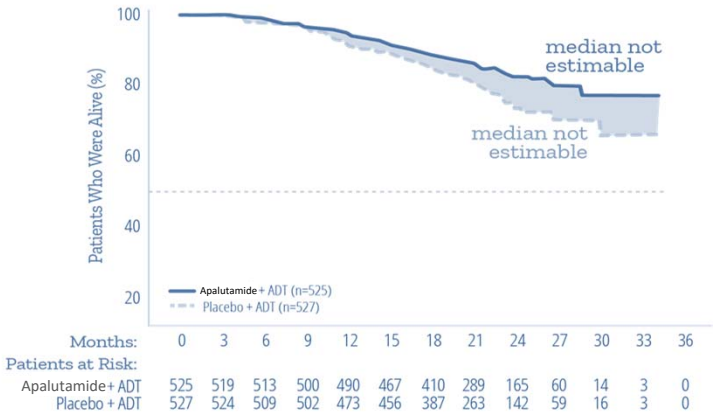
28-day treatment cycle until protocol-defined disease progression or unacceptable toxicity

*All patients received a concomitant GnRH analog or had a prior bilateral orchiectomy.

ECOG PS = Eastern Cooperative Oncology Group performance status; rPFS = radiographic progression-free survival.
†High volume of disease was defined as metastases involving the viscera with 1 bone lesion or the presence of 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bones.1
Chi KN, et al. N Engl J Med. 2019;381(1):13-24.

Dual Primary Endpoint
Apalutamide + ADT Reduced the Risk of Death by 33% vs Placebo + ADT1,2

Overall Survival*



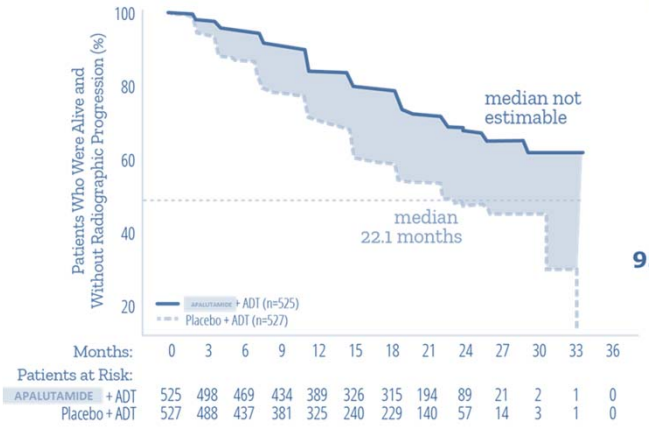
33% reduction in the risk of death

HR=0.67
95% CI: 0.51, 0.89
***P*=0.0053[1]**

CI = confidence interval; HR = hazard ratio.
***Median follow-up time was 22.7 months.[2]**
†OS was defined as time from randomization to date of death from any cause.[2]
1. apalutamide [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Chi KN, et al. *N Engl J Med.* 2019;381(1):13-24.

Dual Primary Endpoint

Radiographic Progression-Free Survival (rPFS)*



52% reduction in the risk of radiographic progression or death

HR=0.48
95% CI: 0.39, 0.60
***P*<0.0001**

At 2 years, **68.2%** of patients in the Apalutamide + ADT arm were alive and without radiographic progression vs **47.5%** of patients in the placebo + ADT arm

*rPFS was defined as the duration from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurred first.2
Chi KN, et al. N Engl J Med. 2019;381(1):13-24.

How will we choose between the up-front agents?

	DOCETAXEL	ABIRATERONE	ENZALUTAMIDE (APALUTAMIDE)
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
Select Toxicities	Peripheral neuropathy, hair loss, pancytopenia ‡	Liver enzymes† electrolytes, HTN	CNS (seizures/ cognitive), falls
Corticosteroids	YES	YES	**NO**
Subsets	High-volume*	Any	Any

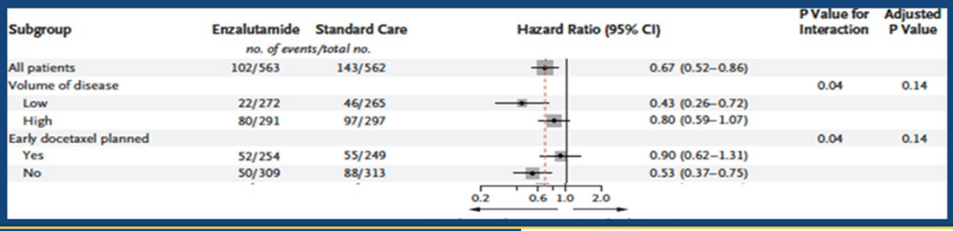
*≥4 bone mets with 1 outside axial skeleton OR visceral mets

†Additional labs necessary for abiraterone

‡Could require growth factors for chemo

Why not combine (sequence) chemotherapy and androgen receptor targeted therapy in mHSPC?

- Less benefit seen in patients treated with docetaxel up-front in ENZAMET
  - No study has shown synergy of AR targeted therapy plus docetaxel although combination of full doses is safe[1,2].
- Less benefit seen in high volume patients
  - 70% received docetaxel whereas <40% of low volume patients received docetaxel
- Dedicated trials will answer whether there is advantage to using both(ex: ARASENS with darolutamide, PEACE1 with abiraterone)



Subgroup	Enzalutamide	Standard Care	Hazard Ratio (95% CI)	P Value for Interaction	Adjusted P Value
	no. of events/total no.				
All patients	102/563	143/562	0.67 (0.52–0.86)		
Volume of disease				0.04	0.14
Low	22/272	46/265	0.43 (0.26–0.72)		
High	80/291	97/297	0.80 (0.59–1.07)		
Early docetaxel planned				0.04	0.14
Yes	52/254	55/249	0.90 (0.62–1.31)		
No	50/309	88/313	0.53 (0.37–0.75)		

1. Tagawa ST et al, Eur Urol 2016; 70:718
2. Morris MJ et al, Clin Cancer Res 2016; 22:3774

ARASENS: Ongoing Phase 3 Trial in mCSPC[1]

International trial conducted at >300 sites in 23 countries

- Newly diagnosed metastatic disease
- ECOG PS 0 or 1
- Planned N = 1,300

R 1:1

- **ADT + docetaxel (x 6 cycles) + darolutamide (600 mg PO BID)**
- **ADT + docetaxel (x 6 cycles) + placebo**

Primary completion date: August 2022

Stratification: Extent of disease and alkaline phosphatase level

- **Primary endpoint:** OS
- **Secondary endpoints:** Time to mCRPC, time to initiation of subsequent anticancer therapy, time to SSE-free survival, time to first SSE, time to first opioid use, time to pain progression, and time to worsening of physical symptoms

1. https://clinicaltrials.gov/ct2/show/NCT02799602.

Guideline Statement 16

16. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. (Conditional Recommendation; Evidence Level: Grade C)

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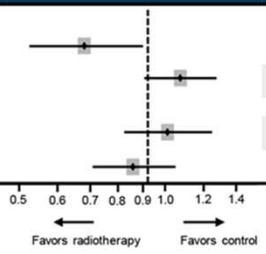
Radiotherapy for Low Metastatic Burden in mCSPC[1]

Overall Survival	Adjusted HR (95% CI)	Survival at 3 y	
		Control, %	Radiotherapy, %
All patients	0.92 (0.80-1.06)	62	65
Low metastatic burden	0.68 (0.52-0.90)	73	81
High metastatic burden	1.07 (0.90-1.28)	54	53

	Control Deaths/ N	Radiotherapy Deaths/N	Interaction *P*	HR (95% CI)
Metastatic burden				
Low burden	116/409	90/410	.0098	0.68 (0.52-0.90)
High burden	252/567	257/553		1.07 (0.90-1.28)
Radiotherapy schedule				
Weekly	179/482	182/497	.27	1.01 (0.82-1.25)
Daily	212/547	188/535		0.86 (0.71-1.05)

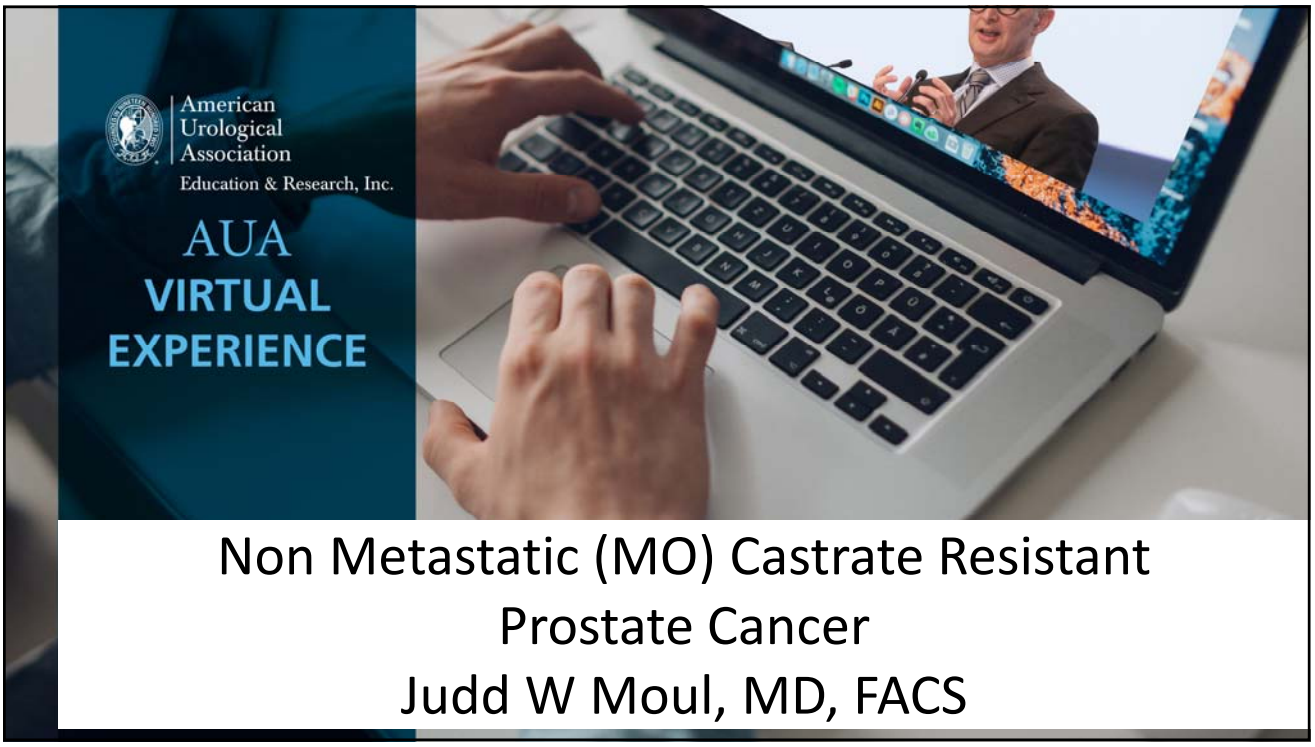


1. Parker CC et al. *Lancet*. 2018:392:2343-2366.

Metastatic Hormone Sensitive Prostate Cancer

Conclusions

- ADT monotherapy is no longer the standard of care
- Treatment intensification strategies are stratified by high or low volume:
  - Docetaxel (high)
  - Abiraterone/prednisone (high or low)
  - Apalutamide (high or low)
  - Enzalutamide (high or low)
- Triple therapy with docetaxel needs further study. Other combination trials are underway.
- Consider primary radiation to prostate and ADT in oligometastasic disease
- Genetic testing is recommended for all patients with metastatic prostate cancer
- Clinical trials should always be considered in cancer patients



Non Metastatic (MO) Castrate Resistant Prostate Cancer

Judd W Moul, MD, FACS

Greetings from Duke University, Durham, North Carolina

Disclosures

- Advisory boards: AJCC
- Honoraria: Astellas, Genomic Health, Janssen, Sanofi, Bayer, Exosome Dx
- Consultant: Theralogix, Best Doctors,
- Grant/research support: Astellas, Pfizer

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Case

- 73-year-old retired grocery chain executive; robust overall health
- Presented 5 years ago:
- Moderate volume Gleason 4+3=7, PSA 13
- Multi-D clinic: elected Radical Retropubic Prostatectomy (RRP)
- Post-op path pT3b Gleason 4+5=9
- Received adjuvant EBRT+ 6 months ADT 6 months post op at time of continence
- PSA began to rise 3 years ago
- At PSA of 5, he restarted ADT
- PSA declined to 0.5 about 7 months after restarting ADT

Case (continued)

- **Currently has PSA of 2.8; castrate serum testosterone**
- **PSA-DT is 9.5 months**
- **Restaging bone scan and CT abdomen/pelvis negative for metastasis**
- **Currently with nm/M0 CRPC**
- **Options?**

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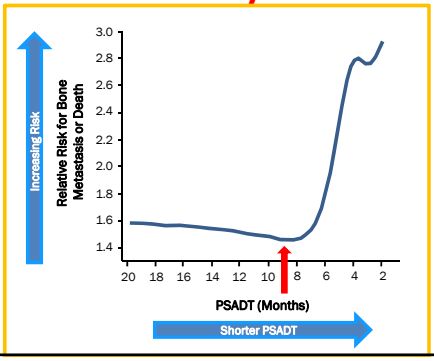
Let me play Devil's Advocate for a moment…

- He is feeling well so why introduce possible fatigue/side effects.
- The Novel HT agents are very expensive and difficult for my office to deal with.
- I am not sure that metastases-free survival is a valid endpoint.
- I will just get a PET-CT and try to prove metastases (M1) and then use docetaxel.
- I will use bicalutamide now and hold the "big-guns" until he really needs them.
- I will monitor him until his PSA-DT gets worse (less than 3-6 months)
- I will monitor him until he gets metastases (M1 Disease) on standard imaging.
- I am just not convinced that these agents now are worth it!
- I am not sure which agent to use since we have three good choices

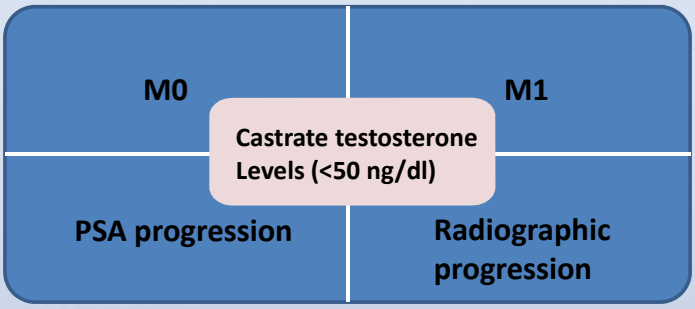
Management of Nonmetastatic CRPC

- Definition:
  - Rising PSA in the setting of a **castrate level of testosterone** (<50 ng/dL)
  - **No tumors seen on imaging (nuclear medicine bone scan and CT scan)**
- Outcome related to PSA doubling time:
  PSA-DT <10 months

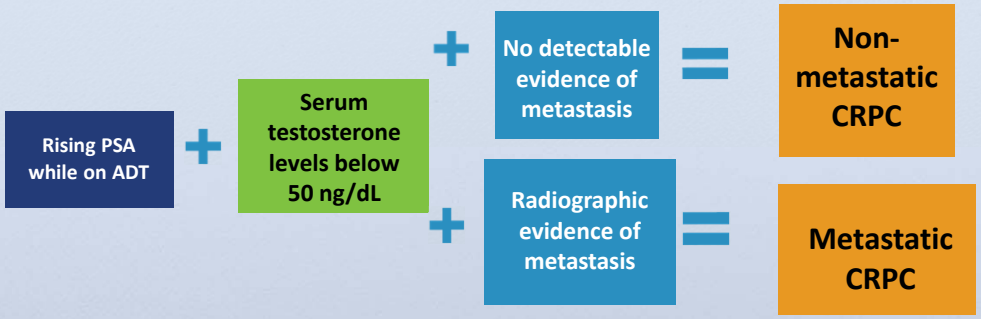


PSADT = prostate-specific antigen doubling time.
Smith et al, 2013; NCCN, 2018.

Definition of CRPC



Identifying Non-Metastatic (M0/NM) CRPC



Cookson MS, et al; American Urological Association. J Urol. 2015;193(2):491-499.

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M0 CRPC: What are we trying to achieve?

- Prevent metastasis-proven
- Preserve quality of life-proven
- Prolong survival- now proven (ASCO June 2020)

M0 CRPC

- **Completed trials and FDA-approved for M0 disease**
- **PROSPER (Enzalutamide)**
- **SPARTAN (Apalutamide)**
- **ARAMIS (Darolutamide)**

M0 CRPC Trial Design Comparison

Trial Parameter	PROSPER[1]	SPARTAN[2]	ARAMIS[3]
Treatment	ADT + enzalutamide (once a day) vs ADT + placebo	ADT + apalutamide (once a day) vs ADT + placebo	ADT + darolutamide (twice a day with food) vs ADT + placebo
Patients	1,401	1,207	1,509
Randomization	2:1	2:1	2:1
Stratification	1. PSADT (< 6 mos vs ≥ 6 mos) 2. Baseline use of a bone-targeting agent (yes vs no)	1. PSADT (≤ 6 vs > 6 months) 2. Baseline use of a bone-targeting agent (yes vs no) 3. N0 vs N1 disease	1. PSADT (≤ 6 vs > 6 months) 2. Baseline use of a bone-targeting agent (yes vs no)
PSADT	≤ 10 months	≤ 10 months	≤ 10 months
PSA at Baseline	≥ 2 µg/L (2 ng/mL)	≥ 2 µg/L (2 ng/mL)	≥ 2 µg/L (2 ng/mL)
ECOG PS	0-1	0-1	0-1
Patients With a History of Seizure or Any Condition That May Predispose to Seizure	Excluded	Excluded	Allowed to enroll
CVD Event Exclusion	Clinically significant CVD		Clinically significant CVD
Primary Endpoint	MFS (OS secondary)	MFS (OS secondary)	MFS (OS secondary)

1. Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474. 2. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.
3. Fizazi K, et al. *N Engl J Med*. 2019:380(13):1235-1246.

M0 CRPC Efficacy Comparison

Trial Parameter	PROSPER[1]	SPARTAN[2]	ARAMIS[3]
Treatment	ADT + enzalutamide (once a day) vs ADT + placebo	ADT + apalutamide (once a day) vs ADT + placebo	ADT + darolutamide (twice a day with food) vs ADT + placebo
MFS, median	36.6 months vs 14.7 months (HR = 0.29)	40.5 months vs 16.2 months (HR = 0.28)	40.4 months vs 18.4 months (HR = 0.41)
Time to PSA progression, median	37.2 months vs 3.9 months (HR = 0.07)	NR vs 3.7 months (HR = 0.06)	33.2 months vs 7.3 months (HR = 0.13)
OS, median	67 vs 56.3 (48 month)	73.9 vs 59.9 months (52 months)	83 vs 77 29.1 months)

- 1. Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474. 2. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.
  3. Fizazi K, et al. *N Engl J Med*. 2019:380(13):1235-1246.

M0 CRPC Trials: Adverse Events of Interest

Safety[a]	PROSPER[1]		SPARTAN[2]		ARAMIS[3]	
	ENZA (n = 930)	Placebo (n = 465)	APA (n = 803)	Placebo (n = 398)	DARO (n = 954)	Placebo (n = 554)
AEs (all grades), %						
Fatigue	33.0	14.0	30.4	21.1	12.1	8.7
Hypertension	12.0	5.0	24.8	19.8	6.6	5.2
Rash	2.3	2.2	23.8	5.5	2.9	0.9
Falls	11.0	4.0	15.6	9.0	4.2	4.7
Fractures	11.2	5.6	11.7	6.5	4.2	3.6
Mental Impairment Disorders	5.0	2.0	5.1	3.0	0.4	0.2
AEs Leading to Discontinuation, %	9.0	6.0	10.6	7.0	8.9	8.7
AEs Leading to Death, n (%)	32 (3.4)	3 (0.7)	10 (1.2)	1 (0.3)	37 (3.9)	18 (3.2)

- [a]AE reporting every 4 weeks in SPARTAN and every 16 weeks in PROSPER and ARAMIS. [b]Ischemic event. AEs in SPARTAN were measured to 28 days after the end of regimen.

- 1. Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474. 2. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418.
  3. Fizazi K, et al. *N Engl J Med*. 2019:380(13):1235-1246.

WC1

Slide 72

WC1 Please note in the original source slide, there is a footnote for b but no footnote symbol in the table that references b

Wendy Chen, 6/20/2019

Apalutamide/SPARTAN: Update 2020 (ASCO 2020)

- Overall Survival: 3nd Analysis
- Median F/U=52 months
- Median OS: 73.9% Apalutamide
- 59.9% Placebo
- HR=0.784 ; P=0.0161
- Met the pre-specified target value for statistical significance (p=0.046)
- 21.6% relative risk reduction of death from prostate cancer.
- Presented by: Eric Jay Small, MD
- https://www.urotoday.com/conference-highlights/asco-2020.html-

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Enzalutamide/PROSPER: Update 2020 (ASCO 2020)

- 27% decrease in the risk for death
- Median follow-up: approximately 48 months
- Median OS duration was 67.0 months among the 933 patients who received enzalutamide and 56.3 months among the 468 patients given placebo.
- Enzalutamide-treated participants: longer time to first use of subsequent antineoplastic therapy than their placebo-treated counterparts, at a median of 66.7 versus 19.1 months.
- Presented by Cora Sternberg (Weill Cornell Medicine, New York)
- https://oncology.medicinematters.com/asco-2020/genitourinary-cancers/antiandrogen-therapy-crpc-survival/18114372

Darolutamide/ARAMIS: Update 2020 (ASCO 2020)

- **31% reduction in the risk for death**
- **Median follow-up of 29.1 month**
- **3-year OS rates were 83% and 77% for the darolutamide and placebo**
- **Darolutamide associated with significant delays in the time to pain progression, first cytotoxic chemotherapy, and first symptomatic skeletal event.**
- Presented by Karim Fizazi (Institut Gustave Roussy and University of Paris Sud, Villejuif, France)
- https://oncology.medicinematters.com/asco-2020/genitourinary-cancers/antiandrogen-therapy-crpc-survival/18114372

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Summary of the three trials: ASCO 2020

- Discussant Tomasz Beer (OHSU Knight Cancer Institute, Portland, Oregon, USA) commented that these findings “make it clear that in castration-resistant prostate cancer, early intensification of hormonal therapy results in an overall survival advantage.”
- He added that “meaningful differences in efficacy between these three studies are not apparent,” and although the median OS estimates and hazard ratios look “a bit better” in the trials with longer follow-up, “none of these studies are fully mature for overall survival,” and the estimates “are likely to change with additional follow-up.”
- https://oncology.medicinematters.com/asco-2020/genitourinary-cancers/antiandrogen-therapy-crpc-survival/18114372

Why the Devil's Advocate is Wrong:

- Two year average metastases-free survival is clinically meaningful and overall survival all three agents now proven (ASCO 2020).
- Novel HT oral agents are generally well tolerated and do not deteriorate QOL
- These patients ARE in urology practices if you just be mindful in looking and empowering staff to look as well
- Generally good reimbursement from payers
- Patients can stay with their urology provider longer
- Patients can avoid systemic chemotherapy longer
- Robust effect on PSA

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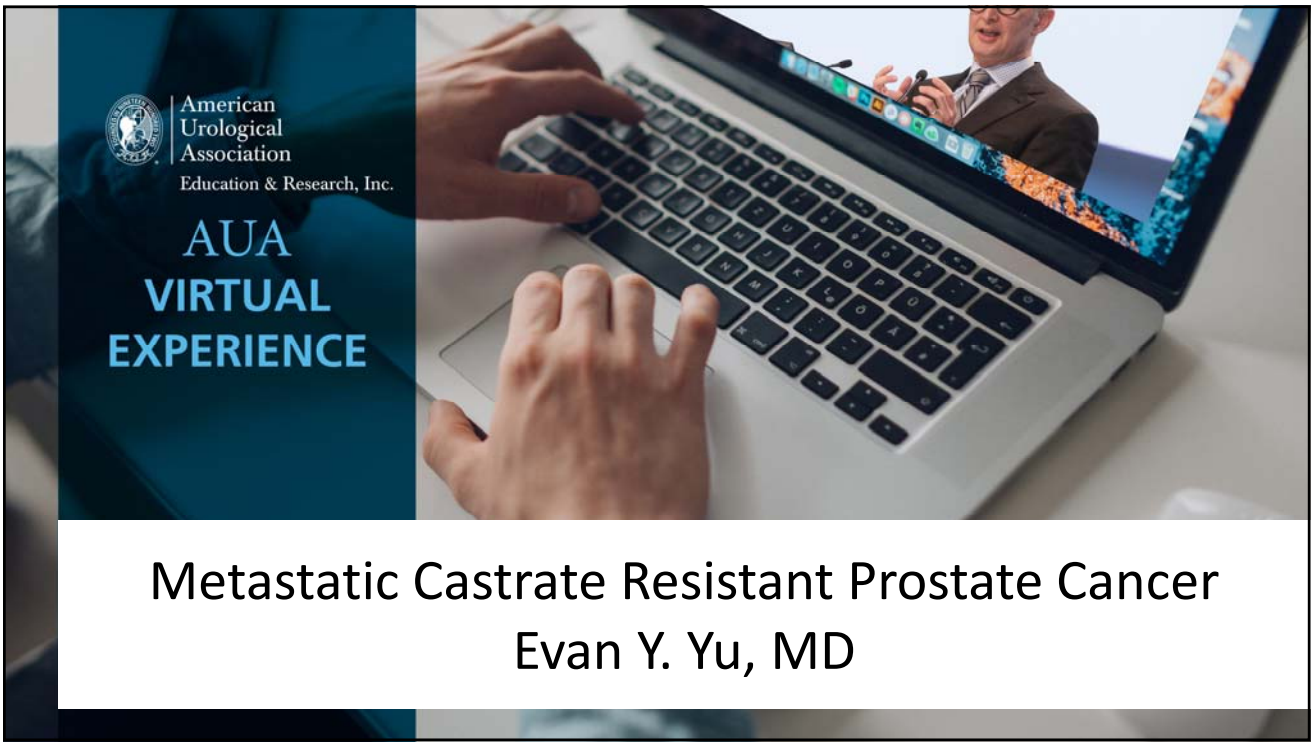
Thank you very much!

Judd.moul@duke.edu

Twitter: @JuddMoul



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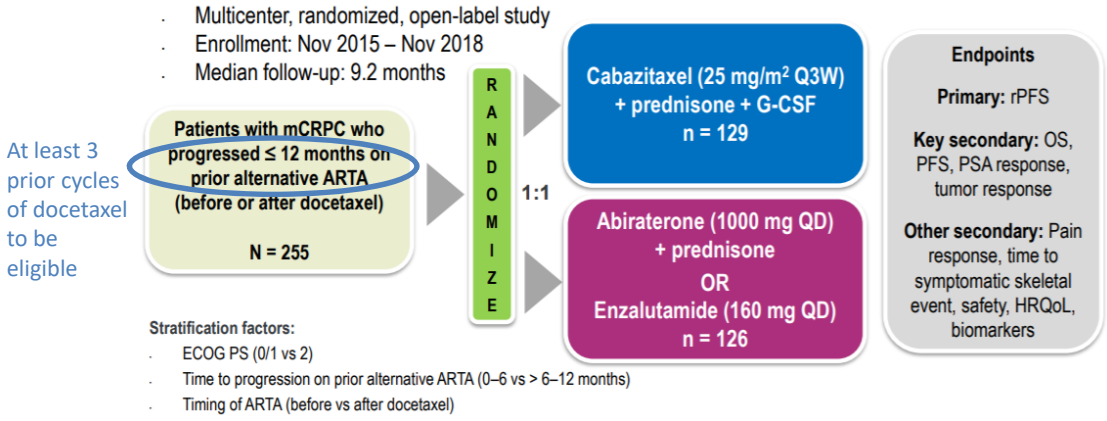
Disclosures

- Consulting Fees: AAA, Abbvie, Amgen, Astrazeneca, Bayer, Clovis, Dendreon, EMD Serono, Incyte, Janssen, Merck, Pharmacyclics, QED, Sanofi-Genzyme, Seattle Genetics, Tolmar
- Contracted Research to Institution: Bayer, Blue Earth, Daiichi-Sankyo, Dendreon, Merck, Pharmacyclics, Seattle Genetics, Taiho

Discussion Topics

- Sequencing agents
- Combination therapy
- DNA repair deficiency
  - Therapeutics
  - Genetic counseling and cascade testing
- Immune-Oncology
- Theranostics

Phase IV CARD Trial Schema



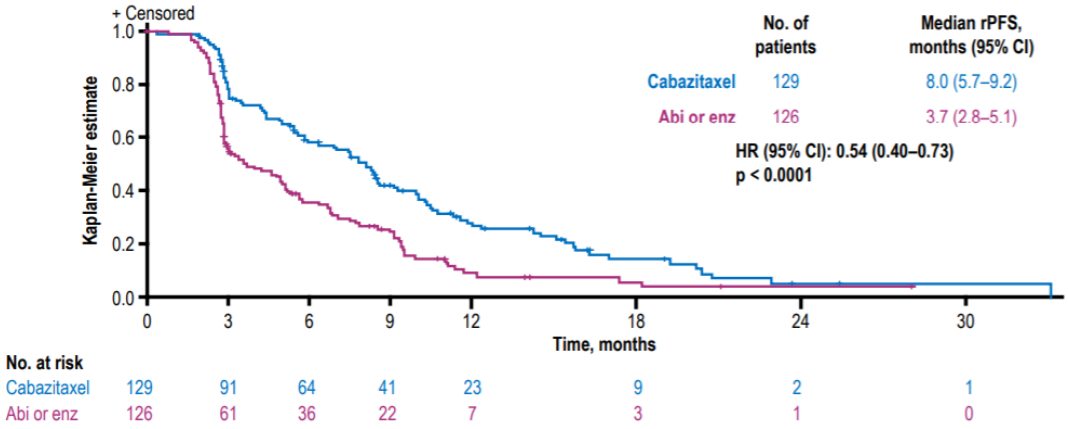
De Wit R et al. N Engl J Med. 2019; 381:2506-18.

CARD Trial: Baseline Demographics

	Cabazitaxel (N = 129)	Abiraterone or enzalutamide (N = 126)
Median age, years (range)	70.0 (46–85)	71.0 (45–88)
≥ 75 years, n (%)	45 (34.9)	34 (27.0)
ECOG PS 0–1, n (%)	123 (95.3)	119 (94.4)
Visceral metastases, n (%)	21 (16.3)	25 (19.8)
Type of progression at study entry, n (%)		
PSA only	11 (8.5)	10 (7.9)
Radiologic (± PSA), no pain	23 (17.8)	16 (12.7)
Pain (± PSA, ± radiologic)	86 (66.7)	90 (71.4)
Gleason 8–10 at diagnosis, n (%)	73 (56.6)	81 (64.3)
M1 disease at diagnosis, n (%)	49 (38.0)	60 (47.6)
Docetaxel/abiraterone in mHSPC, n (%)	14 (10.9)/0	18 (14.3) /1 (0.8)
Prior alternative ARTA, n (%)		
Abiraterone/enzalutamide	56 (43.4)/72 (55.8)	67 (53.2)/59 (46.8)
Received before/after docetaxel	50 (38.8)/79 (61.2)	49 (38.9)/77 (61.1)
Median duration of prior alternative ARTA, months	7.6	8.0

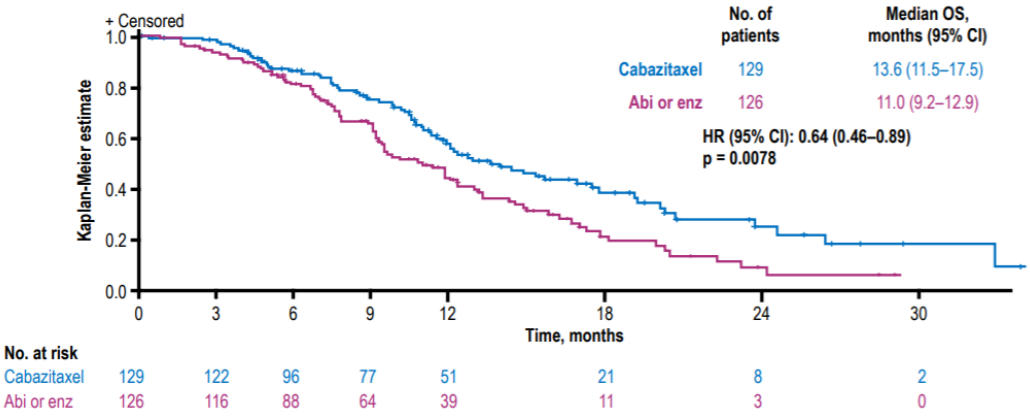
De Wit R et al. N Engl J Med. 2019; 381:2506-18.

CARD Trial: Radiographic PFS



De Wit R et al. N Engl J Med. 2019; 381:2506-18.

CARD Trial: Overall Survival



De Wit R et al. N Engl J Med. 2019; 381:2506-18.

CARD Trial: Safety

Patients, n (%)	Cabazitaxel (N = 126)	Abiraterone or enzalutamide (N = 124)
Any AE	124 (98.4)	117 (94.4)
Any grade ≥ 3 AE	71 (56.3)	65 (52.4)
Serious AE	49 (38.9)	48 (38.7)
AE leading to treatment discontinuation	25 (19.8)	11 (8.9)
AE leading to death*	7 (5.6)	14 (11.3)

*During treatment emergent AE period (from randomization to 30 days after last treatment administration).

De Wit R et al. N Engl J Med. 2019; 381:2506-18.

Alliance A031201 Trial Schema

mCRPC:
-Radiographic mets
-No chemo for mets
-Minimal pain or better

Stratification:
-Prior chemo (non-met)
-Halabi nomogram II

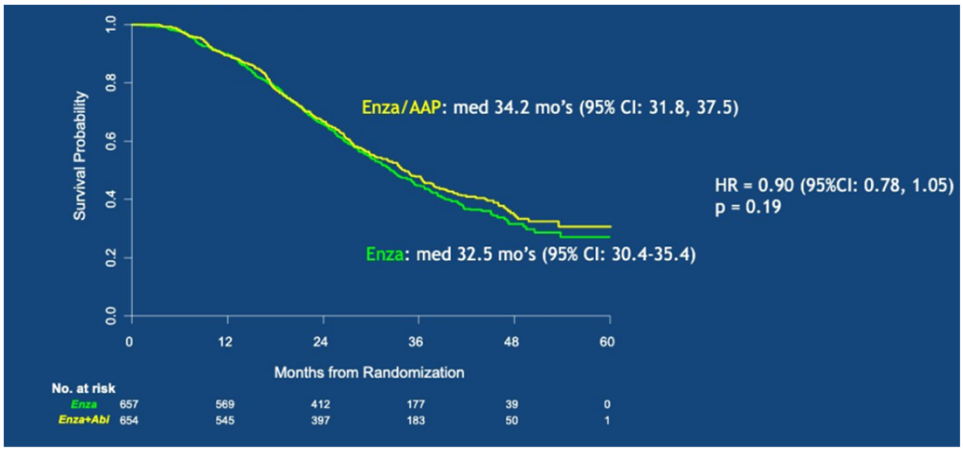
RANDOMIZE

Arm A:
Enzalutamide 160 mg PO daily

Arm B:
Enzalutamide 160 mg PO daily
Abiraterone 1000 mg PO daily
Prednisone 5 mg PO bid

Morris M et al. J Clin Oncol 37(15_suppl):5008-5008, May 2019.

Alliance A031201: Overall Survival



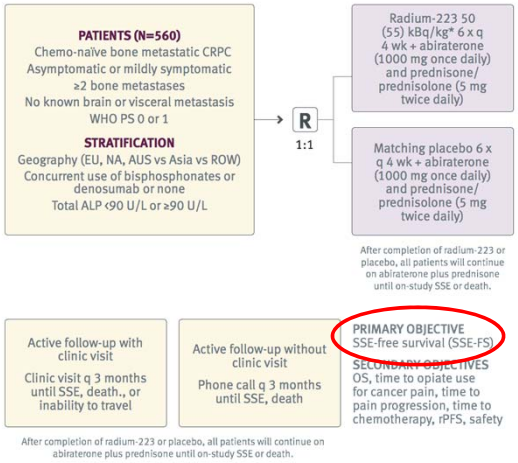
Morris M et al. J Clin Oncol 37(15_suppl):5008-5008, May 2019.

Alliance A031201: Adverse Events

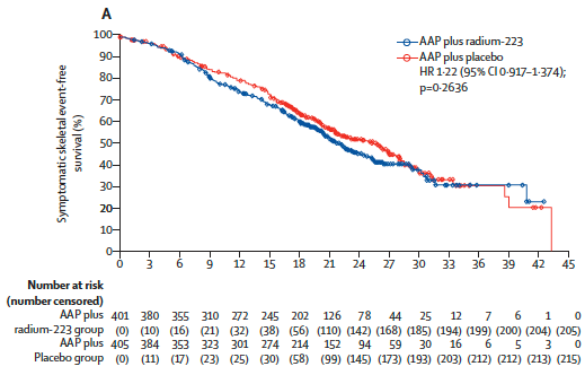
Event	All Grade		Grade 3-4	
	Enza (n=645)	Enza + AAP (n=631)	Enza (n=645)	Enza + AAP (n=631)
Constitutional				
Fatigue	556 (86.2%)	530 (84.0%)	40 (6.2%)	72 (11.4%)
Cardiac				
Acute coronary Event	4 (0.6%)	1 (0.2%)	4 (0.6%)	1 (0.2%)
Atrial fibrillation	8 (1.2%)	16 (2.5%)	3 (0.5%)	7 (1.1%)
Hypertension	415 (64.3%)	417 (66.1%)	146 (22.6%)	195 (30.1%)
Pain				
Arthralgia	291 (45.1%)	227 (36.0%)	5 (0.8%)	5 (0.8%)
Bone pain	304 (47.1%)	263 (41.7%)	29 (4.5%)	17 (2.7%)

Morris M et al. J Clin Oncol 37(15_suppl):5008-5008, May 2019.

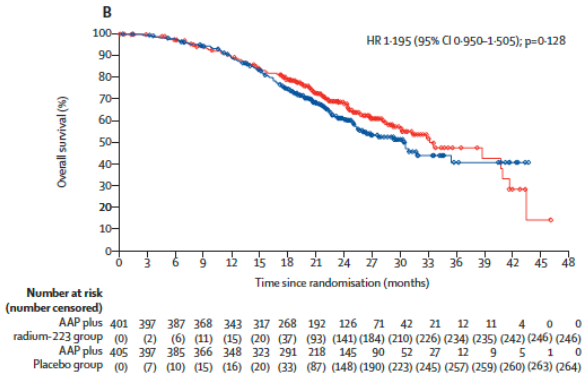
ERA 223 Trial Schema



ERA 223: Survival Analyses



Symptomatic Skeletal Event-free Survival



Overall Survival

Smith M et al. Lancet Oncol 2019; 20:408-19.

ERA 223: Fractures

	AAP plus radium-223 group (n=392)	AAP plus placebo group (n=394)
Fractures		
Patients with at least one fracture by investigator assessment	112 (29%)	45 (11%)
Time to first fracture		
<6 months	45 (11%)	11 (3%)
6 to <12 months	46 (12%)	15 (4%)
12 to <24 months	19 (5%)	16 (4%)
≥24 months	2 (1%)	3 (1%)
Patients with independently reviewed fracture imaging scans	80 (20%)	27 (7%)
Patients with at least one fracture confirmed by independent assessment	76 (19%)	23 (6%)
Bone metastasis at site of fracture	20/76 (26%)	6/23 (26%)
New bone lesion	15/76 (20%)	5/23 (22%)
Old bone lesion	6/76 (8%)	1/23 (4%)
No bone metastasis at site of fracture	60/76 (79%)	17/23 (74%)
Type of fracture		
Pathological	19/76 (25%)	6/23 (26%)
Traumatic	27/76 (36%)	13/23 (57%)
Osteoporotic	37/76 (49%)	4/23 (17%)
Indeterminate	1/76 (1%)	0

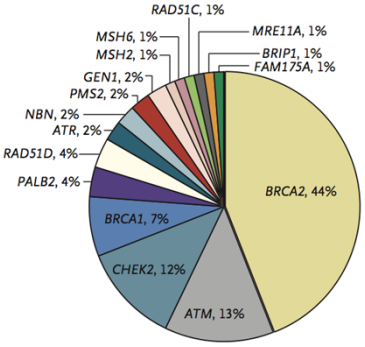
Smith M et al. Lancet Oncol 2019; 20:408-19.

Case

A 70 yo M is diagnosed with new metastatic prostate cancer. Prostate biopsy reveals a Grade Group 5 tumor. He has no family history of any cancers, but he has 2 living younger siblings and 3 healthy adult children with multiple grandchildren. He is started on androgen deprivation therapy with abiraterone acetate. He asks you about genetic predisposition. Your answer?

1. Referral to a genetic counselor
2. Obtain germline testing from a salivary test/cheek swab
3. Send prostate biopsy specimen for next generation sequencing
4. Tell him there is no concern given his family history and age

DNA Repair Alterations in Metastatic Prostate Cancer



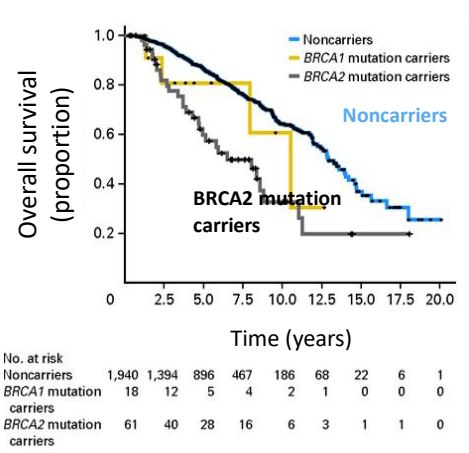
- 11.8% of men with metastatic prostate cancer have a germline alteration in 16 DNA damage repair genes
- Age and family history did not affect mutation frequency

Pritchard CC et al. *N Engl J Med.* 375:443-53.

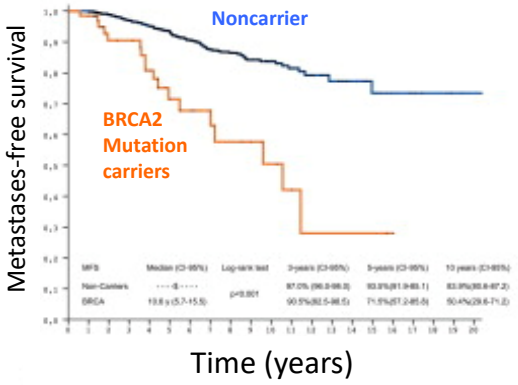
- 23% of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations increases with disease progression

Robinson D et al. *Cell* 2015; 161:1215-28.

BRCA2 Mutation Carriers have a Worse Prognosis



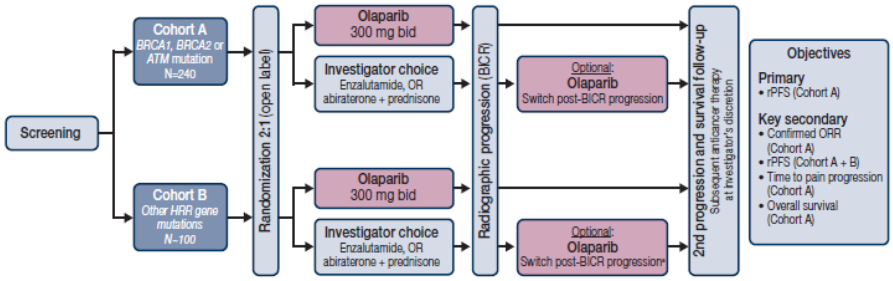
Castro et al. JCO 2013;31:1748-1757



Castro et al (2014) Eur Urol

PROfound Open-label Randomized Phase 3 Trial: Olaparib vs. Enzalutamide or Abiraterone

Patient Population: Men with mCRPC and a HRR mutation who failed prior abiraterone and/or enzalutamide; prior taxane allowed, but no prior DNA-damaging chemo or PARPi



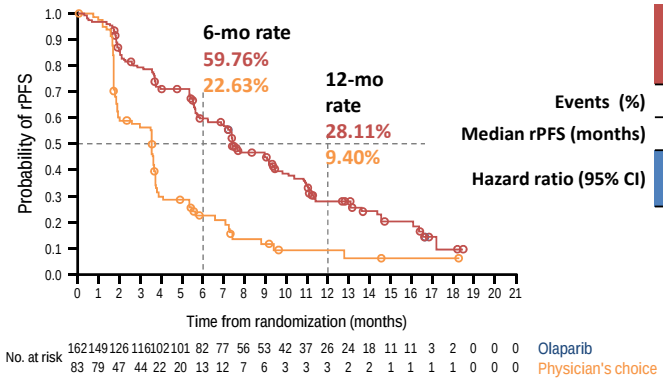
[a]Patients randomized to investigator-choice arm will be given the opportunity to begin treatment with open-label olaparib (300 mg bid), only after objective radiographic progression by BICR. No intervening systemic anticancer therapy, following discontinuation of randomized treatment, will be permitted. Patients may continue on olaparib, as long as they show clinical benefit as judged by the investigator

Central testing for HRR mutations using Foundation Med

ClinicalTrials.gov. NCT02987543; de Bono J, et al. Presented at ASCO 2017; abstract TPS5091.

PROfound rPFS

rPFS by BICR in patients with alterations in *BRCA1*, *BRCA2*, or *ATM* (Cohort A)



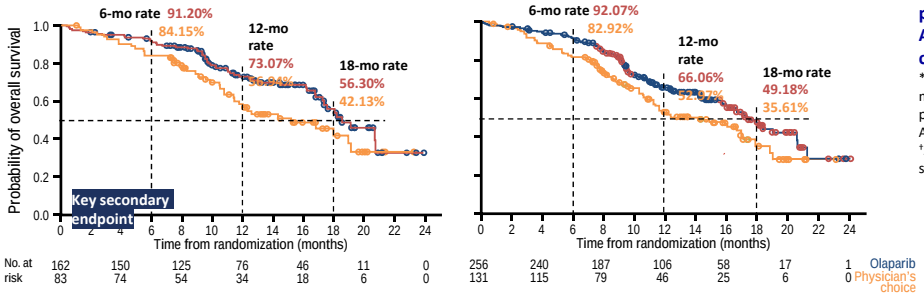
	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

Hussain M et al. ESMO 2019; LBA12 PR

PROfound Interim Overall Survival

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†	

Cohort A+B	Olaparib (N=256)	Physician's choice (N=131)
Median OS (months)	17.51	14.26
Hazard ratio (95% CI)	0.67 (0.49, 0.93) *P*=0.0063 (nominal)	



Of the physician's choice arm patients who progressed, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib

*38% maturity in Cohort A; 41% maturity in Cohort A+B; final analysis planned after ~146 deaths in Cohort A (60% maturity)

†Alpha spend at interim was 0.01; statistical significance not reached

Hussain M et al. ESMO 2019; LBA12 PR

TRITON-2: Phase 2 Study of Rucaparib in mCRPC With HRR Aberrations — ORR[1]

Characteristic	By HRR Gene With Alteration				
	BRCA1/2 (n = 57)	*ATM* (n = 21)	*CDK12* (n = 9)	*CHEK2* (n = 5)	Other (n = 13)
ORR, n (%)[a]	25 (43.9)	2 (9.5)	0	0	5 (38.5)
Complete response, n (%)	3 (5.3)	0	0	0	1 (7.7)[b]
Partial response, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)[c]
Stable disease, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
Progressive disease, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
Not evaluable, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)
Confirmed PSA response rate (all evaluable patients)	51/98 (52%)	2/57 (3.5%)	1/14 (7.1)	1/7 (14.3)	5/14 (35.7%)

- **43.9% confirmed objective responses were reported in 57 patients with *BRCA1/2* mutation**
- **52.0% confirmed PSA response in 98 PSA-evaluable patients with *BRCA1/2* mutation**

[a] Per modified RECIST/PCWG3 criteria. [b] One patient had *FANCA* alteration. [c] Two patients had a *PALB2* alteration; 1 patient each had a *BRIP1* or *RAD51B* alteration.

1. Abida W et al. ESMO 2019. Abstract 846PD.

New PARPi FDA Approvals for Prostate Cancer

In May 2020, based on data from the PROfound study, the FDA approved olaparib for the treatment of patients with pathogenic germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]

(*[a]BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*)

[b] Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer. Accessed June 2, 2020.

In May 2020, based on data from the TRITON2 study, the FDA granted accelerated approval to rucaparib for the treatment of patients with deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy[2]

2. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate. Accessed June 2, 2020.

GENetic Testing for MEN
with metastatic prostate cancer
www.gentlemenstudy.org

Cascading Impact

The Gentlemen Study

PARP inhibitors and platinum chemo, etc.

~1:10 men carries an inherited DNA repair gene mut.

50% chance of inheriting same DNA repair mutation

Tailored screening and risk-reduction

↑risk of prostate cancer, more aggressive

For brothers/sons:

- Screening for at-risk mutation carriers (SPORE P1)
- Neoadjuv PARPi or plat for BRCA1/2m carriers with high risk localized (SWOG)

cancer, more aggressive

Slide Courtesy of Dr. Heather Cheng

FDA Approval for Pembrolizumab is Tissue/Site Agnostic for MSI high and Hypermutated Solid Tumors

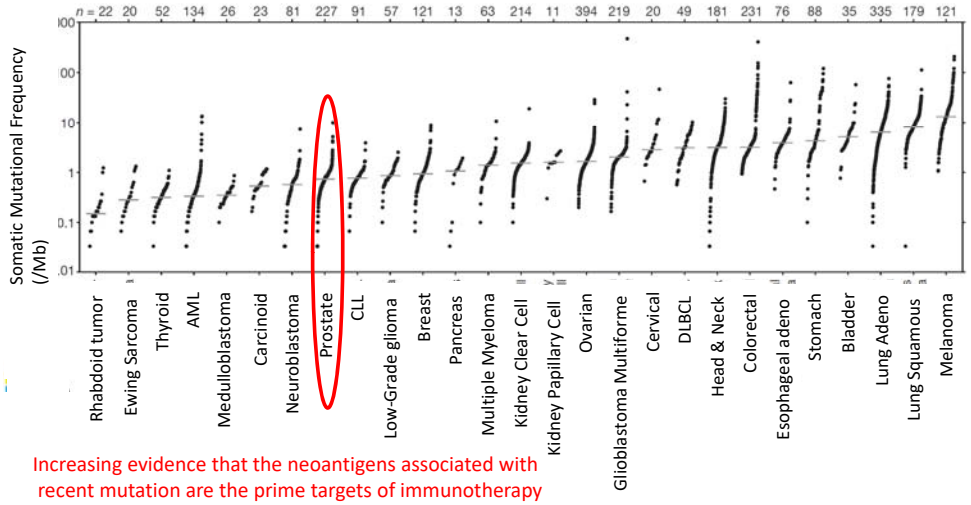
In May 2017, the US FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following patient treatment and who have no satisfactory alternative treatment options[1]

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication. Accessed August 20, 2020.

In June 2020, the FDA granted accelerated approval to pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[2]

2. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors. Accessed August 20, 2020.

Mutational Complexity in Cancer



Increasing evidence that the neoantigens associated with recent mutation are the prime targets of immunotherapy

Lawrence MS et al. *Nature* 2013; 499:214-8.

Mismatch Repair Alterations with MSI in Prostate Cancer

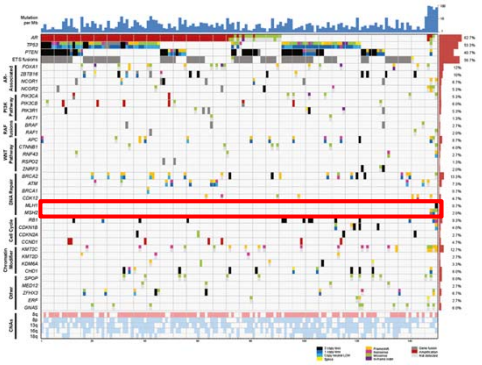
UW Rapid Autopsy

- 7/60 (11.7%) of advanced prostate cancers are hypermutated and all had mismatch repair gene mutations and MSI
- Hypermutation defined as >300 somatic protein altering mutations in metastatic tumors
- All mismatch repair alterations were in MSH2 or MSH6

Pritchard CC et al. Nat Commun. 2014; 5:4988.

SU2C mCRPC Biopsies

- 2.7% harbor MMR alterations in either MLH1 or MSH2, which are consistent with MSI



Robinson D et al. *Cell* 2015; 161:1215-28.

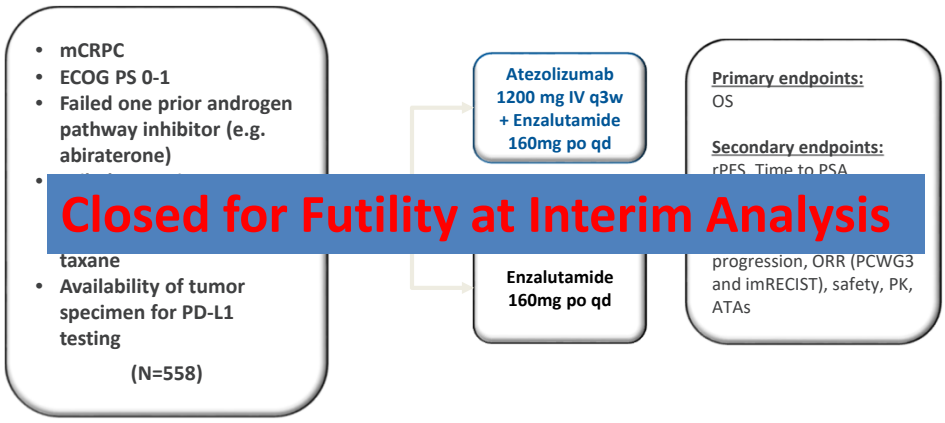
Pembrolizumab (x4 Cycles) Added to Enzalutamide Progressors

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

- 5 of 27 (19%) patients had a confirmed PSA response
- Relapsing responders have responded to retreatment

Graff JN et al. Oncotarget. 2016: 7:52810-7.

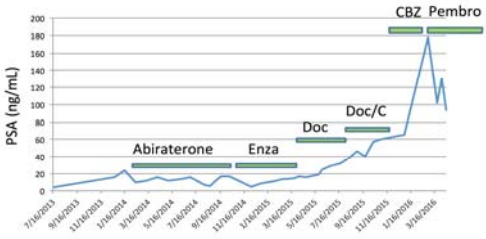
Imbassador 250 Trial



Sweeney C. AACR 2020 Plenary Session

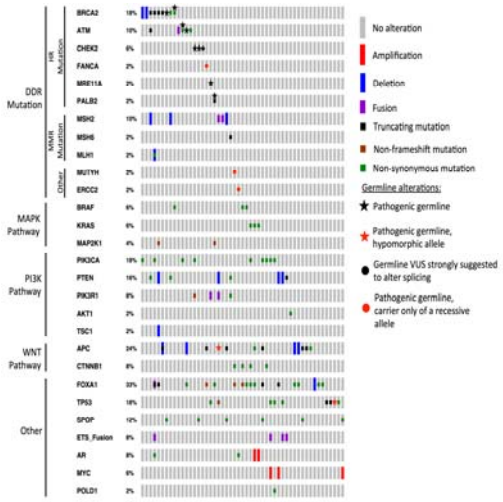
Prostate Ductal Carcinoma Enriches for MMR and DDR

- 4/10 (40%) with MMR
  - MLH1 (1), MSH2 (2), MSH6 (1)



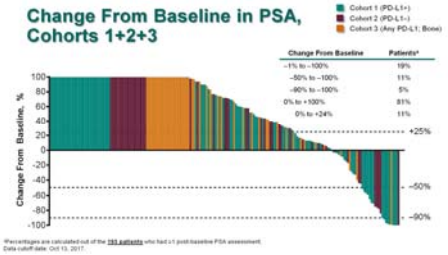
Schweizer MT et al. Oncotarget. 2016; 7:82504-10.

- Increased cases with UW, Johns Hopkins, and University of Calgary collaboration
  - 25/51 (49%) had at least 1 DNA Damage Repair (DDR) gene alteration

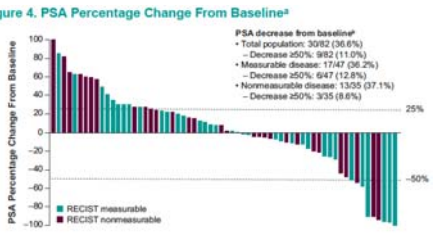


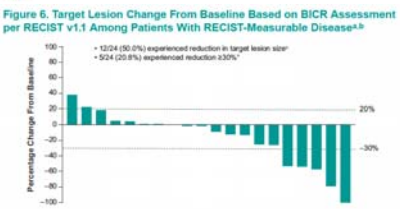
Schweizer MT et al. JCO Precision Oncology 2019; Epub April 2010.

Pembrolizumab for Unselected Prostate Cancer Populations



KEYNOTE-199: Post-docetaxel single agent Pembrolizumab



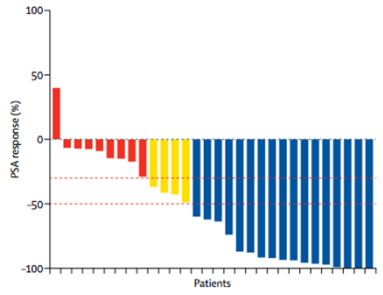


KEYNOTE-365 Cohort A: Post-docetaxel Pembrolizumab + Olaparib

De Bono J et al. *J Clin Oncol* 36, 2018 (suppl; abstr 5007).

Yu EY et al. *J Clin Oncol* 38, 2020 (suppl 6; abstr 100).

^{177}Lutetium-PSMA-617



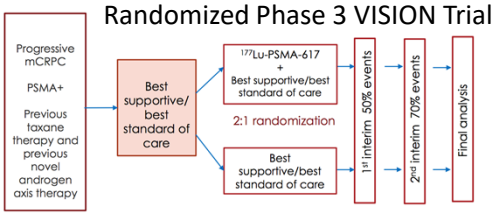
	Bone scintigraphy	Soft-tissue lesions (nodal and visceral;* n=17)	PSMA PET	FDG PET
Complete response	n/a	5 (29%)	3 (10%)	6 (20%)
Partial response	n/a	9 (53%)	9 (30%)	4 (13%)
Stable disease	11 (37%)†	0	0	1 (3%)
Progressive disease	9 (30%)	2 (12%)	8 (27%)	8 (27%)
Not performed (clinical progression or death)	9 (30%)	0	9 (30%)	10 (33%)
Not performed (death from other cause)	1 (3%)	1 (6%)	1 (3%)	1 (3%)

Data are n (%). The FDG PET refers to metabolic responses. PSMA=prostate-specific membrane antigen. *As assessed by Response Evaluation Criteria in Solid Tumors (version 1.1) with Prostate Cancer Clinical Trials Working Group 2 caveats. †Non-progressive disease on bone scintigraphy incudes patients with complete or partial response or stable disease.

Table 2: Imaging response at 3 months after last cycle of LuPSMA received

- ^{68} Ga-PSMA PET positive
- Received 1-2 previous taxanes; if only 1, then must be deemed ineligible or unwilling to receive a second taxane
- ^{177}Lu-PSMA-617 q6 wks X 6
- n=750

Randomized Phase 3 VISION Trial



Additional Secondary Endpoints
- Safety and tolerability
- Health-related quality of life (HRQoL: EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form [BPI-SF])
- Health economics
- Progression-free survival (PFS) (radiological, clinical or PSA progression)
- Biochemical response: PSA levels, alkaline phosphatase levels and lactate dehydrogenase levels

Stratification Factors
- Serum lactate dehydrogenase (LDH) (≤260 IU/L vs. >260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0-1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. no)

Primary Endpoint
- Overall survival

Key Secondary Endpoints (with α control)
- Radiographic progression-free survival (rPFS)
- RECIST response
- Time to first symptomatic skeletal event (SSE)

Hofman MS et al. Lancet Oncol. 2018; 19:825-33.

Key Take Home Points

- For patients with a short-lived response to novel hormonal agents (NHA), chemotherapy with cabazitaxel is superior to use of another NHA
- Treatment intensification successes for mCSPC have not been seen recently in mCRPC
- DNA repair deficiency occurs in 23% of metastatic castration-resistant prostate cancer patients and 12% are germline in metastatic prostate cancer -> cascade testing implications
- Olaparib and Rucaparib have regulatory approval for select DNA repair gene alterations
- Pembrolizumab can be used for MSI high or hypermutated prostate cancer
- Theranostics e.g. ^{177}Lutetium-617 are being tested in a phase 3 trial

Thank you very much!

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Q&A

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