A Specialty Series Review of Management of Patients with

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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A Specialty Series Review of Management of Patients with Non-metastatic Castration-resistant Prostate Cancer

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PROGRAM OVERVIEW

This activity will cover the treatment and management of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

TARGET AUDIENCE

This educational activity is specifically designed for US-based urologists, medical oncologists, radiation oncologists and other health care professionals (internists, primary care physicians, pathologists, physicians-in-training, urology nurses, oncology nurses, nurse practitioners, pharmacists, physician assistants and nurse practitioners) involved and/or interested in the therapeutic management of patients with nmCRPC.

LEARNING OBJECTIVES

On completing the program, attendees should be able to:

- Review the mechanisms of action and clinical profiles, including metastasis-free survival, of newer antiandrogen therapies for nmCRPC
- Explain why and when antiandrogen therapies should be initiated in asymptomatic patients with PC with rising PSA levels
- Design patient management plans that optimize sequencing of treatments used alone or in combination for patients with nmCRPC
- Discuss strategies to minimize side effects associated with the use of antiandrogen therapies in patients with nmCRPC

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Purpose:

This program would be beneficial for nurses involved and/or interested in the therapeutic management of patients with nmCRPC.

CNE Credits:

1.0 ANCC Contact Hour

CNE Accreditation Statement:

Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Faculty Member	Disclosure
Neal D. Shore, MD, FACS	Dr. Shore reports that he serves as a consultant for Abbvie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Clovis Oncology, Dendreon, FerGene, Ferring, Janssen, Merck, Myovant, Nymox, Pfizer, Sanofi-Genzyme, and Tolmar. He also serves on the speakers bureau for Abbvie, Bayer and Jannsen.
Marc A. Bjurlin, DO	Dr. Bjurlin reports that he has no relevant relationships with a commercial entity or manufacturer.
Thomas Cartwright, MD	Dr. Cartwright reports that he serves on the speakers bureau for Amgen and Taiho.
Neil Desai, MD	Dr. Desai reports that he has no relevant relationships with a commercial entity or manufacturer.
Paul Monk, MD	Dr. Monk reports that he serves on the speakers bureau for Janssen. He is also a consultant for Dendreon and is on the Data Safety Monitoring Committee for Sanofi.

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

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2. Participate in the live activity
3. Submit the evaluation form online

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AGENDA

I. Non-metastatic Castration-resistant Prostate Cancer (nmCRPC): An Overview

a. Epidemiology, incidence, and prevalence of nmCRPC
b. Burden of disease
c. Clinical presentation
d. Disease course
e. Role of androgen receptor (AR) in the pathophysiology of prostate cancer
f. Role of prostate specific antigen (PSA) and PSA doubling time in treatment decisions

II. Treatment Options for nmCRPC

a. Recommended treatment options
b. Mechanisms of action of newly-approved antiandrogen therapies indicated for nmCRPC
c. The utility of metastasis-free survival (MFS) for patients undergoing non-metastatic treatments
d. Clinical trial data on the efficacy, safety, and tolerability of:
    a. Apalutamide
    b. Enzalutamide
    c. Darolutamide

III. Personalizing the Management of nmCRPC

a. When to initiate antiandrogen therapies in asymptomatic patients with rising PSA levels
b. Treatment sequencing strategies
c. Treatment combination strategies
d. Managing adverse events

IV. Case Study

V. Conclusions

Newer Antiandrogen Therapies for the Management of Patients with Non-metastatic Castration-resistant Prostate Cancer

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Disclosures

- Neal Shore, MD, FACS, has received consultant fees from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Dendreon, Ferring Pharmaceuticals, and FoundationMed and research funding from Janssen, Merck, Myovant, Nymox, Pfizer, Sanofi Genzyme, and Tolmar.
- During the course of this lecture, Dr. Shore may mention the use of medications for both FDA-approved and non-approved indications.

This activity is supported by an educational grants from Astellas Pharma Global Development, Inc. and Bayer HealthCare Pharmaceuticals Inc.

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Learning Objectives

- Review the mechanisms of action and clinical profiles, including metastasis-free survival, of newer antiandrogen therapies for non-metastatic castration-resistant prostate cancer (nmCRPC)
- Explain why and when antiandrogen therapies should be initiated in asymptomatic patients with prostate cancer with rising prostate-specific antigen levels
- Design patient-management plans that optimize sequencing of treatments used alone or in combination for patients with nmCRPC

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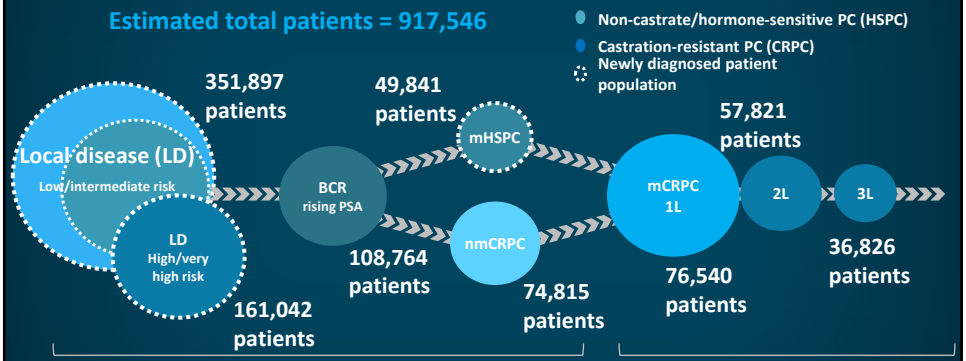
Prostate Cancer (PC) Diagnosis May Occur at Various Stages of Disease and Progress Through Different Pathways



BCR = biochemical recurrence; PSA = prostate-specific antigen; mHSPC = metastatic hormone-sensitive PC; nmCRPC = non-metastatic CRPC; BCR = biochemical recurrence.

Decision Resources Group, December 2018. Drug-treatable population [incidence cases + recurrence cases] for EU5, JPN, US. Area proportional to patient numbers

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The Burden of Castration-Resistant Prostate Cancer (CRPC)

Prevalence	**10–20% of prostate cancer patients develop CRPC within approximately 5 years of follow-up.**
Metastases	>84% of patients have metastases present at the time of CRPC diagnosis; in those without metastases at diagnosis, 33% of patients with CRPC develop metastases within 2 years of their diagnosis.
Survival	The median survival from CRPC diagnosis is 14 months.

Based on data from 71,179 patients across 12 studies observed up to 12 years[1]

- The burden of **nmCRPC** in the US[2]
  - Incidence of 50,000–60,000 men per year
  - Prevalence of 100,000 men
  - Overall mortality of 16%

1. Kirby M, et al. *Int J Clin Pract*. 2011;65:1180-1192. 2. Geynisman DM, et al. *Eur Urol*. 2016;70:971-973.

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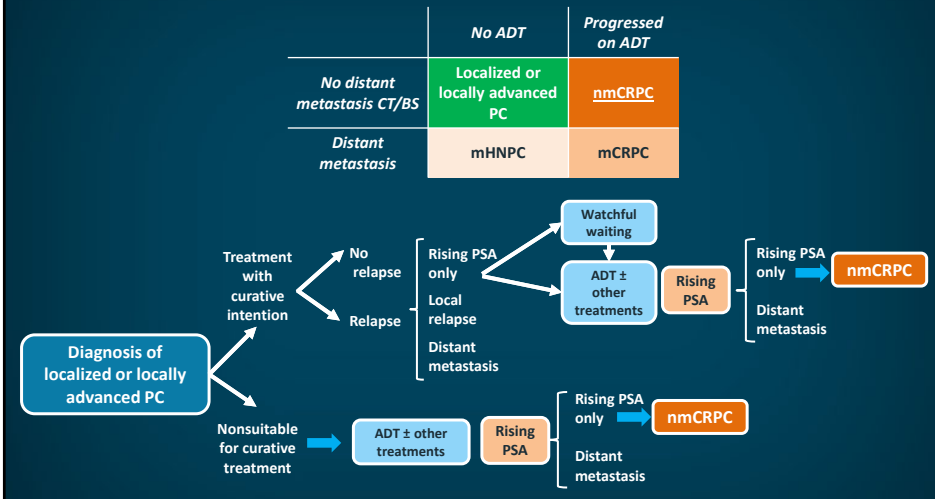
Disease Evolution of nmCRPC



ADT = androgen-deprivation therapy; CT = computed tomography (scan); BS = bone scan; mHNPC = metastatic hormone-naïve PC; mCRPC = metastatic CRPC.

Mateo J, et al. *Eur Urol*. 2019;75:285-293.

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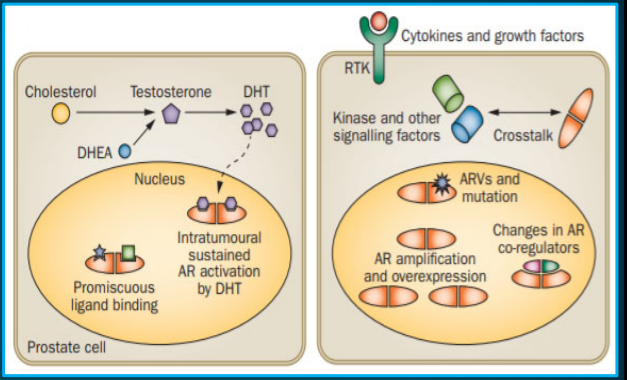
Development of CRPC

Causes of CRPC

- Overexpression of androgen receptor (AR) can sensitize PC cells to low levels of residual androgens.
- Mutated AR may bind other androgenic and non-androgenic steroids.
- Mutated AR may not require ligand binding to translocate and bind to DNA.



AR = androgen receptor; ARV = androgen receptor splice variant; DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone; RTK = receptor tyrosine kinase

Greasley R, et al. *Cancer Manag Res*. 2015;7:153-164. Zong Y, Goldstein AS. *Nat Rev Urol*. 2013;10:90-98.

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Definition of nmCRPC

CRPC is defined as castrate levels of serum testosterone (<50 ng/dL or <1.7 nmol/L) plus either/or biochemical and radiologic disease progression.[1]

	Biochemical progression	Radiologic progression
EAU/ESTRO/SIOG[1]	Three consecutive rises of PSA, one week apart, resulting in two 50% increases over the nadir, and PSA >2 ng/mL	Appearance of new lesions: • ≥2 new bone lesions on bone scan *or* • soft-tissue lesion using RECIST
PCWG2[2]	A rising PSA of ≥25% and absolute increase of ≥2 ng/mL from the nadir, confirmed by a second value obtained ≥3 weeks later	• ≥2 new lesions on bone scan *or* • Progression in nodal or visceral site using RECIST

nmCRPC is defined by evidence of biochemical progression with no radiologic evidence of metastatic disease.[3]

- Index patient: asymptomatic nmCRPC[3]
- Rising PSA despite medical or surgical castration

EAU = European Association of Urology; ESTRO = European Society for Radiotherapy & Oncology; SIOG = International Society of Geriatric Oncology; RECIST = Response Criteria in Solid Tumors; PCWG = Prostate Cancer Clinical Trials Working Group.

1. Cornford P, et al. *Eur Urol*. 2017;71:630-642. 2. Scher HI, et al. *J Clin Oncol*. 2008;26:1148-1159. 3. Cookson MS, et al; American Urological Association. *J Urol*. 2015;193:491-499.

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Defining nmCRPC

- Rising PSA despite medical or surgical castration
- Inclusion criteria for clinical trials included only "high risk" nmCRPC
  - PSA = ≥2
  - PSA-DT = ≤10 months

FDA labeling does not restrict the use of apalutamide, enzalutamide, or darolutamide for nmCRPC patients with respect to PSA-DT

DT = doubling time.

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

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Recommended Management of nmCRPC

- Continue ADT to maintain castration serum levels of testosterone (<50 ng/mL)[1,2]
  - Offer apalutamide, darolutamide, or enzalutamide if PSA-DT is ≤10 months
- For patients with nmCRPC who are at high risk for developing metastatic disease who do not want or cannot have standard therapy:[2]
  - Clinicians may recommend observation with continued androgen deprivation; **or**
  - Clinicians may offer treatment with a second-generation androgen-synthesis inhibitor (eg, abiraterone plus prednisone) if patient is unwilling to accept observation
- Clinicians should not offer systemic chemotherapy or immunotherapy to patients with nmCRPC outside the context of a clinical trial[2]

1. National Comprehensive Cancer Network (NCCN). *Prostate Cancer*. V1.2020. (www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). 2. American Urological Association (AUA) guidelines. (www.auanet.org/guidelines/prostate-cancer-castration-resistant-guideline). Accessed 4/7/2020.

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PSA Doubling Time (PSA-DT) in nmCRPC

- PSA-DT <10 months is associated with a 12x higher risk of bone metastasis and 4x higher risk of death compared with patients with PSA-DT ≥10 months.[1]
- The median time to metastasis is shorter in patients with decreased PSA-DT.[2,3]

Time to Metastasis Based on PSA-DT[2]	
PSA-DT (months)	Median Time to Metastasis (months)
<3.0	9
3.0–8.9	19
9.0–14.9	40
≥15.0	50

mo = month(s).

1. Metwalli AR, et al. *Urol Oncol*. 2014;32:761-768. 2. Howard LE, et al. *BJU Int*. 2017;120:E80-E86.
3. Moreira DM, et al. *Urology*. 2016;96:171-176.

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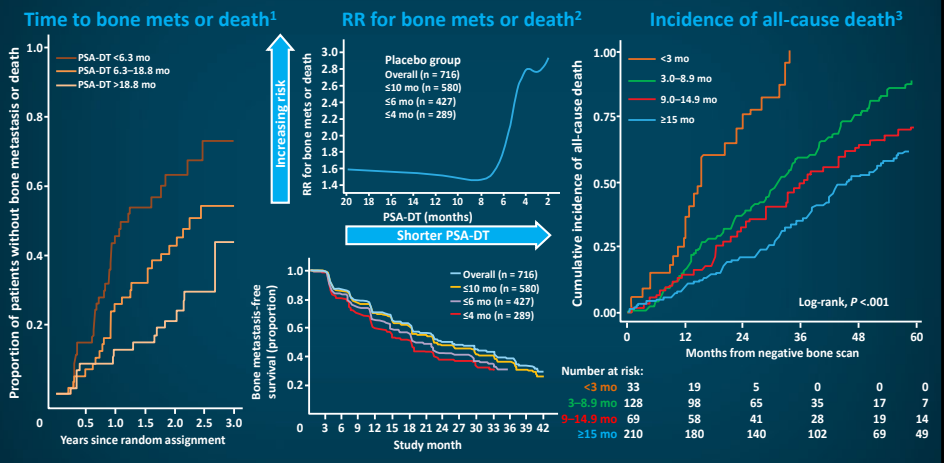
Risk of Bone Metastases or Death for Men with nmCRPC Based on PSA-DT



mets = metastases; RR = relative risk.

1. Smith MR, et al. *J Clin Oncol*. 2005;23:2918-2925. 2. Smith MR, et al. *J Clin Oncol*. 2013;31:3800-3806.
3. Howard LE, et al. *BJU Int*. 2017;120:E80-E86.

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Treatment Selection for nmCRPC Patients

- Clinical considerations
  - Age
  - Life expectancy
  - Comorbidities
  - Stage and grade of cancer
  - Side effects
- Patient considerations
  - Quality of life
  - Symptoms
  - PSA (anxiety)
  - Survival
  - Cost
  - Accessibility

American Cancer Society (ACS). Treating prostate cancer (www.cancer.org/cancer/prostate-cancer/treating.html). Accessed 4/7/2020.

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Risk-Benefit Analysis: Shared Decision-Making

3 "P" goals

Prolong survival

Preserve quality of life

Prevent complications of therapy

+

4th "P" (decision-making)

Preference value (risk tolerance)

- performance status (ECOG)
- concomitant medications
- comorbidities and therapeutic benefit

ECOG = Eastern Cooperative Oncology Group.

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Factors Increasing Earlier Conversion of M0 to M1

- Initial biopsy: Gleason grade/number of positive cores/% core involvement
- Duration of ADT response (before converting to CRPC)
- Age at diagnosis
- Family history/genetic mutations

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Calculating PSA-DT: Not So Simple but It's Quick…

Specific period of time over which PSA levels are measured?

Exclude PSA measures taken many years before?

Logarithmically transform PSA values before analysis?

≥3 measurements required over a minimum total length of time?

Certain minimum period required between PSA measurements?

Are PSA measurements close together statistical "noise"?

Vickers AJ, Brewster SF. *Br J Med Surg Urol.* 2012;5:162-168.

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Anti-androgen Therapies for nmCRPC

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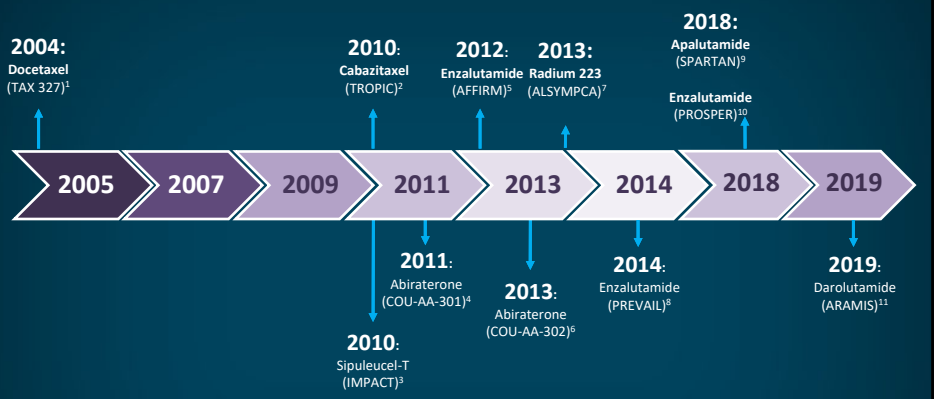
CRPC Treatment Evolution



While the greater availability of therapeutic agents benefits patients, the multiple options and sequencing of medications complicates clinical decision-making.

1. Tannock IF, et al. *N Engl J Med*. 2004;351:1502-1512. 2. de Bono JS, et al. *Lancet*. 2010;376:1147-1154. 3. Kantoff PW, et al. *N Engl J Med*. 2010; 363:411-422. 4. de Bono JS, et al. *N Engl J Med*. 2011;364:1995-2005. 5. Scher HI, et al. *N Engl J Med*. 2012;367:1187-1197. 6. Ryan CJ, et al. *N Engl J Med*. 2013;368:138-148. 7. Parker C, et al. *N Engl J Med*. 2013;369:213-223. 8. Beer TM, et al. *N Engl J Med*. 2014;371:424-433. 9. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418. 10. Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474. 11. Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246.

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Enzalutamide, Apalutamide, and Darolutamide

- Enzalutamide and apalutamide are second-generation antiandrogens that target androgen receptors with inhibitory function[1]:
  - Prevent binding of androgens to the AR
  - Inhibit translocation of the AR into the nucleus
  - Interfere with binding of the AR to the DNA
- Darolutamide, which is an androgen-receptor antagonist that is structurally distinct from apalutamide and enzalutamide, is characterized by low blood–brain barrier penetration and may have improved tolerability.[1–3]

1. Heidegger I, et al. *Urol Oncol*. 2020;Epub ahead of print. 2. Zurth C, et al. *J Clin Oncol*. 2018;36(6 suppl):abstract 345.
3. Zurth C, et al. *J Clin Oncol*. 2019;37(7 suppl):abstract 156.

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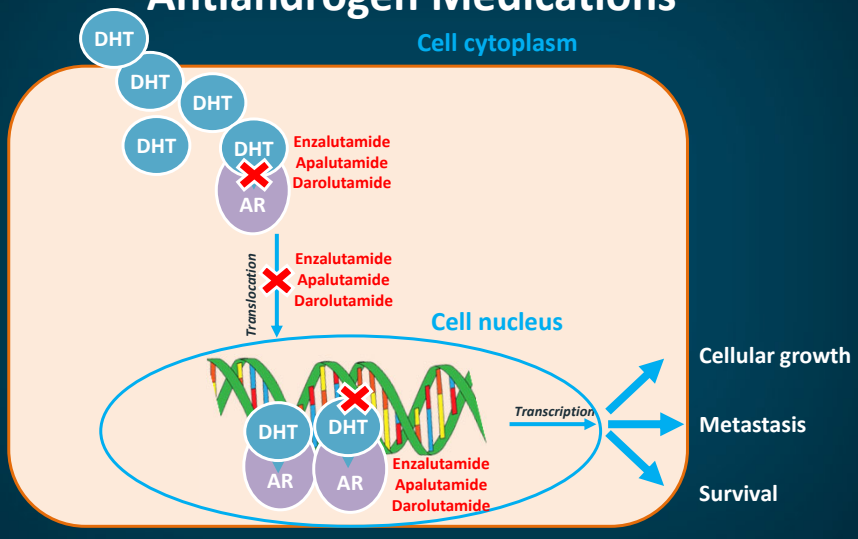
Mechanism of Action of Antiandrogen Medications



DHT = dihydrotestosterone

Heidegger I, et al. *Urol Oncol*. 2020:Epub ahead of print.

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3 Trials in nmCRPC With MFS as Primary Endpoint

MFS = metastasis-free survival.

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

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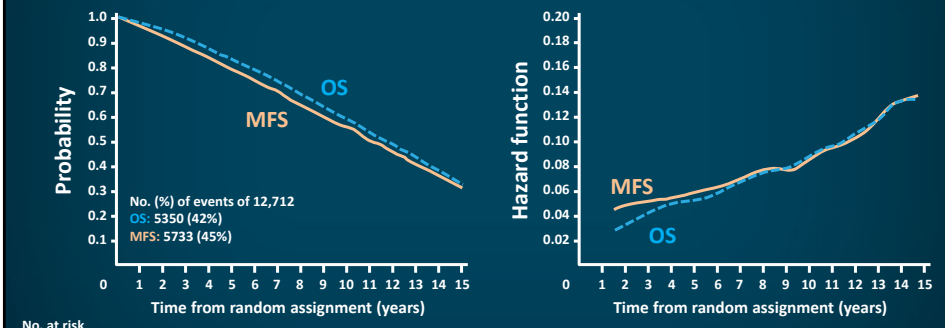
Metastasis-Free Survival

- MFS is a strong surrogate for OS in localized prostate cancer.
- Delaying time to metastasis has the potential to delay cancer-related morbidity and prolong overall survival.



No. at risk

OS	12,712	11,321	8162	4714	1853	726
MFS	12,712	10,831	7656	4394	1711	668

OS = overall survival.

Xie W, et al. *J Clin Oncol*. 2017;35:3097-3104.

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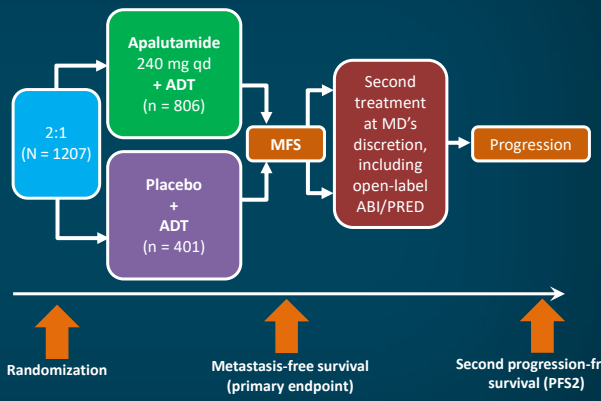
SPARTAN: Apalutamide vs Placebo: Study Design

Phase 3, placebo-controlled, randomized international study

Eligibility
- nmCRPC
  - Pelvic nodes <2 cm below iliac bifurcation (N1) allowed
  - Rising PSA despite castrate testosterone level (≤50 ng/dL)
- PSA-DT ≤10 months

On-study requirement
- Continuous ADT

Stratifications
- PSA-DT >6 mo or ≤6 mo
- Bone-sparing agents, yes/no
- N0 or N1



ABI = abiraterone acetate; PRED = prednisone; PFS = progression-free survival.

Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418. Small EJ, et al. *J Clin Oncol*. 2018;36(6 suppl):abstract 161.

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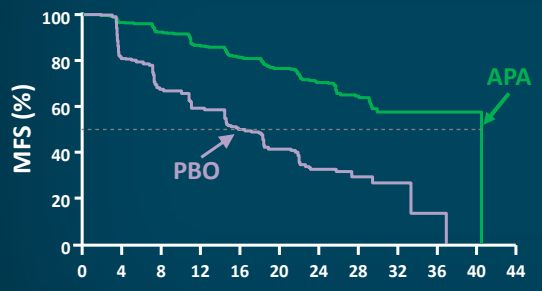
SPARTAN Primary Endpoint: Metastasis-Free Survival

72% risk reduction in distant progression or death



Time to MFS	APA + ADT n = 806	PBO + ADT n = 401
Median	40.5 mo	16.2 mo

HR = 0.28 (95% CI, 0.23–0.35), *P* <.001

No. at risk												
APA	806	713	652	514	398	282	180	96	36	16	3	0
PBO	401	291	220	153	91	58	34	13	5	1	0	0

APA = apalutamide; PBO = placebo; HR = hazard ratio; CI = confidence interval.

Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418. Small EJ, et al. *J Clin Oncol*. 2018;36(6 suppl):abstract 161.

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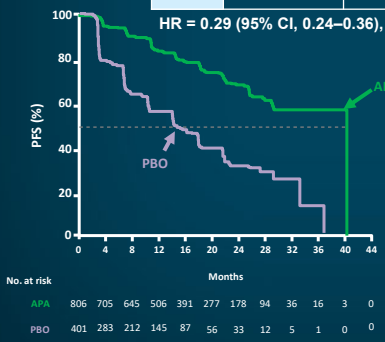
SPARTAN: Secondary Endpoints

Progression-free survival
71% risk reduction in local progression, distant progression, or death

PFS	APA + ADT n = 806	PBO + ADT n = 401
Median	40.5 mo	14.7 mo

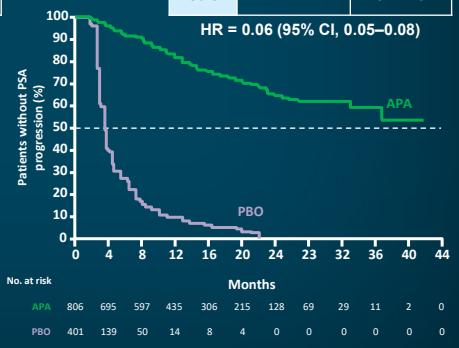
HR = 0.29 (95% CI, 0.24–0.36), *P* <.001



Time to PSA progression

Time to PSA Progression	APA + ADT n = 806	PBO + ADT n = 401
Median	NR	3.7 mo

HR = 0.06 (95% CI, 0.05–0.08)



NR = not reached.

Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418. Small EJ, et al. *J Clin Oncol*. 2018;36(6 suppl):abstract 161.

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SPARTAN: Adverse Events (AEs)

	APA n = 803		PBO n = 398	
Any grade 3 or 4 AE, %	45		34	
Serious AE, %	25		23	
AE leading to discontinuation, %	11		7	
Patients remaining on treatment*, %	61		30	
AE, grades, %	**All**	**3/4**	**All**	**3/4**
Fatigue	30.4	0.9	21.1	0.3
Rash	23.8	5.2	5.5	0.3
Weight loss	16.1	1.1	6.3	0.3
Arthralgia	15.9	0	7.5	0
Falls	15.6	1.7	9.0	0.8
Fractures	11.7	2.7	6.5	0.8
Hypothyroidism	8.1	0	2.0	0
Seizure	0.2	0	0	0

*At clinical cutoff date.

Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418. Small EJ, et al. *J Clin Oncol*. 2018;36(6 suppl):abstract 161.

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PROSPER: Enzalutamide vs Placebo Study Design

- Design: multinational, phase 3, randomized, double-blind study
- Primary endpoint: MFS
- Secondary endpoints: OS, time to pain progression, chemotherapy use, new antineoplastic use, PSA progression, PSA response rate, QoL, and safety

- nmCRPC
  - Rising PSA despite castrate testosterone level (≤50 ng/dL)
  - Baseline PSA ≥2 ng/mL
  - PSA doubling time ≤10 months
- Stratifications
  - PSA-DT <6 or >6 months
  - Baseline use of bone-targeting agent
- N = 1401

R

Enzalutamide 160 mg/d + ADT

Placebo + ADT

To radiographic progression

QoL = quality of life.

Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474. NCT02003924. (https://clinicaltrials.gov/ct2/show/NCT02003924). Accessed 4/8/2020.

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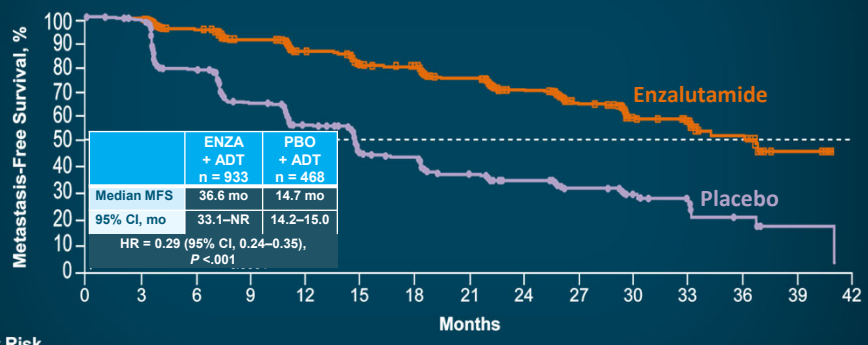
PROSPER Primary Endpoint: MFS

Median MFS was ≈22 months longer with enzalutamide than with placebo. There was a 71% reduction in relative risk of radiographic progression or death.



No. at Risk

ENZA + ADT	933	865	759	637	528	431	418	328	237	159	87	77	31	4	0
PBO + ADT	468	420	296	212	157	105	98	64	49	31	16	11	5	1	0

ENZA = enzalutamide.

Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474.

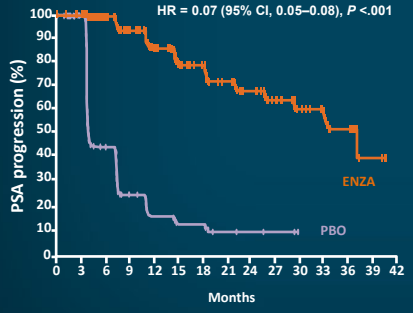
28

PROSPER: Secondary Endpoints

Median time to PSA progression ≈33 months longer with ENZA than with PBO (93% relative risk reduction)

Time to PSA Progression		
	ENZA+ADT	PBO+ ADT
Median	37.2 mo	3.9 mo
95% CI	33.1–NR mo	3.8–4.0 mo

HR = 0.07 (95% CI, 0.05–0.08), *P* <.001



Median time to 1st use of new antineoplastic Tx ≈22 months longer with ENZA than with PBO (79% relative risk reduction)

Time to Antineoplastic Tx		
	ENZA+ADT	PBO+ ADT
Median	39.6 mo	17.7 mo
95% CI	37.7–NR mo	16.2–19.7 mo

HR = 0.21 (95% CI, 0.17–0.26), *P* <.001

Median time to first use of new antineoplastic treatment was ≈22 months longer with enzalutamide than with placebo (79% relative risk reduction).

Tx = treatment.

Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474.

29

PROSPER: Adverse Events of Special Interest

AE, any grade	Enzalutamide + ADT n = 930 n (%)	Placebo + ADT n = 465 n (%)
Hypertension*	114 (12)	25 (5)
Major adverse cardiovascular event†	48 (5)	13 (3)
Mental impairment disorders‡	48 (5)	9 (2)
Hepatic impairment	11 (1)	9 (2)
Neutropenia	9 (1)	1 (<1)
Convulsion	3 (<1)	0
Posterior reversible encephalopathy syndrome	0	0

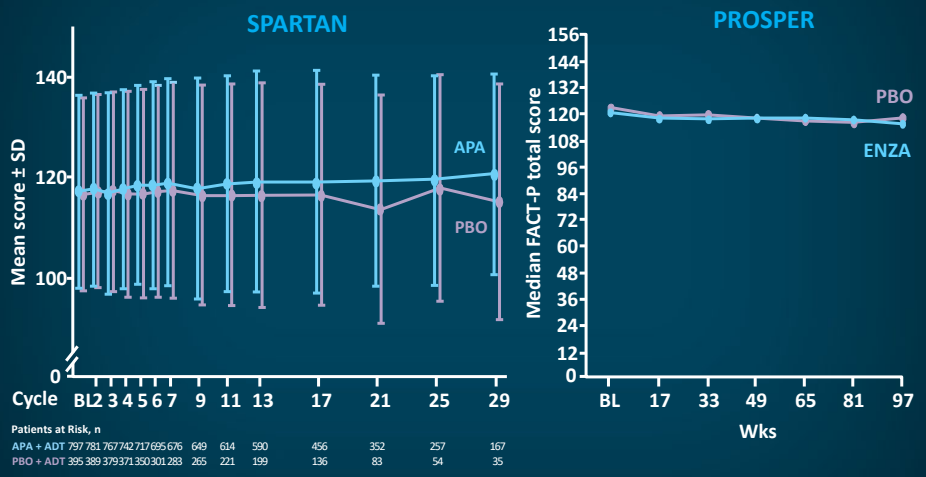
In both arms, the incidence of major adverse cardiovascular events was higher in patients with a history of cardiovascular disease, hypertension, diabetes mellitus, or hyperlipidemia, or aged ≥75 years.

*Includes increased blood pressure. †Includes acute myocardial infarction, hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions, and heart failure. ‡Includes memory impairment, disturbance in attention, cognitive disorders, amnesia, dementia Alzheimer's type, senile dementia, mental impairment, and vascular dementia.

Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474. Hussain M, et al. *J Clin Oncol*. 2018;36(6 suppl): abstract 3.

30

SPARTAN and PROSPER
Effect of Treatment on QoL Assessed With FACT-P

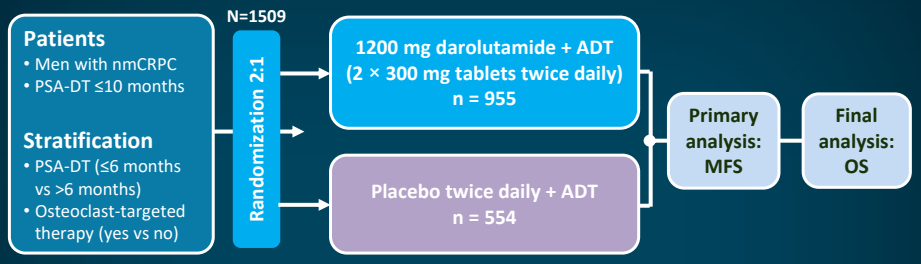


FACT-P = Functional Assessment of Cancer Therapy-Prostate; SD = standard deviation; BL = baseline.

1. Saad F, et al. *Lancet Oncol.* 2018;19:1404-1416. 2. Tombal B, et al. *Lancet Oncol.* 2019;20:556-569.

31

ARAMIS Trial Design



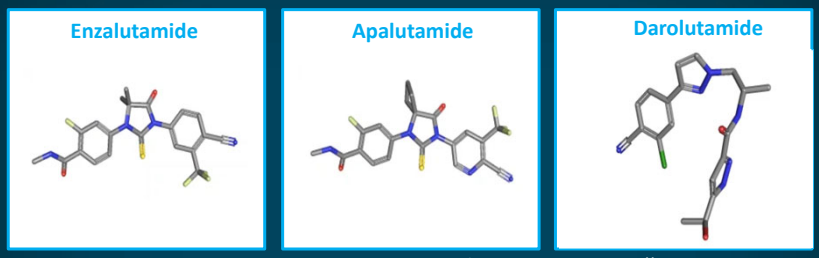
- **Primary endpoint (significance level of 0.05)**
  - MFS
- **Secondary endpoints (significance level of 0.05 between primary and final analyses)**
  - OS
  - Time to pain progression
  - Time to first cytotoxic chemotherapy
  - Time to first SSE
  - Safety
- **Exploratory endpoints**
  - PFS
  - Time to PSA progression
  - PSA response rate
  - Time to first prostate cancer-related invasive procedure
  - Time to initiation of subsequent antineoplastic therapy
  - Time to ECOG performance status deterioration
  - QoL

SSE = symptomatic skeletal event.

Fizazi K, et al. *N Engl J Med.* 2019;380:1235-1246.

32

Darolutamide: Structurally Unique Androgen Receptor Antagonist



Images from PubChem database: https://pubchem.ncbi.nlm.nih.gov.

- Darolutamide is structurally distinct from apalutamide and enzalutamide. [1,2]
- Darolutamide shows lower blood-brain barrier penetration than apalutamide and enzalutamide.[1–3]
- Darolutamide has minimal interaction with hepatic cytochrome P450 metabolism, giving it a low potential for drug-drug interactions.[4]

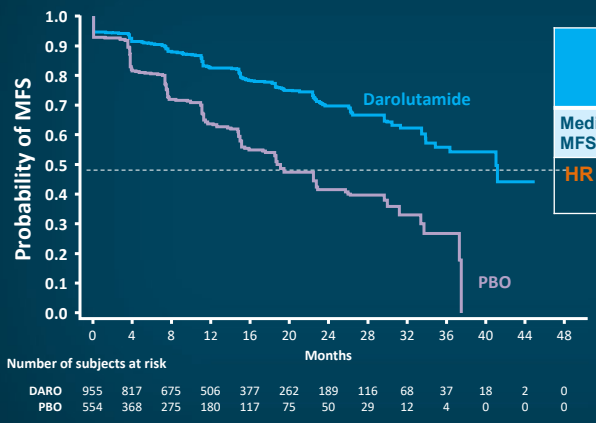
CNS = central nervous system.

1. Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246. 2. Zurth C, et al. *J Clin Oncol*. 2019;37(7 suppl): abstract 156.
3. Zurth C, et al. *J Clin Oncol*. 2018;36(6 suppl):abstract 345. 4. Zurth C, et al. *J Clin Oncol*. 2019;37(7 suppl): abstract 297.

33

Primary Endpoint: MFS

59% risk reduction of distant metastases or death



	DARO + ADT n = 955	PBO + ADT n = 554
Median MFS	40.4	18.4
HR = 0.41 (95%CI, 0.34–0.50), *P* <.001		

Number of subjects at risk

DARO	955	817	675	506	377	262	189	116	68	37	18	2	0
PBO	554	368	275	180	117	75	50	29	12	4	0	0	0

Median follow-up time at primary analysis was 17.9 months.

DARO = darolutamide.

Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246.

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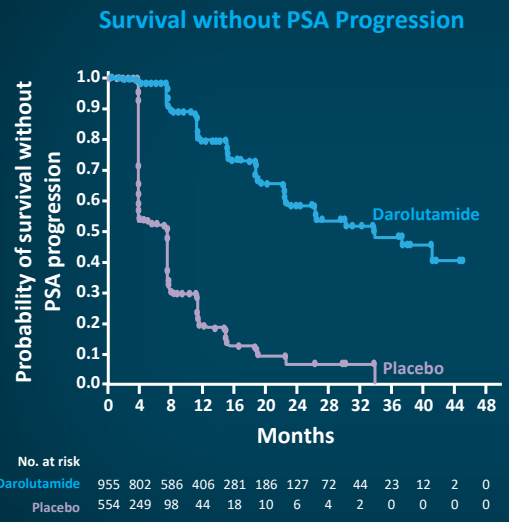
Darolutamide: Survival without PSA Progression



	DARO + ADT n = 955	PBO + ADT n = 554
Median survival without PSA progression, mo	32.2	7.3
95% CI	25.9–NR	3.9–7.4
HR = 0.13 (95%CI, 0.11–0.16), *P* <.001		

Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246.

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ARAMIS: Adverse Events of Interest

AE, all grades, n (%)	Darolutamide (n = 954)	Placebo (n = 554)
Fatigue/asthenic conditions	151 (15.8)	63 (11.4)
Dizziness (including vertigo)	43 (4.5)	22 (4.0)
Cognitive disorder	4 (0.4)	1 (0.2)
Memory impairment	5 (0.5)	7 (1.3)
Seizure (any event)	2 (0.2)	1 (0.2)
Bone fracture	40 (4.2)	20 (3.6)
Falls (including accident)	40 (4.2)	26 (4.7)
Hypertension	63 (6.6)	29 (5.2)
Coronary artery disorders	31 (3.2)	14 (2.5)
Heart failure	18 (1.9)	5 (0.9)
Rash	28 (2.9)	5 (0.9)
Weight decreased (any event)	34 (3.6)	12 (2.2)
Hypothyroidism	2 (0.2)	0

Fizazi K, et al. *N Engl J Med*. 2019;380:1235-1246.

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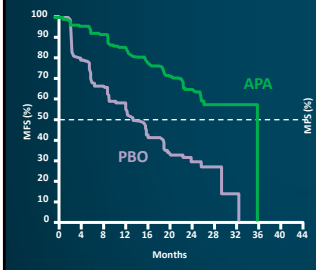
Metastasis-Free Survival

Apalutamide: SPARTAN

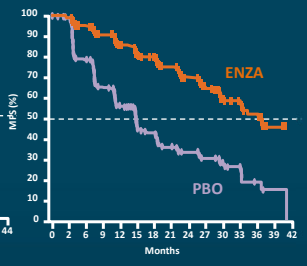
	APA + ADT	PBO + ADT
Median MFS	40.5 mo	16.6 mo
HR = 0.28 (95%CI, 0.23–0.35), *P* <.0001		



- **72% reduction in distant progression or death**
- 24-month increase in MFS

Enzalutamide: PROSPER

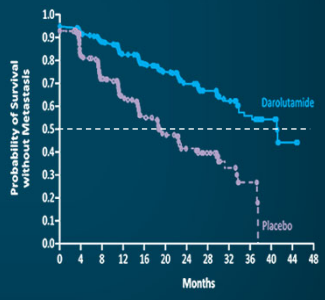
	ENZA + ADT	PBO + ADT
Median MFS	36.6 mo	14.7 mo
HR = 0.29 (95%CI, 0.24–0.35), *P* <.001		



- **71% reduction in distant metastases or death**
- 22-month increase in MFS

Darolutamide: ARAMIS

	DARO + ADT	PBO + ADT
Median MFS	40.4 mo	18.4 mo
HR = 0.41 (95%CI, 0.34–0.50), *P* <.001		



- **59% reduction in distant metastases or death**
- 22-month increase in MFS

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

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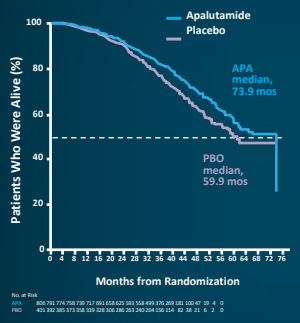
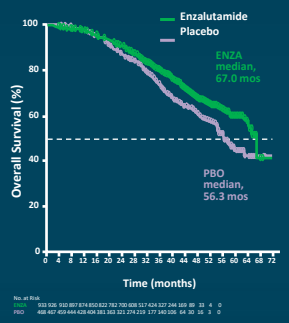
Secondary Endpoint: Updated Overall Survival

SPARTAN[1] Apalutamide



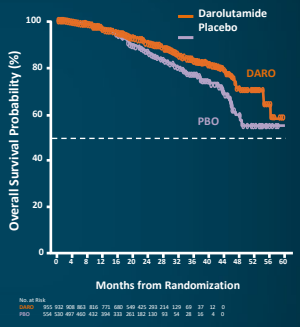
- 22% reduction in risk of death
- HR = 0.78 (95% CI, 0.64-0.96)
- *P* = 0.0161

PROSPER[2] Enzalutamide



- 27% reduction in risk of death
- HR = 0.73 (95% CI 0.61-0.89)
- *P* = 0.001

ARAMIS[3] Darolutamide



- 31% reduction in risk of death
- HR = 0.69 (95% CI, 0.53-0.88);
- *P* = 0.003

1. Small EJ, et al. *ASCO* 2020. Abstract 5516. 2. Sternberg CN, et al. *ASCO* 2020. Abstract 5515. 3. Fizazi K, et al. *ASCO* 2020. Abstract 5514.

38

Are There SPARTAN, PROSPER, ARAMIS Trial Differences?

- MFS definition: PROSPER = 112-day metric; ARAMIS small % mCRPC
- Inclusion criteria: SPARTAN/ARAMIS, pelvic lymph nodes <2.0 cm; PROSPER, <1.5 cm
- Bone health agents: ~10% PROSPER and SPARTAN; ~3% ARAMIS
- Data: MFS HRs (SPARTAN = 0.28, PROSPER = 0.29, ARAMIS = 0.41); OS pending for all
- Differences in baseline tumor burden and localized therapy
- Differences in adverse event definitions/collection

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

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Demographic and Disease Characteristics at Baseline

SPARTAN: apalutamide

Characteristic	APA n = 806	PBO n = 401
Age—yr		
Median	74	74
Range	48–94	52–97
Median time from initial diagnosis to randomization—yr	7.95	7.85
PSA-DT		
Median—mo	4.40	4.50
≤6 mo—no. (%)	576 (71.5)	284 (70.8)
>6 mo—no. (%)	230 (28.5)	117 (29.2)
Use of bone-sparing agent—no. (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
Classification of local or regional nodal disease—no. (%)		
N0	673 (835)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Previous PC treatment—no. (%)		
Prostatectomy or radiation therapy	617 (76.6)	307 (76.6)
GNRH analogue agonist	780 (96.8)	387 (96.5)
First-generation antiandrogen agent	592 (73.4)	290 (72.3)

PROSPER: enzalutamide

Characteristic	ENZA + ADT n = 933	PBO + ADT n = 468
Median age (range), y	74 (50–95)	73 (53–92)
ECOG PS, no. (%)		
0	747 (80)	382 (82)
1	185 (20)	85 (18)
Median serum PSA (range), ng/mL	11.1 (0.8–1071.1)	10.2 (0.2–467.5)
Median PSA-DT (range), mo	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA-DT category, no. (%)		
<6 mo	715 (77)	361 (77)
≥6 mo	217 (23)	107 (23)
Use of bone targeting agent, no. (%)		
No	828 (89)	420 (90)
Yes	105 (11)	48 (10)

ARAMIS: darolutamide

Characteristic		DURA n = 955	PBO n = 554
Median age (range)—yr		74 (48–95)	74 (50–92)
Geographic region—no. (%)	North America	108 (11)	76 (14)
	Asia-Pacific	119 (12)	67 (12)
	Rest of world	728 (76)	411 (74)
Median time from initial diagnosis (range)—mo		86.2 (2.6–337.5)	84.2 (0.5–344.7)
Lymph nodes seen on central imaging review—no. (%)	Yes	163 (17)	158 (29)
	No	792 (83)	396 (71)
Median serum PSA level (range)—ng/ml		9.0 (0.3–858.3)	9,7 (1.5–885.2)
PSA-DT	Median (range)—mo	44 (0.7–11.0)	4.7 (0.7–13.2)
	≤6 mo—no. (%)	667 (70)	371 (67)
	>6 mo—no. (%)	288 (30)	183 (33)
Median serum testosterone level (range)—nmol/liter		0.6 (0.2–25.9)	0.6 (0.2–7.3)
ECOG PS—no. (%)	0	650 (68)	391 (71)
	1	305 (32)	163 (29)
Prior use of bone-sparing agent—no. (%)	Yes	31.(3)	32 (6)
	No	924 (97)	522 (94)
Prior hormonal therapy agents received—no. (%)	1	177 (19)	103 (19)
	2 or more	727 (76)	420 (76)
	Not applicable	51 (5)	31 (6)

GNRH = gonadotropin-releasing hormone; PS = performance status.

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

40

Warnings and Precautions

- Permanently discontinue apalutamide and enzalutamide in patients who develop seizures.
- Discontinue enzalutamide if posterior reversible encephalopathy syndrome or hypersensitivity develops.
- Ischemic heart disease with enzalutamide and apalutamide: optimize management of cardiovascular risk factors; discontinue for grade 3/4 events
- Evaluate for fracture and fall risk with apalutamide and enzalutamide. Treat patients with bone-targeted agents according to guidelines.
- All 3 agents may cause fetal harm or loss of pregnancy. Advise patients with female partners of reproductive potential on the use of effective contraception.

Enzalutamide (Xtandi®) prescribing information (PI) 2019 (www.astellas.us/docs/us/12A005-ENZ-WPI.pdf?v=1). Apalutamide (Erleada®) PI 2019 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf). Darolutamide (Nubeqa®) PI 2019 (http://labeling.bayerhealthcare.com/html/products/pi/Nubeqa_PI.pdf). All accessed 4/7/2020.

41

No Direct Head-to-Head Comparator Data

- Regarding toxicities and tolerance
- Impact on QoL and other functional measures
- How underlying comorbidities are affected
  - Cardiovascular disease
  - Hypertension
  - History of falls or seizure
  - Frailty
  - Impact on osteoporosis or osteopenia/fracture

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How Many nmCRPC Patients Have Metastases by PSMA-PET Imaging?

- 200 men with nmCRPC by conventional imaging had PSMA-PET imaging.
  - M1 disease in 55%; 58% had PSA-DT ≤10 months
  - M0 disease in 46%; 42% had PSA-DT ≤10 months
- Clearly, PSMA-PET imaging will identify more patients with nmCRPC who have very early M1 CRPC.

Questions

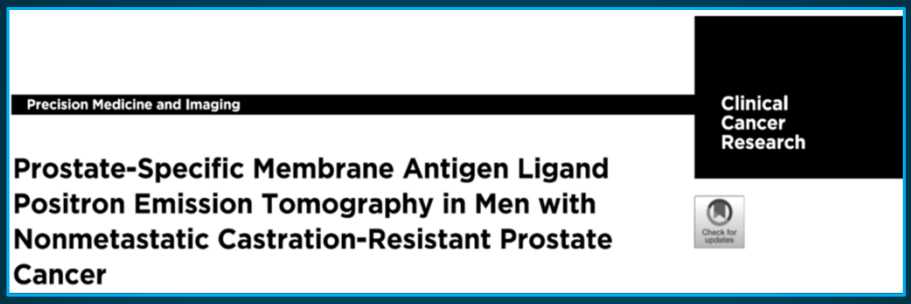
- Should the "M1" nmCRPC patient be treated with therapy for mCRPC, or should he be treated with a 2nd-generation androgen antagonist (without prospective data)?
- Can PSMA-PET imaging +/– PSA-DT be used to identify patients who could delay systemic therapy and perhaps be treated with SBRT or other salvage approaches?

PSMA-PET = prostate-specific membrane antigen ligand positron emission tomography; SBRT = stereotactic body radiotherapy.

Fendler WP, et all. *Clin Cancer Res.* 2019;25:7448-7454.

43

PSMA-PET in a "SPA-Like" M0 CRPC Population That Is Negative by Conventional Imaging



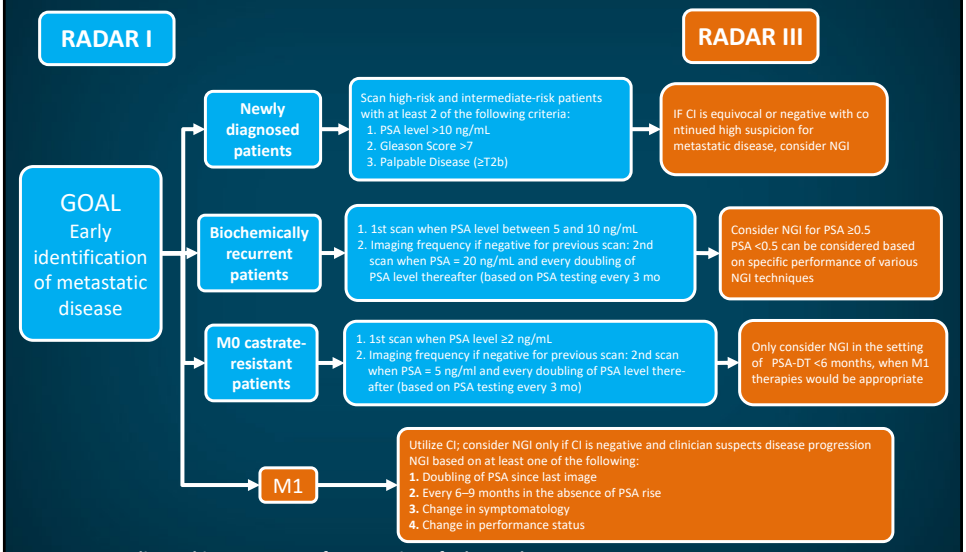
PSMA-PET was positive in 196 of 200 patients overall.

55% of patients had any distant metastatic disease despite negative conventional imaging.

Fendler WP, et all. *Clin Cancer Res.* 2019;25:7448-7454.

44

RADAR III: Recommendations



RADAR = Radiographic Assessments for Detection of Advanced Recurrence; CI = conventional imaging (in this context); NGI = next-generation imaging.

Crawford ED ,et al. *J Urol.* 2019;201:682-692.

45

Pros/Cons of Treating nmCRPC?

- Are we adequately assessing unrecognized toxicity for individual patients?
- Long-term effect of treatment on mCRPC is evolving. Will a more aggressive phenotype develop earlier in mCRPC due to longer exposure to ARTs?
- Is treating men with slow PSA-DT/nmCRPC detrimental? Does the risk outweigh the benefit?
- Are we adequately assessing cardio-neuro-oncologic risk? How can we optimize multidisciplinary management?
- Is there ubiquity of accessibility? Is financial toxicity adequately assessed?
- Are PET imaging modalities creating an obsolescent disease state?

ART = androgen receptor-targeted therapy;

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Ongoing Questions for Treating nmCRPC

- In 2020, there are 3 trials that have demonstrated level-one evidence of achieving a MFS endpoint for nmCRPC (with defined PSA-DT)
- Additional real-world experience/data is being gathered to better understand varying post-approval/market toxicities of these agents
- Are there improved questionnaires; testing batteries; or genetic, pharmacogenomic, and other biomarkers that can predict patient-specific toxicities?
- How will conventional imaging in conjunction with NGI better characterize different subtypes of nmCRPC for clinical trials and determine other possible salvage and/or systemic management for nmCRPC patients?

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Case Study

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Patient Case Study

65-year-old man with rising PSA

History of disease
- 6 years ago, he underwent RP for Gleason 4+4, iPSA = 7.9
- Metastatic evaluation s/p RP NED BS/CT abdomen/pelvis
- 16 months post-RP, detectable, rising PSA

Treatment
- Salvage RT administered, PSA = 0.46
- 6 months post-RT, PSA = 0.75

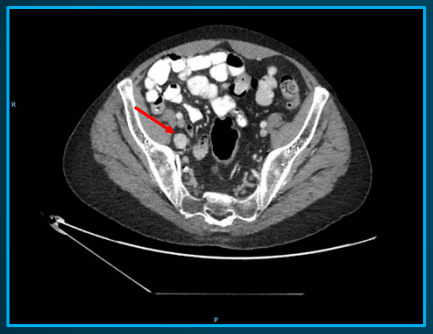
Clinical progression
- Started on ADT 3 months later when PSA = 1.09
- PSA nadirs to undetectable level; over past year PSA valued every 3 months: 0.04, 0.80, 1.23, 2.45 (testosterone at last visit = 15 ng/dL)

RP = radical prostatectomy; iPSA = initial PSA; s/p = status post; NED = no evidence of disease; RT = radiotherapy.
Speaker's own data.

49

Patient Case Study (continued)

Bone scan shows mild, degenerative joint disease



Treatment choices within the EU:
- Apalutamide, enzalutamide, or darolutamide
- Node removal
- Node stereotactic radiation
- Abiraterone
- Observation

What would you choose?

EU = European Union.
Speaker's own data.

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Summary

- **nmCRPC:** enzalutamide, apalutamide, and darolutamide resulted in meaningful and significant reduction in relative risk of developing M1. All 3 are FDA approved with a similar NCCN recommendation.
  - Therapy decisions should take disease risk, PSA-DT, comorbidities, life expectancy, and potential for physical and monitory toxicities into account. It requires balancing risks and benefits.
- **Future directions**
  - Personalized therapy/precision medicine/role of better imaging
  - Novel multi-targeted combination therapy
  - Advance therapies to earlier, high-risk disease states
- **Metastases**
  - Result in significant consequences for patients[1]
  - Incur multiple complications, depending on site and number[2]
- **Early treatment**
  - Can prolong metastasis-free survival, avoiding the consequences of metastases longer[3,4]

Ultimately, each patient should be treated on an individual basis, considering all factors, such as comorbidities, PSA kinetics, and metastatic burden.[5]

1. Prostate Cancer UK. prostatecanceruk.org/media/2495256/advanced-prostate-cancer-managing-symptoms-and-getting-support-ifm.pdf. Accessed 4/7/2020. 2. Gandaglia G, et al. *Eur Urol.* 2015;68:325-333. 3. Hussain M, et al. *N Engl J Med.* 2018;378:2465-2474. 4. Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418. 5. Speaker's own opinion.

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Thank You!

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A Specialty Series Review of the Management of Patients with Non-metastatic Castration-resistant Prostate Cancer

Resource	Address
Kirby M, et al. **Characterising the castration-resistant prostate cancer population: a systematic review**. *Int J Clin Pract*. 2011;65:1180-1192.	https://www.ncbi.nlm.nih.gov/pubmed/21995694
Wong MC, et al. **Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries.** *Eur Urol*. 2016;70:862-874.	https://www.ncbi.nlm.nih.gov/pubmed/27289567
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