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Incorporation of Androgen Receptor Antagonists into the Management of Non-Metastatic (M0) Prostate Cancer

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

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Disclosures

Advisory Committee and Consulting Agreements:
AbbVie Inc, Amgen Inc, Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Gilead Sciences Inc, Hexal AG, Hinova Pharmaceuticals Inc, Janssen Biotech Inc, Lilly, Novartis, Orion Corporation, Pfizer Inc

Contracted Research:
Amgen Inc, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Janssen Biotech Inc, Lilly

For a patient with biochemical recurrence after local therapy for prostate cancer (M0 hormone-sensitive disease with negative MRI and PSMA-PET results), is PSA doubling time the most important factor that you consider when making the decision whether to initiate androgen deprivation therapy (ADT)? If yes, what PSA doubling time would prompt you to initiate ADT?

	PSA doubling time (PSADT) most important	PSADT to initiate ADT
 EMMANUEL S ANTONARAKIS, MD	Yes, along with absolute PSA level	<3 mo for all patients, 3-6 mo for many but not all patients
 A OLIVER SARTOR, MD	No	—
 HOWARD I SCHER, MD	Yes	Would also consider pathologic findings at surgery, comorbidities, PSA levels
 MATTHEW R SMITH, MD, PHD	Yes	<6 months
 CORA N STERNBERG, MD	No	—

For a patient who experiences PSA-only progression while receiving an LHRH agonist (M0 castration-resistant prostate cancer with negative MRI and PSMA-PET results), is PSA doubling time the most important factor that you consider when making the decision whether to initiate secondary hormone therapy? If yes, what PSA doubling time would prompt you to initiate secondary hormone therapy?

	PSA doubling time (PSADT) most important	PSADT to initiate secondary hormone treatment
 EMMANUEL S ANTONARAKIS, MD	Yes, along with absolute PSA level	Only if <10 months and especially if <6 months
 A OLIVER SARTOR, MD	No	—
 HOWARD I SCHER, MD	No	—
 MATTHEW R SMITH, MD, PHD	Yes	<10 months
 CORA N STERNBERG, MD	Yes	<10 months

For a 60-year-old patient who experiences PSA-only progression while receiving an LHRH agonist for whom you have decided to add secondary hormone therapy, which agent would you generally recommend?

Which agent would you generally recommend if the patient were 80 years old?

	Age 60	Age 80
 EMMANUEL S ANTONARAKIS, MD	Apalutamide	Apalutamide
 A OLIVER SARTOR, MD	Apalutamide or enzalutamide	Unsure would offer any treatment
 HOWARD I SCHER, MD	Apalutamide or enzalutamide	Depends on prior treatment history
 MATTHEW R SMITH, MD, PHD	Apalutamide or enzalutamide	Apalutamide or enzalutamide
 CORA N STERNBERG, MD	Enzalutamide	Apalutamide or enzalutamide

Do you employ intermittent rather than continuous ADT in any of your patients with prostate cancer?

 EMMANUEL S ANTONARAKIS, MD	Yes (biochemical recurrence with rapid PSA doubling time)
 A OLIVER SARTOR, MD	Yes (M0 disease)
 HOWARD I SCHER, MD	Yes (no significant metastatic disease or high-grade rapid recurrence)
 MATTHEW R SMITH, MD, PHD	Yes (PSA-only disease, small burden of nodal metastases)
 CORA N STERNBERG, MD	Yes (PSA nadired to a very low number multiple times and patient at low risk)

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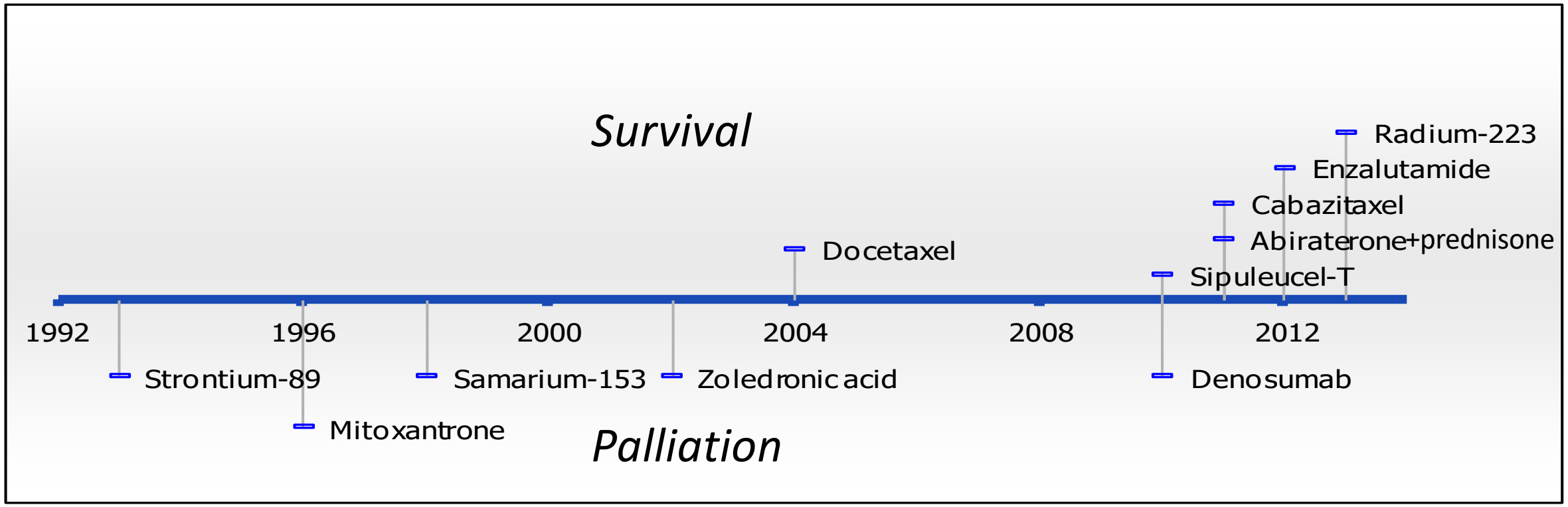
Timeline of FDA Approvals in Metastatic Castration-Resistant Prostate Cancer (mCRPC)



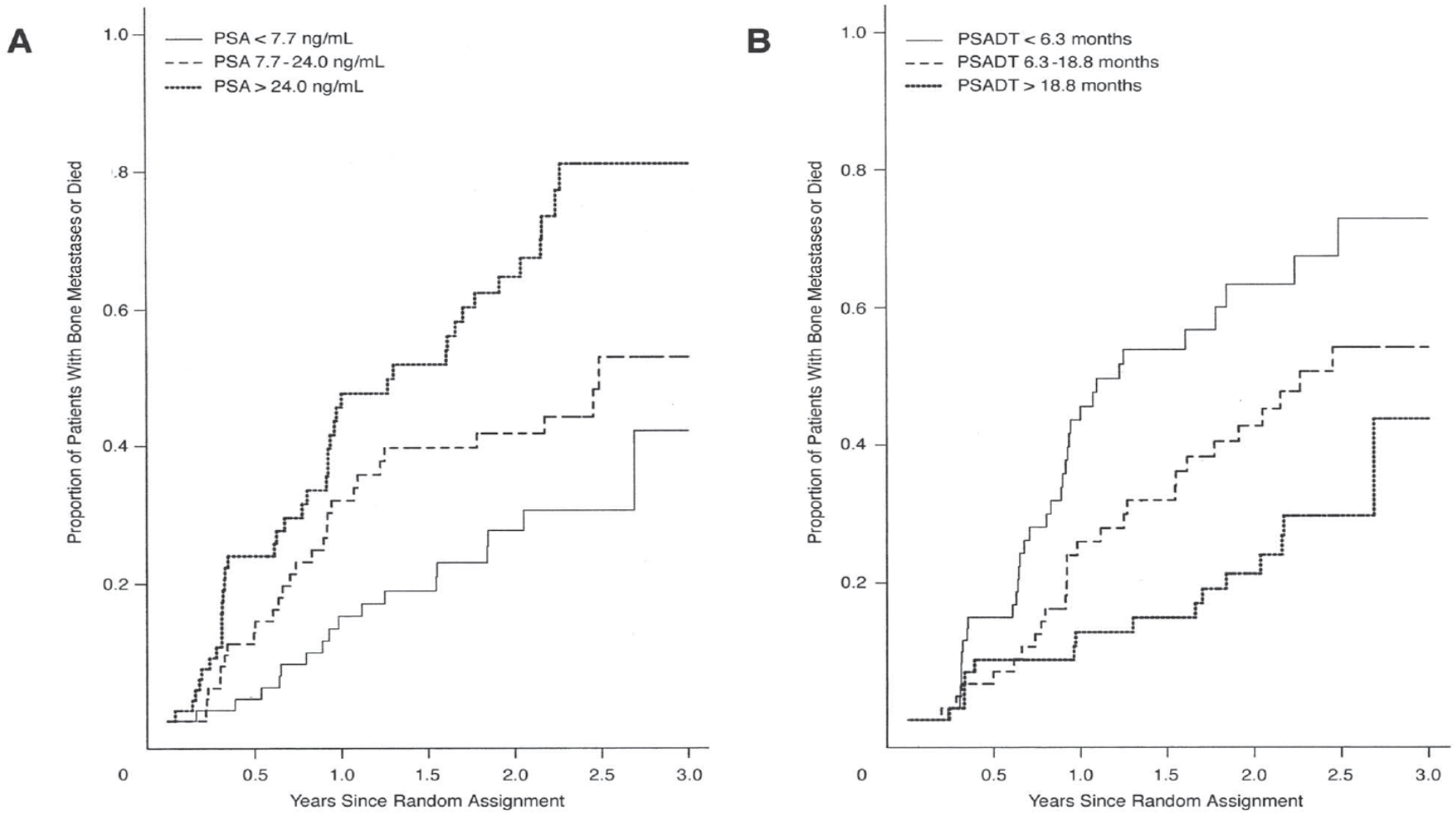
Metastatic disease was defined by conventional imaging (e.g. bone scan, CT scans)

Context

- Men with nmCRPC are at significant risk for metastatic disease and prostate cancer–specific death[1]
- Metastases are a major cause of morbidity and mortality[2,3]
- Prevention of metastases represents an important unmet medical need

1. Smith MR, et al. *J Clin Oncol*. 2013;31:3800-3806
2. Scher HI, et al. *PLoS One*. 2015;10;e0139440
3. Gartrell BA, et al. *Nat Rev Clin Oncol*. 2014;11:335-345

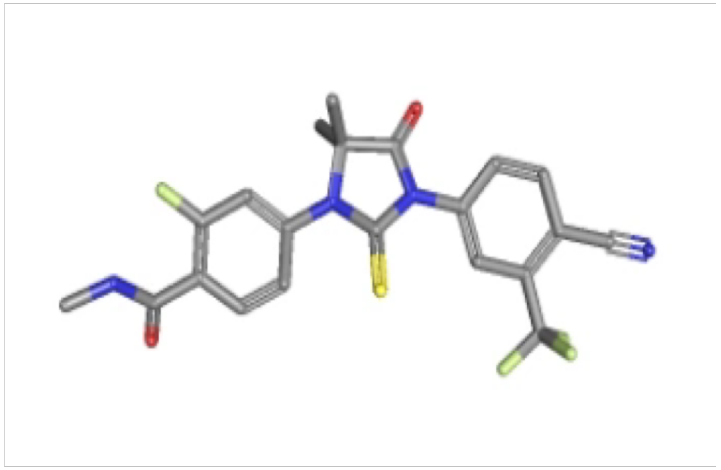
PSA and PSADT Are Associated with Shorter Time to Metastases



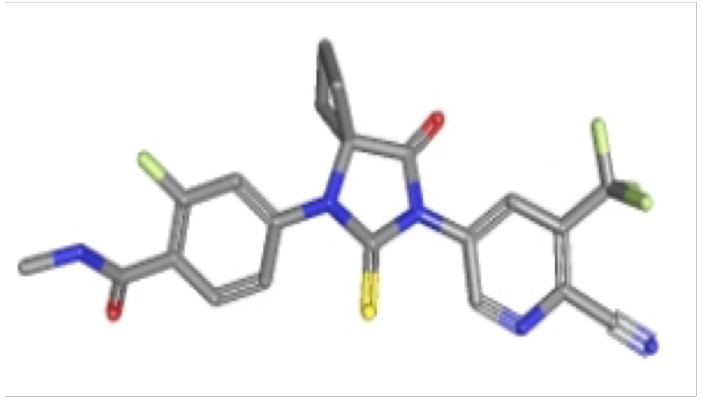
Smith MR, et al. *J Clin Oncol* 2005; 23: 2918-2925

Next-Generation Androgen Receptor Inhibitors

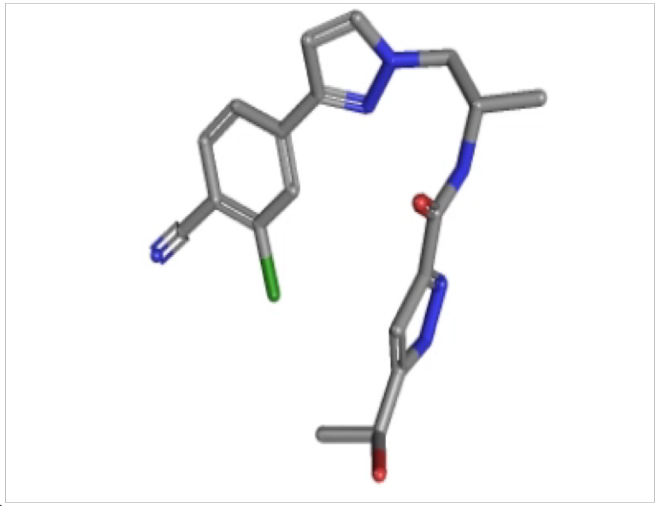
Enzalutamide



Apalutamide



Darolutamide



- Apalutamide and enzalutamide have similar structures
- Darolutamide is structurally distinct from apalutamide and enzalutamide, characterized by low blood–brain barrier penetration[1,2], and may have improved tolerability

1. Zurth C et al. J Clin Oncol 2018; Abstract 345
2. Zurth C et al. Genitourinary Cancers Symposium 2019; Abstract 156

FDA Approval of Apalutamide and Enzalutamide

- First approved drugs for nmCRPC
- First approvals based on metastasis-free survival (MFS)

www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm596796.htm (*accessed 4/02/2018*)

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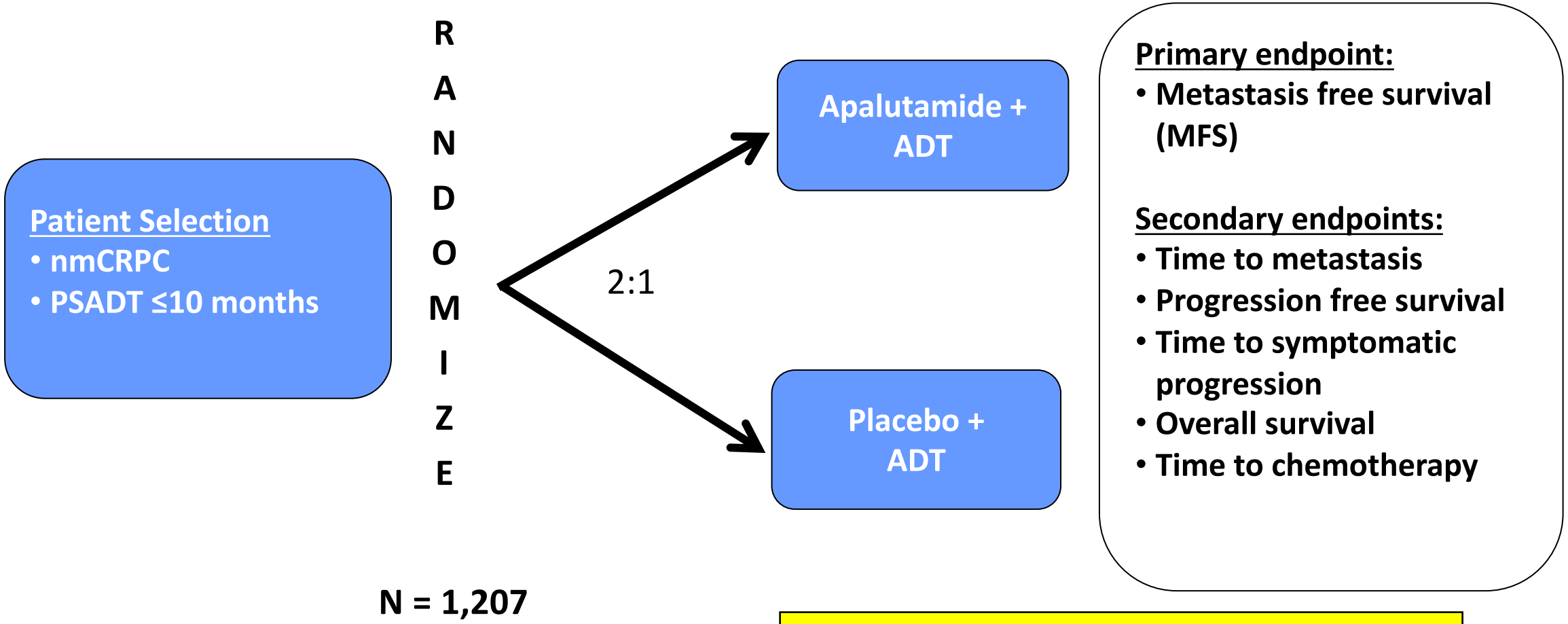
SPARTAN Study Design



N = 1,207

78% of patients in placebo group received subsequent approved therapy for mCRPC

Smith MR, et al. *N Eng J Med* 2018; 378:1408-18.

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PROSPER Study Design

Patient Selection
- M0 CRPC
- Rising PSA despite castrate testosterone level (≤50 ng/dL)
- Baseline PSA ≥2 ng/mL
- PSA doubling time ≤10 mos

R A N D O M I Z E

2:1

- Enzalutamide + ADT
- Placebo + ADT

Primary endpoint:
- Metastasis free survival (MFS)

Secondary endpoints:
- Safety
- Time to PSA progression
- Time to use of new antineoplastic therapy
- OS
- PSA response
- Quality of life

N = 1,401

48% of patients in placebo group received subsequent therapy after treatment discontinuation

Hussain M et al. 2018 Genitourinary Cancers Symposium; Abstract 3. Hussain M et al. *N Engl J Med* 2018;378(26):2465-74.

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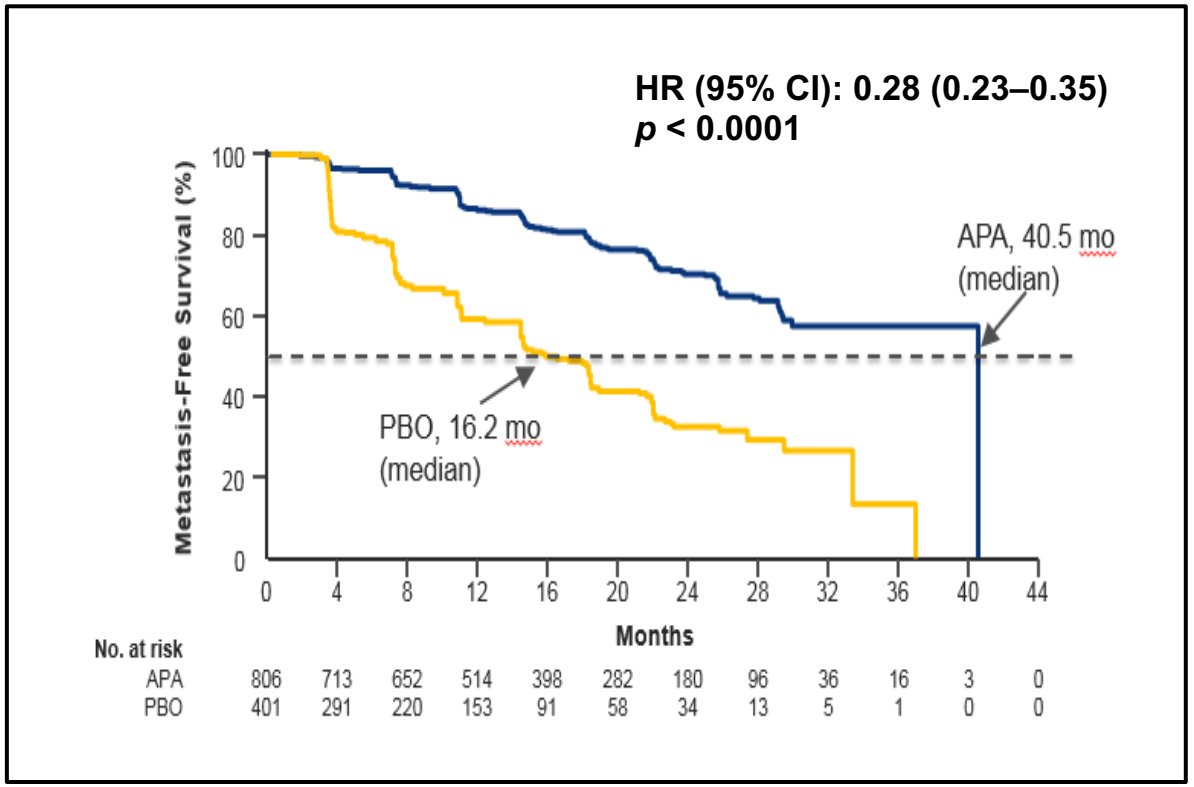
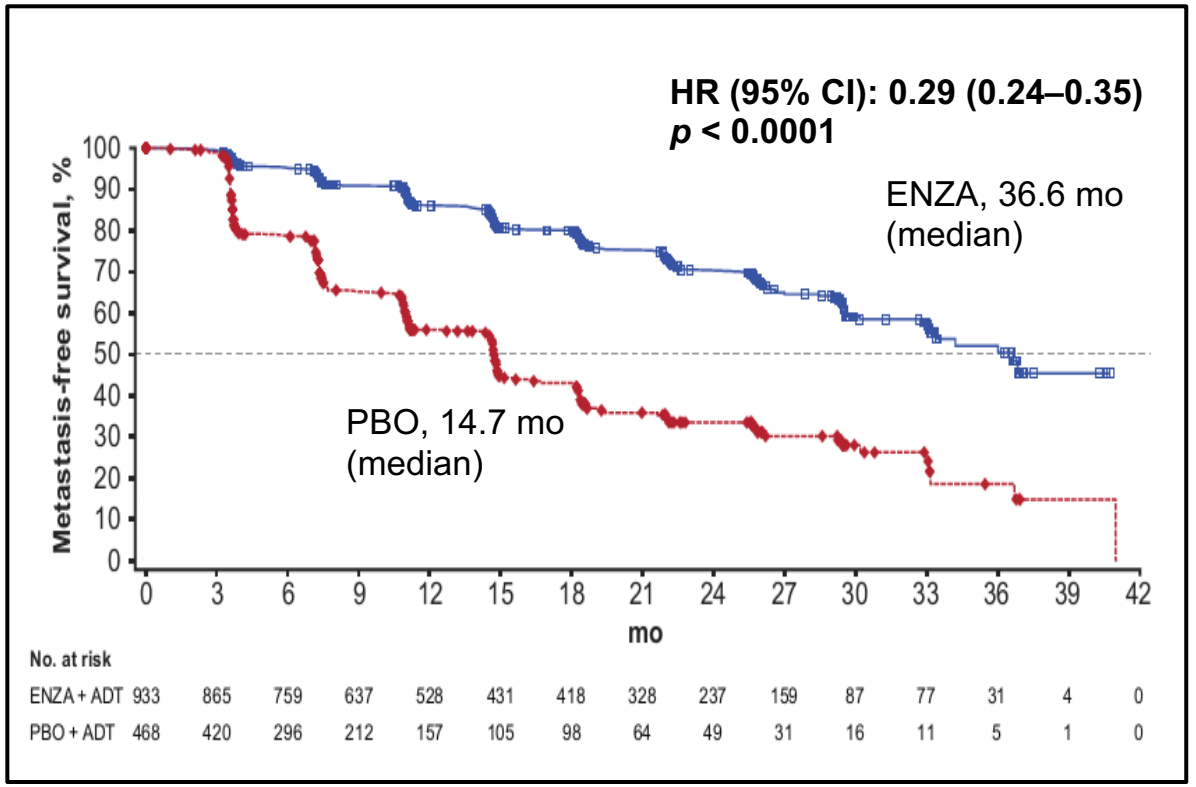
Metastasis-Free Survival (MFS)

SPARTAN[1]



- 72% reduction of distant progression or death
- Median MFS: APA 40.5 months vs PBO 16.2
- 24-month increase in MFS

PROSPER[2]



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 months vs PBO 14.7
- 22-month increase in MFS

1. Smith MR, et al. N Engl J Med 2018.
2. Hussain M, et al. N Engl J Med 2018

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SPARTAN: Prespecified Secondary and Exploratory Endpoints

End Point	Apalutamide (N=806)	Placebo (N=401)	Hazard Ratio (95% CI)	P Value
Secondary end points (mo)†				
Median time to metastasis	40.5	16.6	0.27 (0.22–0.34)	<0.001
Median progression-free survival	40.5	14.7	0.29 (0.24–0.36)	<0.001
★ Median time to symptomatic progression	NR	NR	0.45 (0.32–0.63)	<0.001
★ Median overall survival	NR	39.0	0.70 (0.47–1.04)	0.07
★ Median time to the initiation of cytotoxic chemotherapy	NR	NR	0.44 (0.29–0.66)	—
Exploratory end points				
Median second-progression–free survival (mo)	NR	39.0	0.49 (0.36–0.66)	
Median time to PSA progression (mo)	NR	3.7	0.06 (0.05–0.08)	
Patients with a PSA response (%)	89.7	2.2	40 (21–77)‡	
Patient-reported outcomes§				
Change in total FACT-P score from baseline to 29 months¶	−0.99±0.98	−3.29±1.97	—	
Change in total EQ VAS score from baseline to 29 months‖	1.44±0.87	0.26±1.75	—	

Smith MR, et al. *N Eng J Med* 2018; 378:1408-18

★ 'late' clinical events that follow metastases

PROSPER: Prespecified Secondary Endpoints

End Point	Enzalutamide Group (N=933)	Placebo Group (N=468)	Hazard Ratio (95% CI)	P Value
Secondary end points				
PSA progression				
Median time to progression — mo	37.2	3.9	0.07 (0.05–0.08)	<0.001
Patients with progression — no. (%)	208 (22)	324 (69)	—	—
Use of subsequent antineoplastic therapy				
Median time to first use — mo	39.6	17.7	0.21 (0.17–0.26)	<0.001
Patients with use — no. (%)	142 (15)	226 (48)	—	—
Overall survival				
Median survival — mo	NR	NR	0.80 (0.58–1.09)	0.15
Patients who died — no. (%)	103 (11)	62 (13)	—	—
Confirmed PSA response ≥50% — no. (%)	712 (76)	11 (2)	—	—
FACT-P score degradation‡				
Median time to score degradation — mo	11.1	11.1	0.92 (0.79–1.08)	—
Patients with score degradation — no. (%)	506 (54)	239 (51)	—	—

Hussain M et al. *N Engl J Med* 2018;378(26):2465-74.

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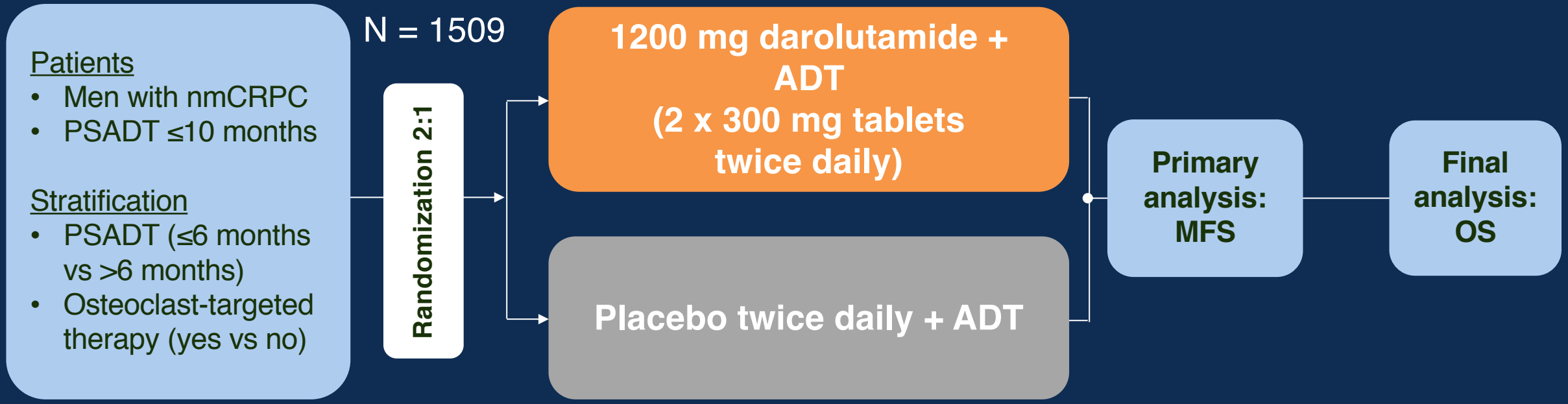
Adverse Events

	SPARTAN[1]		PROSPER[2]	
	APA (n = 803)	PBO (n = 398)	ENZA (n = 933)	PBO (n = 468)
Safety	AE reporting every 4 weeks		AE reporting every 4 months	
AEs, %				
Any grade	97%	93%	87%	77%
Grade ≥ 3	45%	34%	31%	23%
Serious AEs	25%	23%	24%	18%
AEs leading to discontinuation	11%	7%	9%	6%
AEs leading to death	1.2% (n = 10)	0.3% (n = 1)	3.4% (n = 32)	0.6% (n = 3)
Major CV event	1*	1*	5	3
Seizures	0.24% (n = 2)	0	0.32 % (n = 3)	0

1. Smith MR, et al. *N Engl J Med* 2018.
2. Hussain M, et al. *N Engl J Med* 2018

Compared to placebo, apalutamide and enzalutamide were associated with higher rates of fatigue, falls, fractures, and seizures

ARAMIS Trial Design



Primary endpoint (significance level 0.05)

- Metastasis-free survival
  - Defined as distant metastases or death from any cause
  - Radiological assessment at 16-week intervals
  - Any patients with baseline metastases identified by independent central efficacy review were included as a baseline event

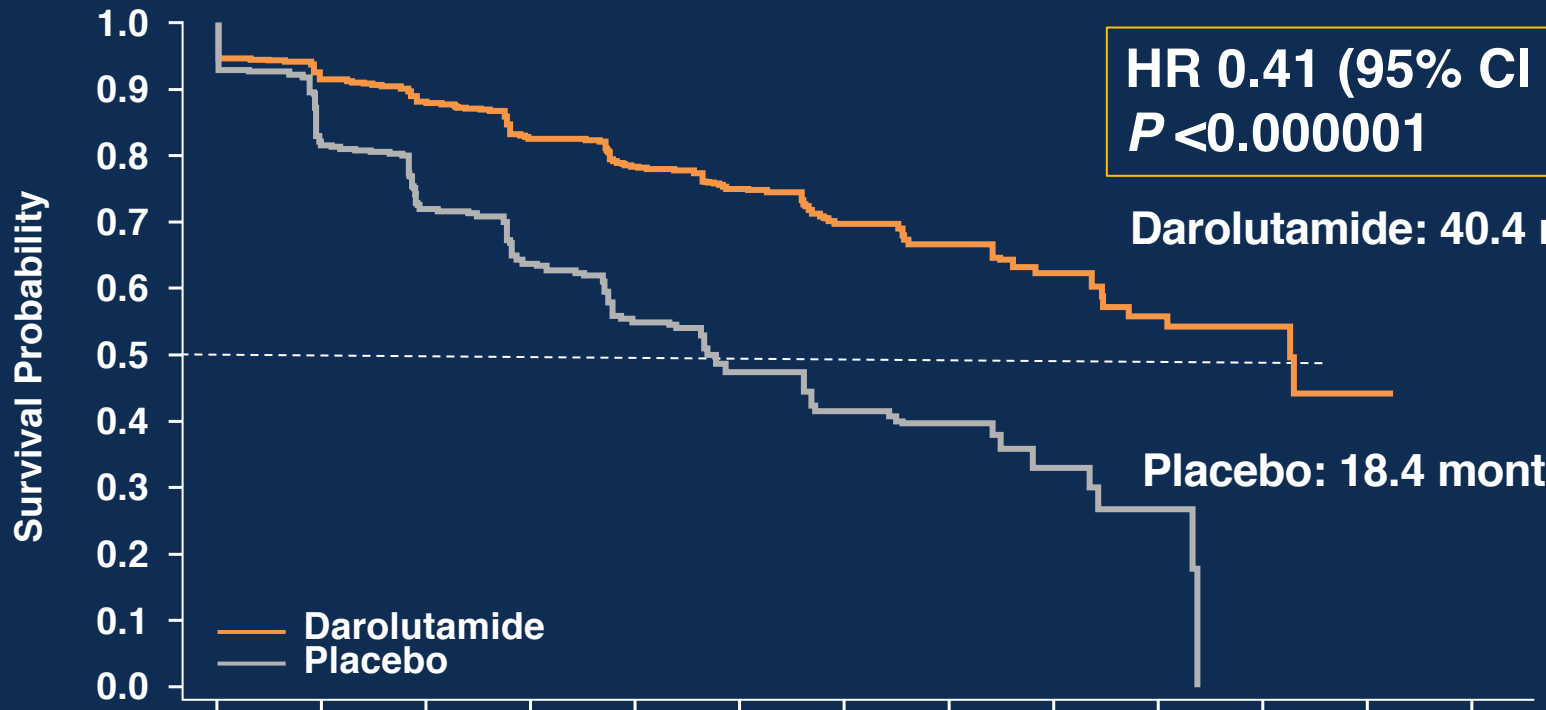
Secondary endpoints (hierarchical testing; interim α=0.0005)

- Overall survival
- Time to pain progression
- Time to first symptomatic skeletal event
- Time to first cytotoxic chemotherapy
- Safety

ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time.

Metastasis-free Survival

59% risk reduction of distant metastases or death



HR 0.41 (95% CI 0.34–0.50)
***P* <0.000001**

Darolutamide: 40.4 months (median)

Placebo: 18.4 months (median)

Number of subjects at risk

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

Median follow-up time at primary analysis was 17.9 months

CI, confidence interval; HR, hazard ratio.

Presented by: Karim Fizazi

ARAMIS: Incidence of TEAEs

Adverse Event, n (%)	Darolutamide (N = 954)		Placebo (N = 554)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious	237 (24.8)	151 (15.8)	111 (20)	70 (12.6)
Discontinuation	85 (8.9)	32 (3.3)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhea	66 (6.9)	0 (0)	31 (5.6)	1 (0.2)
Constipation	60 (6.3)	0 (0)	34 (6.1)	0 (0)
Pain in extremity	55 (5.8)	0 (0)	18 (3.2)	1 (0.2)
Anemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0 (0)	23 (4.2)	0 (0)
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0 (0)
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)

TEAE, treatment-emergent adverse event.

ARAMIS: TEAEs of interest

Adverse Event, 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)	1 (0.2)

TEAE, treatment-emergent adverse event.

Conclusions

- SPARTAN and PROSPER provide strong support for FDA approval of apalutamide and enzalutamide for nmCRPC
- Improvements in MFS were large and consistent across subgroups
- In SPARTAN, clinical benefit supported by improvements in key secondary endpoints, including ‘late’ clinical events that followed detection of metastases
- Apalutamide and enzalutamide are associated with increased incidence of fatigue, falls, fractures, and seizures
- Darolutamide improves MFS and is not associated with greater risk for falls, fractures, or seizures