Management of Non-metastatic Castration-Resistant Prostate Cancer (nmCRPC)

Putting Current Evidence into Practice

The scientific content of this program was developed by the Canadian Urological Association.

Disclosure of Commercial Support

- This program has received financial support from Bayer in the form of an educational grant.
- This program has received in-kind support from Bayer in the form of logistical support.

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All faculty have adhered to the:

- CMA Code of Ethics and Professionalism (2018)
- CMA Guidelines for Physician Interactions with Industry (2007)
- Innovative Medicines Canada (2020)

Learning Objectives

By participating in this educational session, health care providers can expect to:

- Describe the rationale for treating men with prostate cancer earlier in the non-metastatic CRPC state
- Identify patients who are appropriate for treatment of their nmCRPC
- Discuss treatment options in the management of nmCRPC
- Describe appropriate follow-up of patients with nmCRPC
- Devise strategies for implementing nmCRPC management practices

Rationale for treating earlier in the nmCRPC state

Definition of CRPC

Castrate serum testosterone < 1.7 nmol/L[1]

AND EITHER

Non-metastatic

Biochemical progression
↑ in PSA > 25% and > 2 ng/mL above nadir, confirmed by progression at 2 timepoints at least 3 weeks apart (PCWG3)[2]

OR

Metastatic

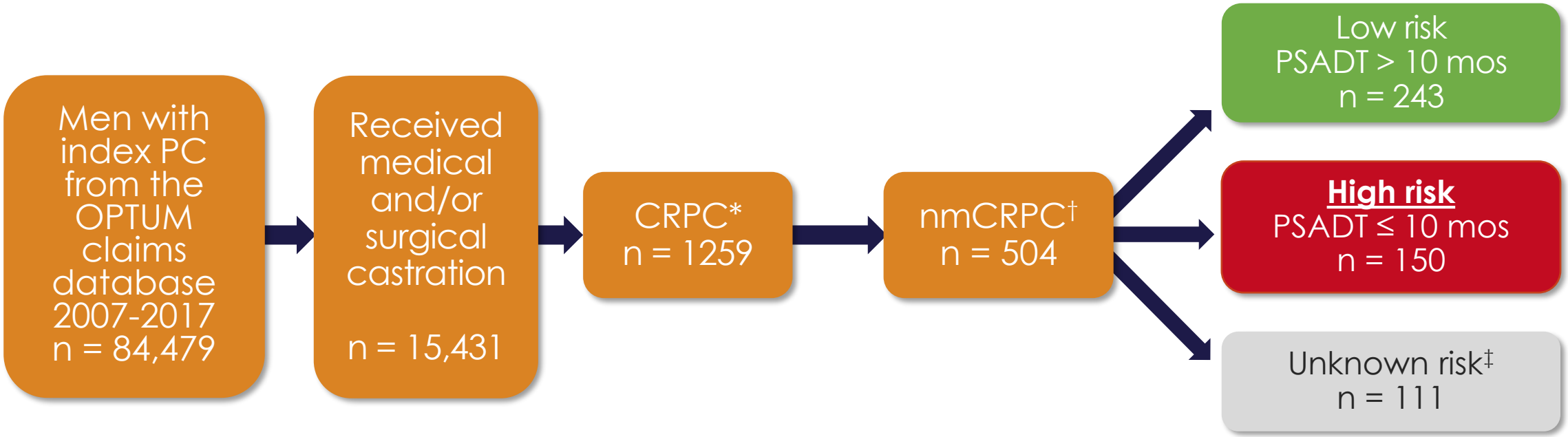
Radiological progression
Appearance of ≥ 2 bone lesions on bone scan or enlargement of soft tissue lesion (RECIST)

- Definitions based on conventional bone scan and CT Scan
- PSMA-PET frequently positive in "nmCRPC" patients

CT = Computed tomography; PSA = Prostate-specific antigen;
PSMA-PET = Prostate-specific membrane antigen - positron emission tomography;
RECIST = Response Evaluation Criteria in Solid Tumours

1. Mottet N, et al. Eur Urol 2017;71:618-29
2. Scher HI, et al. J Clin Oncol 2016;34:1402-18

Population-Based Study on the Association of PSADT With MFS and OS in nmCRPC



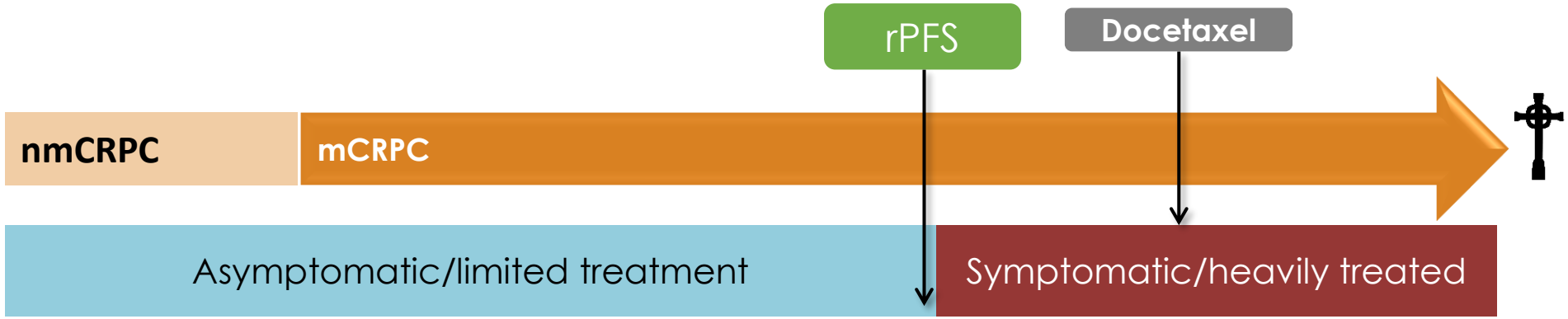
- ~30% of CRPC patients had a PSADT ≤ 10 mos

*Using Prostate Cancer Working Group 2 criteria (Scher HI, et al. J Clin Oncol 2008;26:1148-59)
†Patients received continuous androgen deprivation therapy (ADT) coverage as in the phase 3 SPARTAN trial (Smith MR, et al. N Engl J Med. 2018;378:1408-18)
‡Nonevaluable PSADT due to inadequate PSA lab values

MFS = Metastasis-free survival; OS = Overall survival; PC = Prostate cancer; PSADT = PSA doubling time

Saad F, et al. AUA 2018 (Abstr PD10-04)

Reducing the Time Spent In More Advanced Disease States is an Important Goal of Prostate Cancer Managemen



Early treatment

EXPANSION (increasing OS)

COMPRESSION (reducing time with symptoms, buying quality time)

mCRPC = Metastatic castration-resistant prostate cancer
rPFS = Radiographic progression-free survival

Tombal B. Ann Oncol 2012;23(Suppl 10):x251–8
Mateo J, et al. Eur Urol 2019;75:285–93

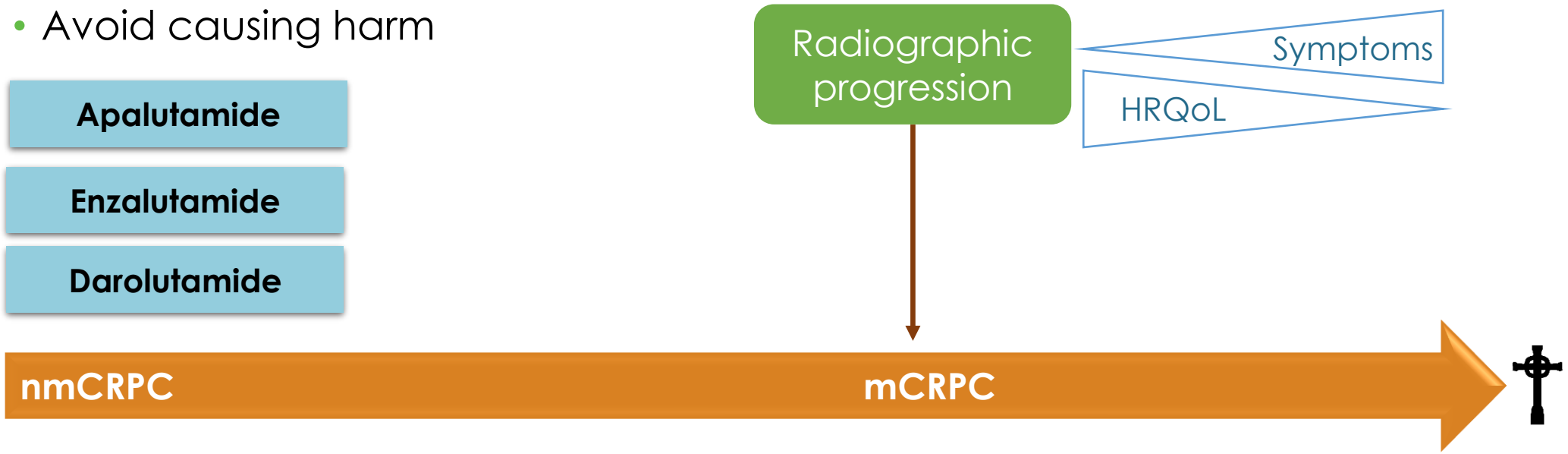
Rationale for the nmCRPC Trials: Prolong the Low Burden/Asymptomatic Stage[1,2]

- Maintain HRQoL as long as possible
- Delay the metastatic/heavy treatment phase of the disease
- Extend OS
- Avoid causing harm

Apalutamide

Enzalutamide

Darolutamide



HRQoL = Health-related quality of life

1. Tombal B. Ann Oncol 2012;23(Supplement 10):x251–8
2. Mateo J, et al. Eur Urol 2019;75:285–93

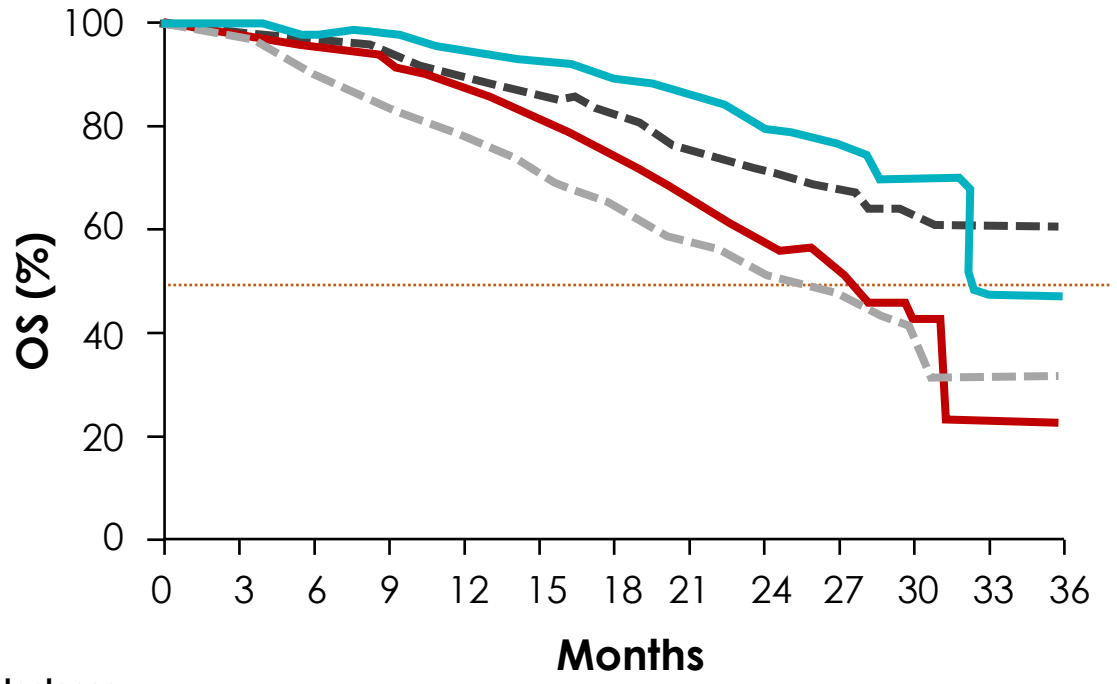
Better Outcomes for Patients With mCRPC Who Are Treated Early

Quartile	Q1	Q2	Q3	Q4
Baseline PSA (ng/mL)	< 15.6	15.6 to < 39.5	39.5 to < 106.2	≥ 106.2
		OS		
HR (95% CI) p value	0.53 (0.39-0.72) < 0.001	0.71 (0.54-0.93) 0.014	0.87 (0.67-1.11) 0.257	1.00 (reference)

- The lower the baseline PSA, the greater the impact of abiraterone + prednisone on overall survival

Ryan C, et al. Lancet Oncol 2015;16:152-60

Better Outcomes for Patients With mCRPC Who Are Treated Early



< 4 bone metastases													
Enzalutamide	441	439	435	428	419	399	311	223	145	80	21	1	0
Placebo	426	422	407	398	380	359	275	187	122	59	18	2	0
≥ 4 bone metastases													
Enzalutamide	431	424	415	396	378	346	255	172	99	48	12	1	0
Placebo	419	413	374	346	321	285	209	141	91	43	9	0	0

Patients with < 4 bone metastases

Enzalutamide

Placebo

Enzalutamide reduces risk of death by **38%**

HR 0.62 (CI 95%, 047-0.84)

Patients with ≥ 4 bone metastases

Enzalutamide

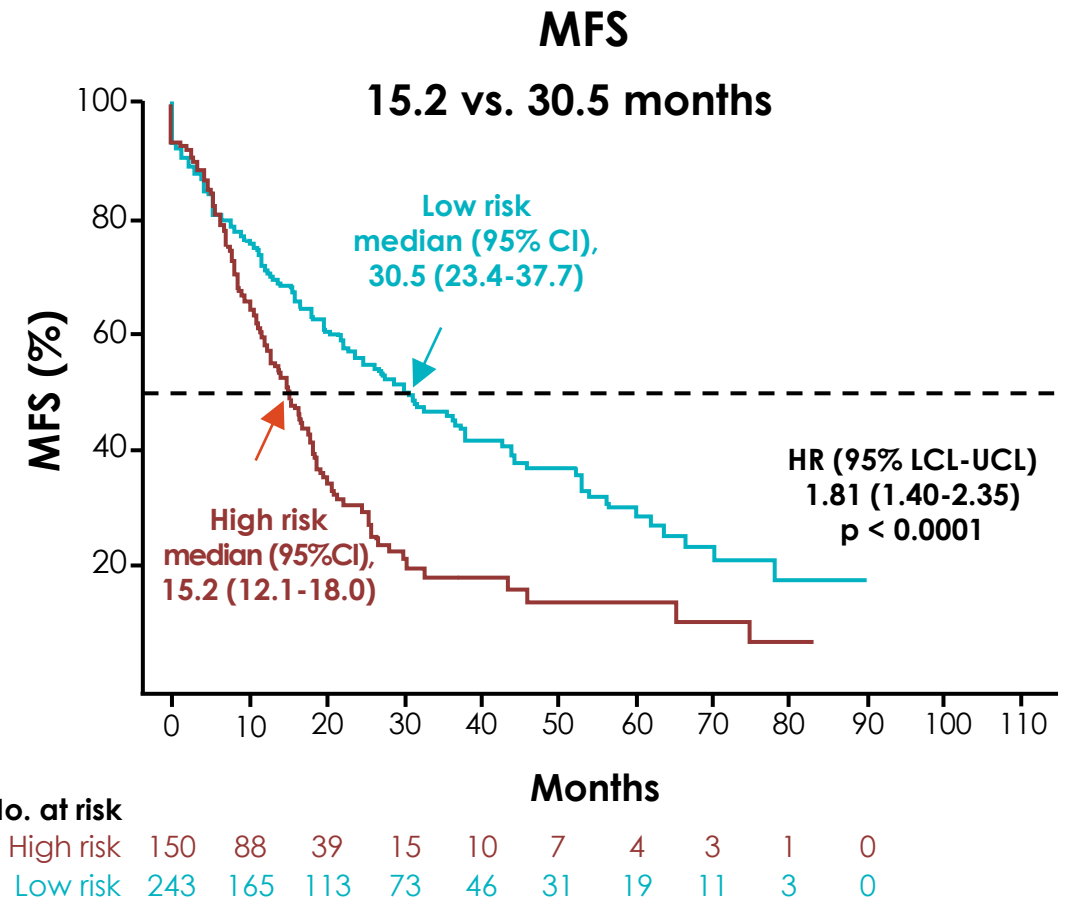
Placebo

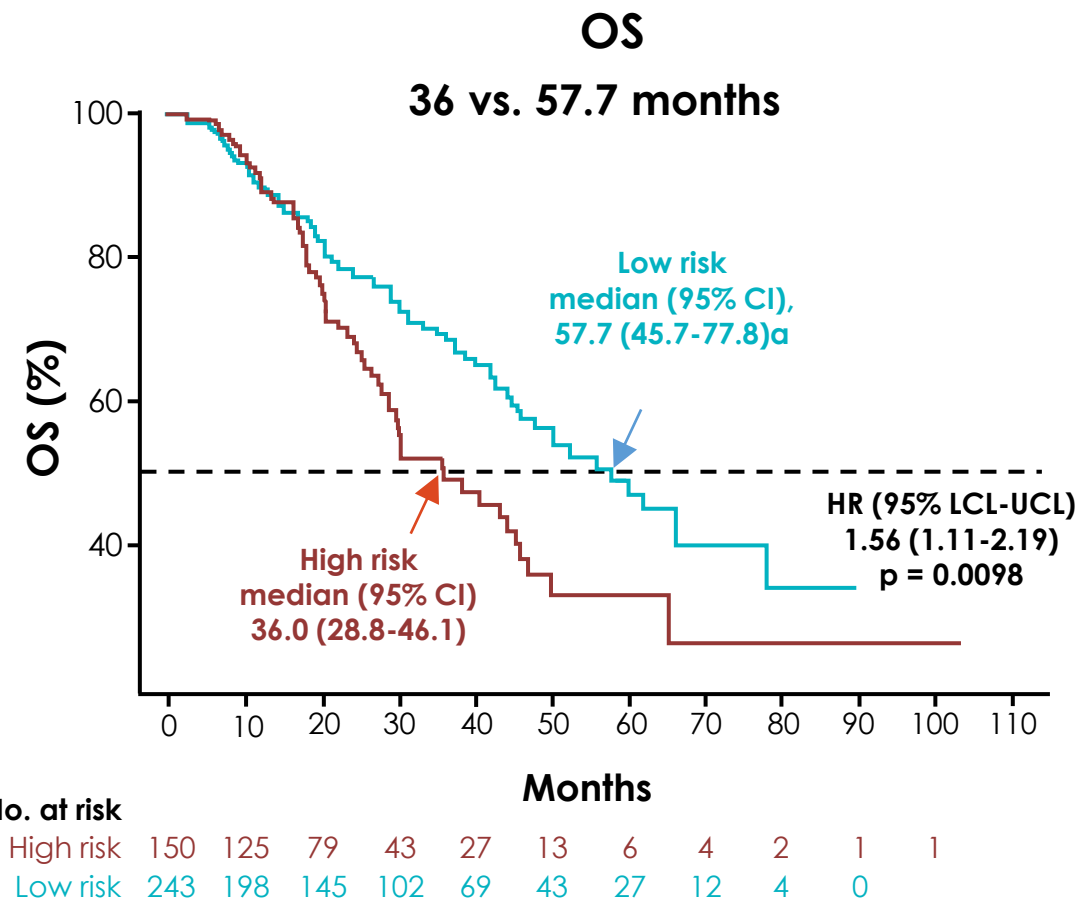
Enzalutamide reduces risk of death by **25%**

HR 0.75 (CI 95%, 0.67-0.92)

Evans CP, et al. Eur Urol 2016;70:675-83

Real-World MFS and OS in Patients With nmCRPC (PSADT ≤ 10 months vs. > 10 months)





- Of the identified nmCRPC patients, ~30% were high risk (PSADT ≤ 10 months)

Saad F, et al. J Urol 2018;199(Suppl 4):e229. Abstr PD10-04

Identification of the high-risk nmCRPC patient

Case Presentation – "Brian"

- "Brian" is a 65-year-old man with nonmetastatic prostate cancer. His past medical history includes hypertension controlled with diltiazem

- February 2015 - Radical prostatectomy
- pT3aN0R1
- Gleason 4+3
- Nadir PSA 0.32 ng/mL
- CT and bone scan negative

- August 2015 - Salvage radiation (no ADT)
- June 2018
  - PSA 6.5 ng/mL
  - CT and bone scan negative
  - Started on an LHRH analogue only

LHRH = Luteinizing hormone-releasing hormone

Brian – Follow-up

- December 2018
  - PSA nadired at 0.9 ng/mL
- April 2019
  - PSA 1.3 ng/mL
  - T < 0.7 nmol/L

- February 2020
  - PSA 5.3 ng/mL
  - T < 0.7 nmol/L
- Bone scan/CT negative for metastases
- ECOG PS 0

ECOG PS = Eastern Cooperative Oncology Group Performance Status
T = Testosterone

Discussion Questions

- How would you determine Brian's treatment options?
- Which clinical and patient characteristics would you look for to help you make your decision?
- Brian underwent PSA and T testing in April 2019 and February 2020. How frequently do you monitor PSA in your patients undergoing ADT for nmCRPC?

Diagnostic Imaging in the nmCRPC patient

Imaging Guidelines for nmCRPC – CUA 2021

Most common imaging techniques:

- Nuclear bone scan
- Abdominal/pelvic CT scan
- Chest CT or chest X-ray optional
- Role for PSMA-PET unclear
  - Largely available only through clinical trials in Canada

Timing of Imaging:

- PSADT < 10 months or elevated PSA (> 20 ng/mL)

  ➡ Every 3 to 6 months

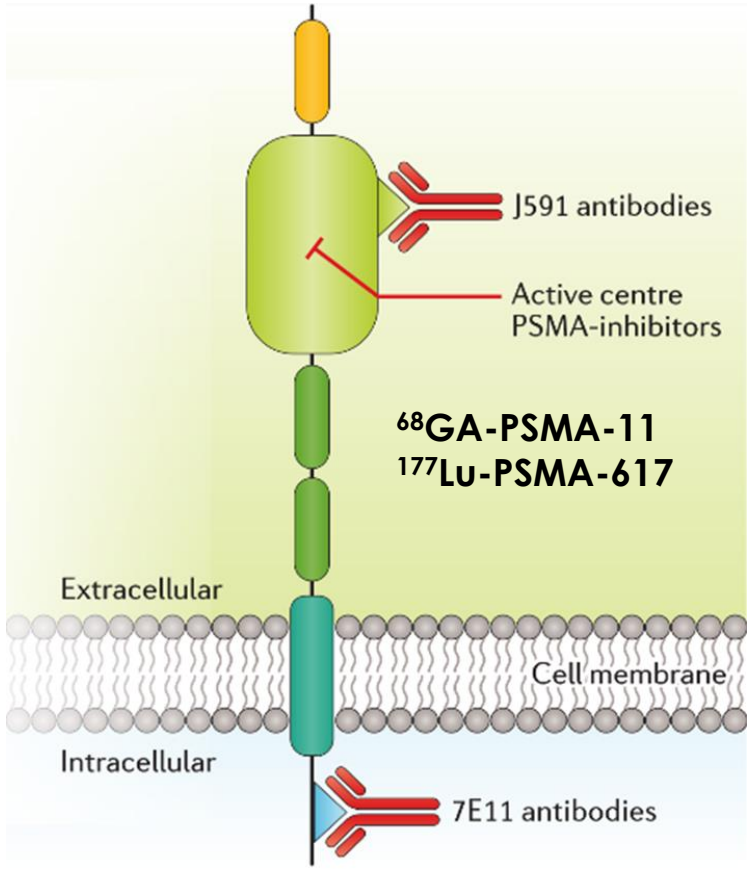
- PSADT > 10 months

  ➡ Every 6 to 12 months

Saad F, et al. Can Urol Assoc J 2021;15:E81-E90

Prostate Specific Membrane Antigen (PSMA) as a Target for Imaging in Prostate Cancer

- Cell surface protein highly expressed in all PCa
- Expressed in some healthy tissues (eg, salivary glands) and neovasculature of other tumours (but not normal vasculature)
- Expression increases with:
  - Tumour aggressiveness
  - Metastatic disease
  - Disease recurrence
- Substrate internalized after binding:
  - Enhanced uptake and retention in the tumour
  - High image quality for diagnostics

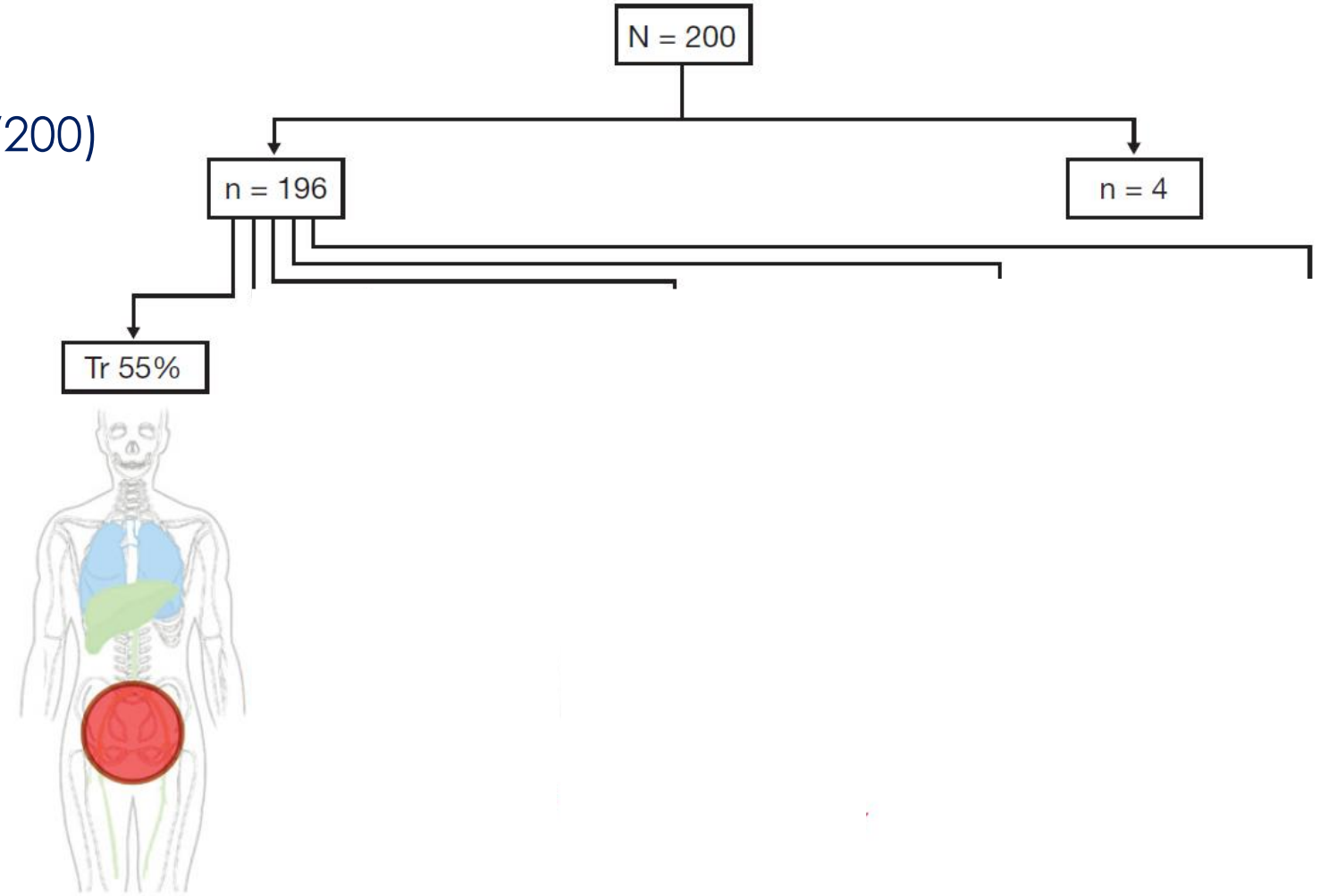


PCa = Prostate cancer

Maurer T, et al. Nat Rev Urol 2016;13:226-35

Majority of nmCRPC Patients with NED by Conventional Imaging Found to have N1 and M1 Disease by PSMA PET/CT

- PSMA PET/CT was positive in 98% (196/200)



[a]Lung (n = 4), liver (n = 5), peritoneum (n = 4), connective tissue (n = 1). The size of the red circules is proportional to lesion prevalence

Fendler WP, et al. Clin Cancer Res 2019;25:7448-54

Meta-analysis: ^{68}Ga-PSMA-11 PET for Imaging of Intermediate- to High-risk Patients Before Definitive Therapy and After Biochemical Recurrence

Studies using pathology as a gold standard

	Initial staging	Biochemical recurrence
n	226 patients in 5 studies	256 patients in 15 studies
Sensitivity	0.74 (95% CI 0.51–0.89)	0.99 (95% CI 0.96–1.00)
Specificity	0.96 (95% CI 0.85–0.99)	0.76 (95% CI 0.02–1.00)
Positive predictive value	0.93 (95% CI 0.86–0.99)	0.99 (95% CI 0.96–1.00)
Negative predictive value	0.85 (95% CI 0.75–0.93)	0.76 (95% CI 0.02–1.00)
Accuracy	0.86 (95% CI 0.79–0.92)	0.98 (95% CI 0.94–1.00)

Hope TA, et al. J Nucl Med 2019;60:786-93

Availability and Practicality of PSMA-PET for Men With Prostate Cancer

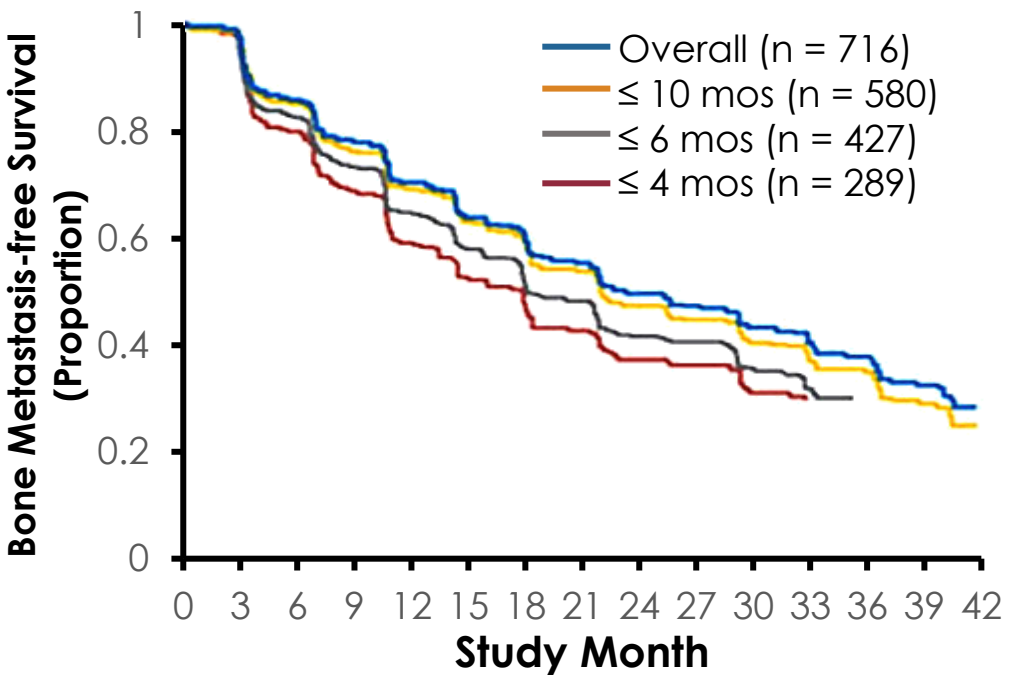
- PSMA-PET is still considered experimental and is not available in all centres/cities.

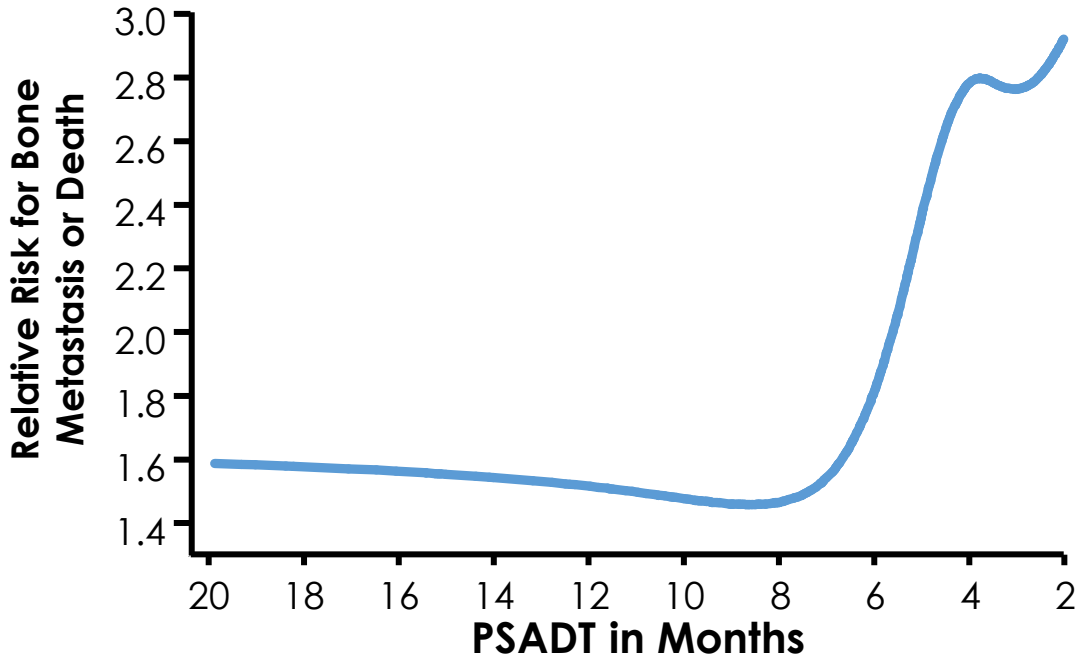
Discuss the availability of PSMA-PET in your region/centre and the logistics of obtaining PSMA-PET for your patients with prostate cancer

Importance of PSADT in identifying the high-risk patient

Relationship Between PSADT and Risk for Bone Metastasis or Death*

716 men from the placebo arm of Study 147 evaluating denosumab vs. placebo in men with nonmetastatic PCa at high risk for bone metastases



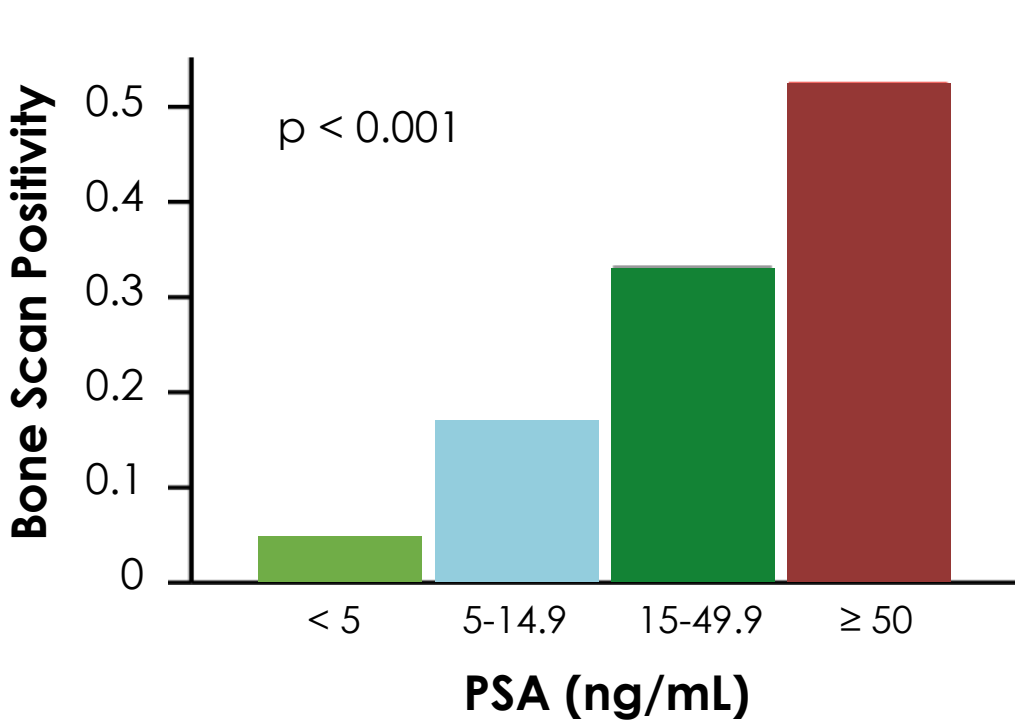


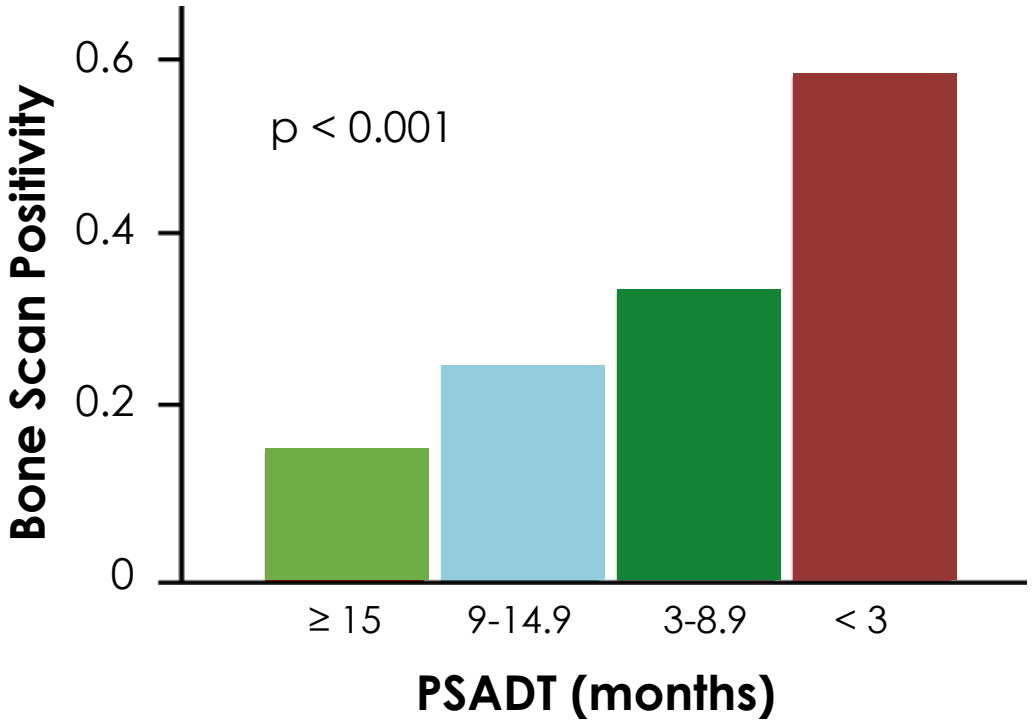
- The shorter the PSADT, the greater the risk of bone metastases or death.

*Placebo arm of Study 147

Smith MR, et al. J Clin Oncol 2013;31:3800-6

PSA and PSADT as Predictors of Metastasis in CRPC





- A PSA between 5 and 15 ng/mL revealed 10% to 15% of patients with bone metastases among those with a slow PSADT (≥ 9 months), and 26% of patients with bone metastases among those with a more rapid PSADT (< 9 months).

Freedland S, et al. BJU Int 2016;118:570-7

Our Patient Brian

- December 2018
  - PSA nadired at 0.9 ng/mL
- April 2019
  - PSA 1.3 ng/mL
  - T < 0.7
- February 2020
  - PSA 5.3 ng/mL
  - T < 0.7

PSADT 5.0 months

Calculation of PSADT

$$\mathbf{PSADT = PSA_{initial} * e^{mt}}$$

- Many EMRs have PSADT calculators
- Many online calculators are also available, e.g.:

  https://www.mskcc.org/nomograms/prostate/psa_doubling_time
- Ensure sufficient PSA results are collected to calculate PSADT
- Patients with more rapid PSADTs require more frequent PSA measures to ensure that opportunities for treatment are not missed

Treatment options for nmCRPC

Prostate Cancer Disease States and Key Phase III Trials

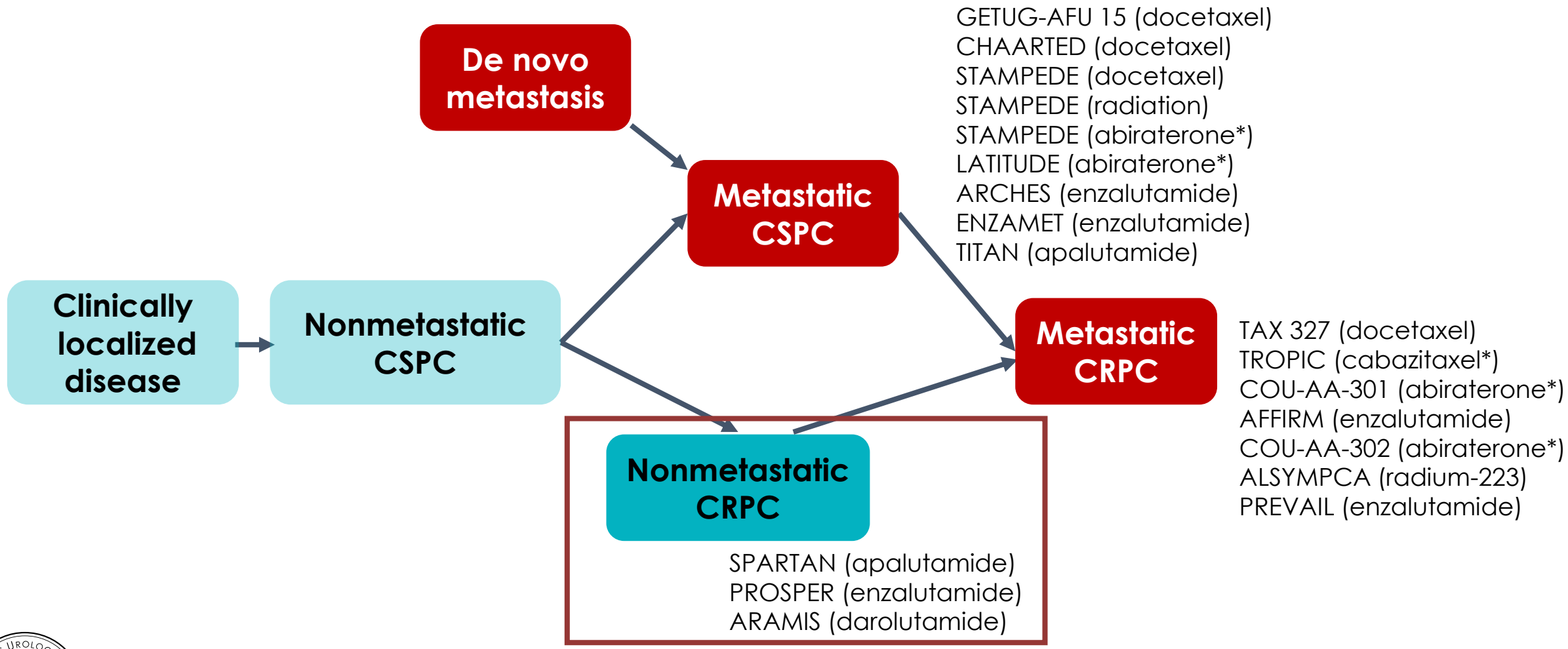


Figure adapted from Aggarwal RR, et al. Oncology (Williston Park) 2017;31:467-74;

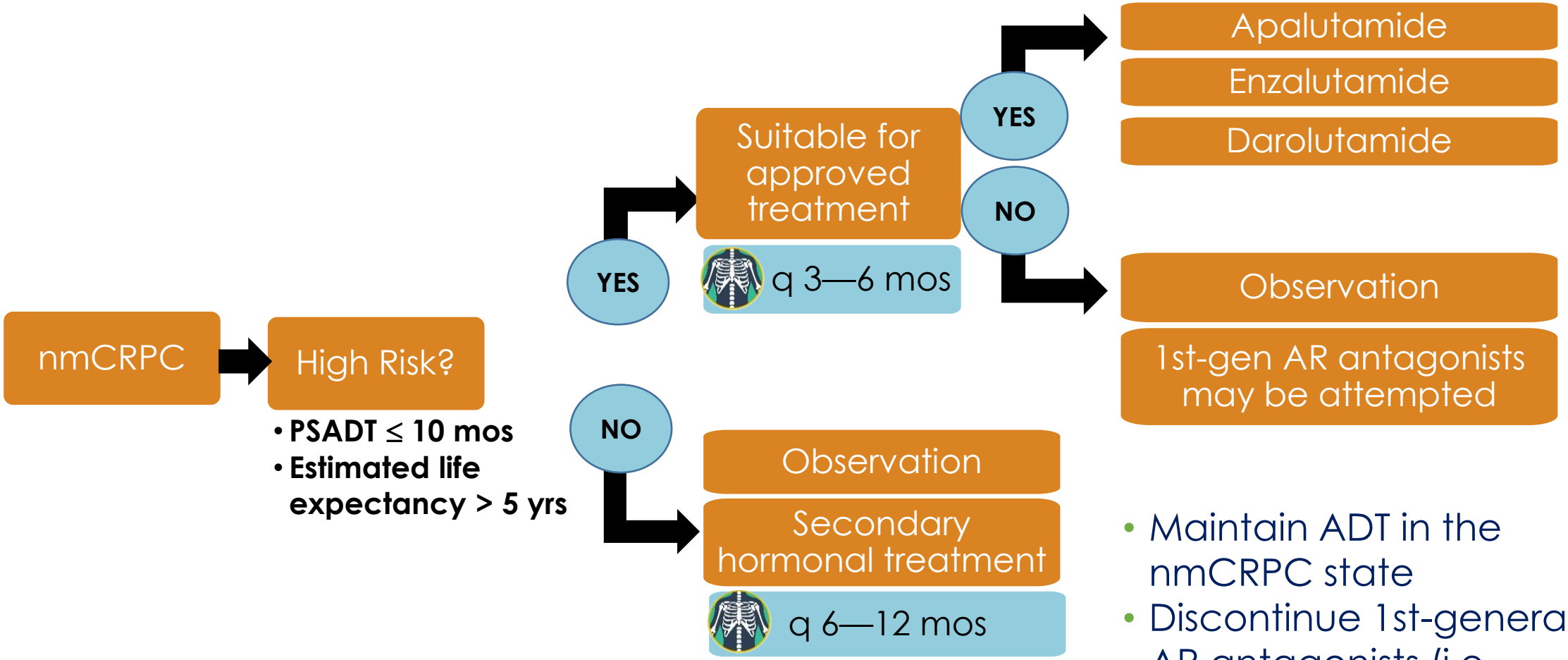
Scher HI, et al. J Clin Oncol 2016;34:1402-18; Armstrong AJ, et al. J Clin Oncol 2019;37:2974-86; Chi KN, et al. N Engl J Med 2019;381:13-24; Davis ID, et al. N Engl J Med 2019;381:121-31; Smith MR, et al. N Engl J Med 2018;378:1408-18; Hussain M, et al. N Engl J Med 2018;378:2465 -74

*Treatment included prednisone
CSPC = Castrate-sensitive prostate cancer

Discussion Question

- What are the potential treatment options for “Brian”?

Approach to nmCRPC – CUA 2021



- Maintain ADT in the nmCRPC state
- Discontinue 1st-generation AR antagonists (i.e., bicalutamide, flutamide, etc.)

= Imaging frequency

Saad F, et al. Can Urol Assoc J 2021;15:E81-E90
Kokorovic A, et al. Can Urol Assoc J 2020;10.5489

Evolving Use of Bicalutamide in Prostate Cancer

- Short course (4 weeks) with initial dose of LHRH agonist to reduce impact of testosterone surge
- In combination with LHRH agonist or antagonist in metastatic PCa – Decreasing use
- In men undergoing finite LHRH treatment (e.g., 6-18 mos) often around radiation therapy or adjuvant and neoadjuvant trials
- In men with early progression toward CRPC without prior ARAT use

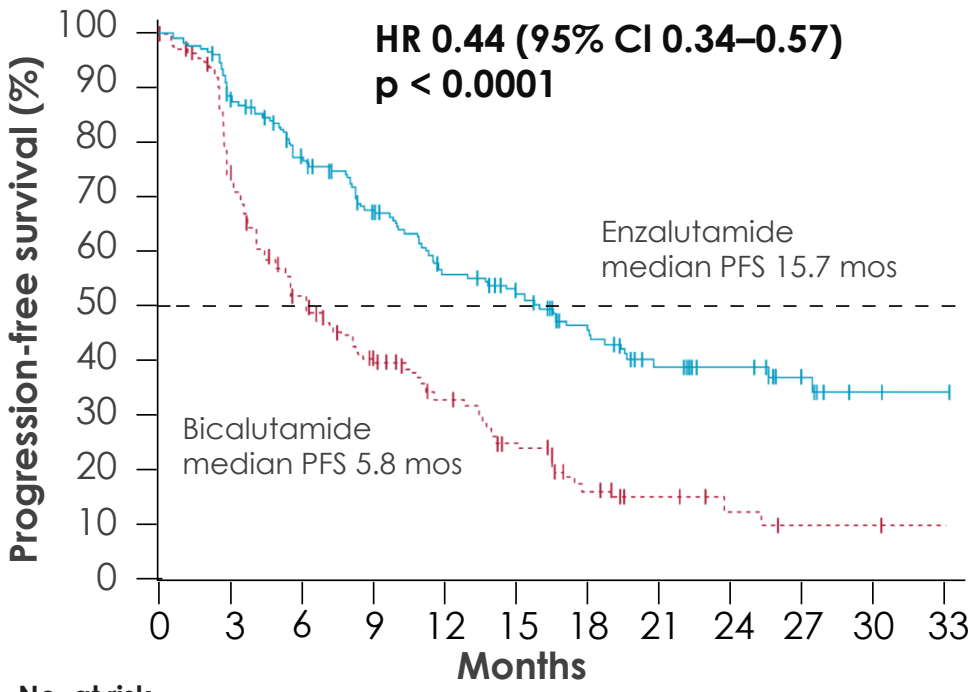
→ **BUT** results of STRIVE[2] and TERRAIN[3] suggest the preferred use of ARAT rather than bicalutamide in these men

HSPC = Hormone-sensitive prostate cancer

1. Heidenreich A, et al. Eur Urol 2014;65:467-79
2. Penson DF, et al. J Clin Oncol 2016;34:2098-106
3. Shore ND, et al. Lancet Oncol 2016;17:153-63

Bicalutamide vs. Enzalutamide in Patients with PCa Progressing on LHRH Agents

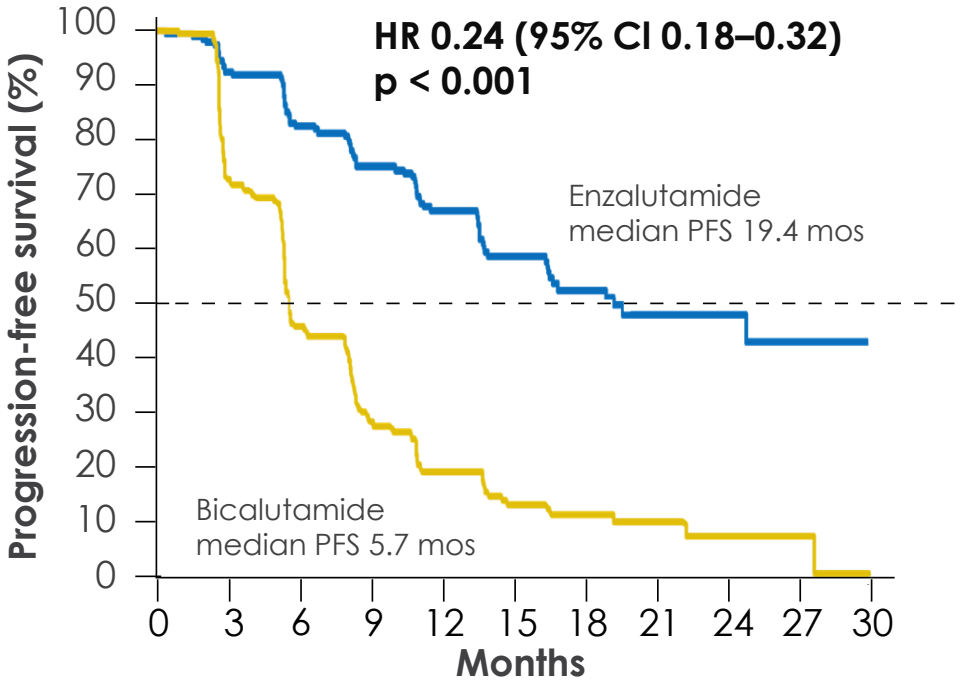
TERRAIN[1]



No. at risk

ENZA	184	159	131	107	86	71	52	33	21	13	8	5
BICA	191	133	85	61	44	30	13	7	4	2	2	1

STRIVE[2]



No. at risk

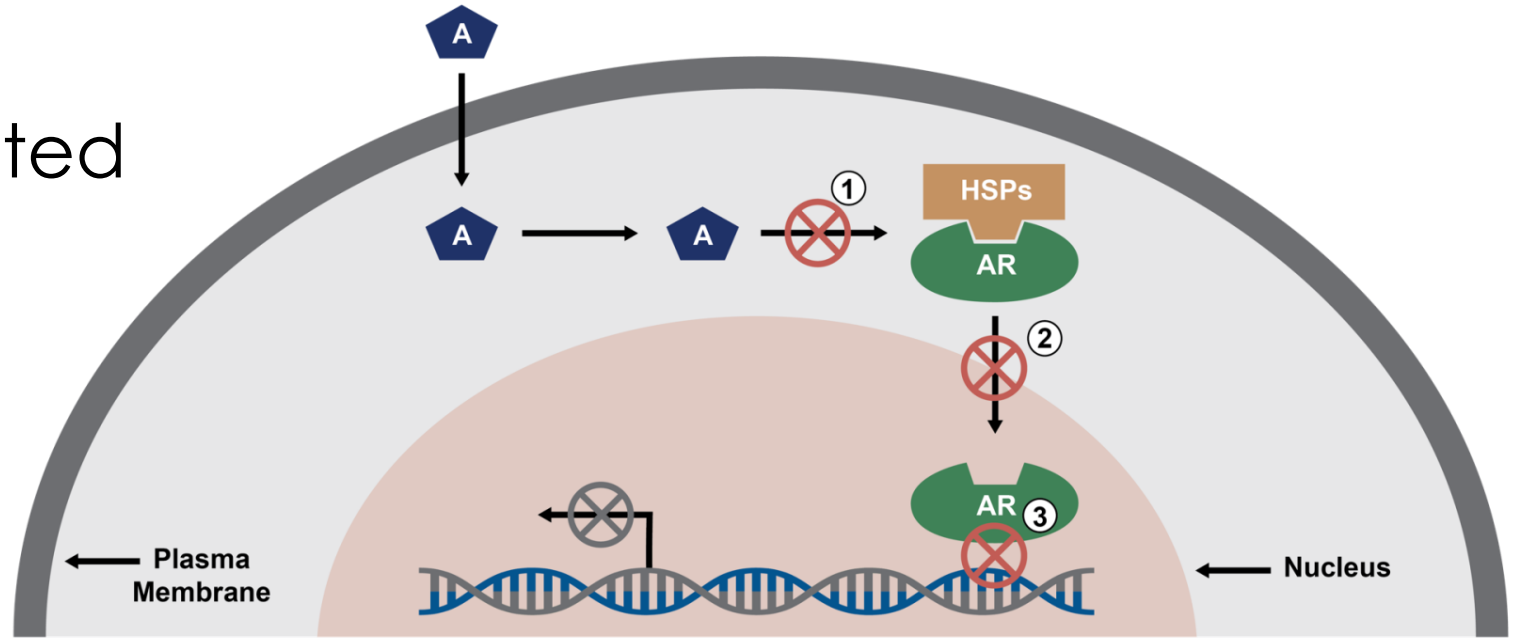
ENZA	198	171	150	131	101	66	43	24	16	5	0
BICA	198	138	80	51	29	17	9	5	3	1	0

BICA = Bicallutamide; ENZA = Enzalutamide;
LHRH = Luteinizing hormone-releasing hormone

1. Penson DF, et al. J Clin Oncol 2016;34:2098-106
2. Shore ND, et al. Lancet Oncol 2016;17:153-63

Enzalutamide, Apalutamide, and Darolutamide

- Inhibit binding of androgens (A) to androgen receptors (ARs)
- Inhibit nuclear translocation of ARs
- Inhibit AR-mediated DNA binding



Rice MA, et al. Front Oncol 2019;9:801

Overview of the nmCRPC Phase 3 Trials

	ARAMIS[1]	SPARTAN[2]	PROSPER[3]
Intervention	**Darolutamide vs. Placebo**	**Apalutamide vs. Placebo**	**Enzalutamide vs. Placebo**
Sample size	1,509	1,207	1,401
Primary endpoint	MFS (time to metastasis or death)		
Eligibility criteria	nmCRPC with PSA > 2 ng/mL and PSADT ≤ 10 mos		
Neuro-condition exclusions	None	History of seizure or any condition that may predispose to seizure	

1. Fizazi K, et al. N Engl J Med. 2019;380:1235–46
2. Smith MR, et al. N Engl J Med 2018;378:1408–18
3. Hussain M, et al. N Engl J Med 2018;378:2465–74

nmCRPC Phase 3 Trials: Baseline Characteristics

Characteristic	ARAMIS (n = 1,509)[1]		SPARTAN (n = 1,207)[2,3]		PROSPER (n = 1,401)4	
	DARO + ADT	PBO + ADT	APA + ADT	PBO + ADT	ENZA + ADT	PBO + ADT
Median age, years	74	74	74	74	74	73
ECOG PS, %						
0	68	71	77	78	80	82
1	32	29	23	22	20	18
Median baseline PSA, ng/mL	9.0	9.7	7.78	7.96	11.1	10.2
Median PSADT*						
≤ 6 months	70%	67%	71.5%	70.8%	77%	77%
> 6 months	30%	33%	28.5%	29.2%	23%	23%
Median duration of treatment, mos	14.8	11.0	31.4	11.5	18.4	11.1

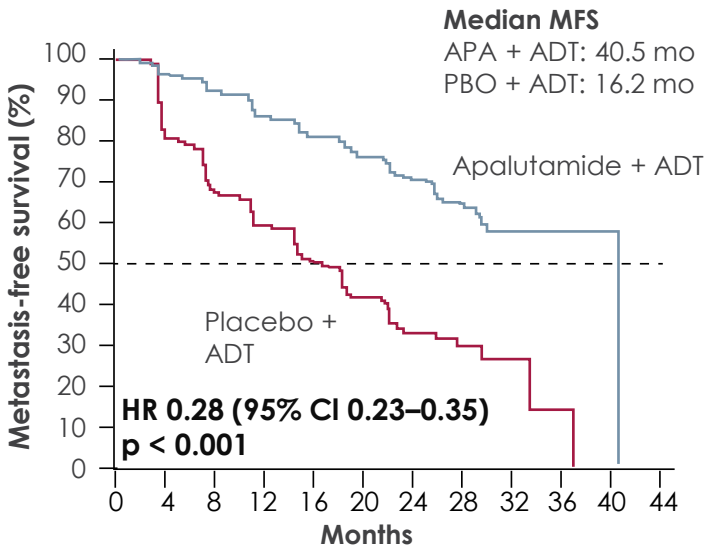
*Median PSADT was ~4.5 months across the trials – well below the inclusion criterion of ≤ 10 months

APA = Apalutamide; DARO = Darolutamide; ENZA = Enzalutamide; NR = Not reported; PBO = Placebo

1. Fizazi K, et al. N Engl J Med 2019;380:1235-6; 2. Smith MR, et al. N Engl J Med 2018;378:1408-18; 3. Small EJ, et al. Ann Oncol 2019;30:1813-20; 4. Hussain M, et al. N Engl J Med 2018;378:2465–74

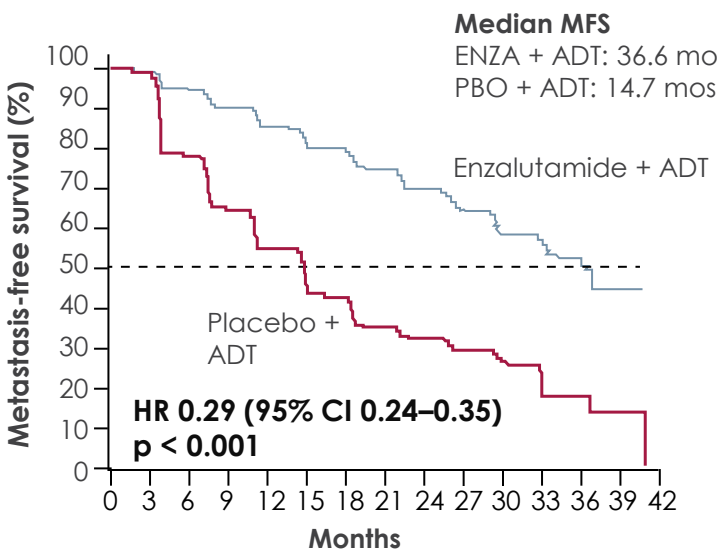
nmCRPC Phase 3 Trials: Primary Endpoint – MFS

Apalutamide (SPARTAN)[1]



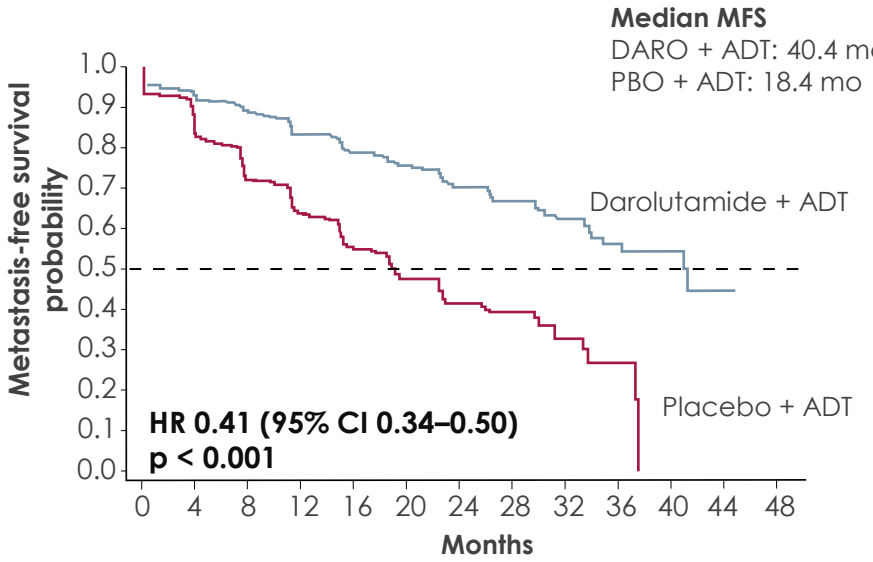
No. at risk												
APA + ADT	806	713	652	514	398	282	180	96	36	16	3	0
PBO + ADT	401	291	220	153	91	58	34	13	5	1	0	0

Enzalutamide (PROSPER)[2]



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

Darolutamide (ARAMIS)[3]



No. at risk													
DARO + ADT	955	817	675	506	377	262	189	116	68	37	18	2	0
PBO + ADT	554	368	275	180	117	75	50	29	12	4	0	0	0

ADT = Androgen deprivation therapy; APA = Apalutamide; DARO = Darolutamide; ENZA = Enzalutamide; HR = Hazard ratio; PBO = Placebo

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

Slide provided by Dr. Fred Saad

nmCRPC Phase 3 Trials: Secondary Endpoints

End Points (median)	ARAMIS (DARO vs. PBO)[1,2] n = 1,508	SPARTAN (APA vs. PBO)[3-5] n = 1,207	PROSPER (ENZA vs. PBO)[6-8] n = 1,401
OS	NR vs. NR (HR = 0.69; p = 0.003)	73.9 vs. 59.9 mos (HR = 0.784; p = 0.0161)	67.0 vs. 56.3 mos (HR = 0.73; p = 0.0011)
PFS	36.8 mos vs. 14.8 mos (HR = 0.38, p < 0.001)	40.5 mos vs. 14.7 mos (HR = 0.29; p < 0.001)	–
PFS2	–	55.6 vs. 43.8 mos (HR = 0.55; p < 0.0001)	–
Time to symptomatic progression*	40.3 mos vs. 25.4 mos (HR = 0.65, p < 0.001)	NR vs. NR (HR = 0.45; p < 0.001)	36.83 mos vs. NR (HR = 0.75; p = 0.028)
Time to PSA progression	33.2 mos vs. 7.3 mos (HR = 0.13, p < 0.001)	NR vs. 3.7 mos (HR = 0.06)	37.2 mos vs. 3.9 mos (HR = 0.07; p < 0.001)
Time to metastasis	–	40.5 mos vs. 16.6 mos (HR = 0.27; p < 0.001)	–
Time to 1st use of new agent	NR vs. NR (HR = 0.33, p < 0.001)	NR vs. NR (HR=0.60)† (cytotoxic chemotherapy)	39.6 mos vs. 17.7 mos (HR = 0.21; p < 0.001) (antineoplastic therapy)

*Secondary endpoint reported is time to pain progression; †P value test not done due to OS not crossing O'Brien-Fleming efficacy boundary of 0.00008.

APA = Apalutamide; ENZA = Enzalutamide; NR = Not reached; PBO = Placebo; PFS = Progression-free survival; PFS2 = Second-progression-free survival

1. Fizazi K, et al. N Engl J Med 2019;380:1235-6; 2. Fizazi K, et al. ASCO 2020 (Abstr 5514); 3. Smith MR, et al. N Engl J Med 2018;378:1408–18; 4. Small EJ, et al. Ann Oncol 2019;30:1813-20; 5. Small EJ, et al. ASCO 2020 (Abstr 5516); 6. Hussain M, et al. N Engl J Med 2018;378:2465–74; 7. Sternberg CN, et al. ASCO 202 (Abstr5515) 8. Tombal B, et al. Lancet Oncol 2019;20:556-9

nmCRPC Trials: Safety Results

	ARAMIS (Daro vs PBO)[1,2]		SPARTAN (APA vs PBO)[3,4]		PROSPER (ENZA vs PBO)[5,6]	
	All Grades (%)		All Grades (%)		All Grades (%)	
	Daro	PBO	APA	PBO	ENZA	PBO
AE leading to discontinuation	8.9	8.7	15	7.3	17	9
Hypertension	7.0	5.8	28	21	18	6
Rash	3.1	1.1	26	6.3	4	3
Fatigue	13.2	8.3	33	21	37	16
Asthenia	4.0	3.1	NR	NR	10	7
Fracture	5.5	3.6	18.0	7.5	18	6
Fall	5.2	4.9	22	9.5	18	5
Seizure	0.2	0.2	0.6	0	<1	0
Dizziness	4.5	4.0	9.3	6.3	12	6
Hypothyroidism	0.2	0	9.8	2.0	NR	NR
Mental and cognitive changes						
Cognitive/memory impairment	0.5	1.3	NR	NR	8	2
Mental impairment disorder	2.0	1.8	5.1	3.0	5	2

Note: Scheduled study visits for adverse events occurred with different frequencies across trials

*Treatment-emergent AEs †AEs of interest, irrespective of relationship to study drug

1. Fizazi K, et al. N Engl J Med 2019;380:1235-46
2. Fizazi K, et al. N Engl J Med 2020;383:1040-9
3. Smith MR, et al. N Engl J Med 2018;378:1408-18
4. Smith MR, et al. Eur Urol 2021;79:150-8
5. Hussain M, et al. N Engl J Med 2018;378:2465-74
6. Sternberg CN, et al. N Engl J Med 2020;382:2197-206

Management of Side Effects of AR-Targeted Therapies – **Fatigue**

Advise patients to:

- Be active and aim for 30 mins of moderate exercise/day
- Rest when needed
- Eat well and stay hydrated
- Avoid driving or using machinery when tired

1. Cancer Care Ontario. https://www.cancercareontario.ca/en/node/57146
2. Cancer Care Ontario. https://www.cancercareontario.ca/en/node/44321
3. ERLEADA Product Monograph] 2021

Management of Side Effects of AR-Targeted Therapies – **Rash**

- Usually macular or maculopapular
- Onset: median of 82 days
- Resolves in ~60 days in most patients
- Rash recurred in ~1/2 of those re-challenged with apalutamide
- Protect from dry skin
  - Use skin moisturizer
  - Sun and cold protection
  - Sunscreen: UVA + UVB and SPF ≥ 30

1. Cancer Care Ontario. https://www.cancercareontario.ca/en/node/57146
2. Cancer Care Ontario. https://www.cancercareontario.ca/en/node/44321
3. ERLEADA Product Monograph] 2021

Management of Side Effects of AR-Targeted Therapies – **Mild Joint, Muscle Pain or Cramps**

Advise patients to:

- Take pain medication as prescribed
- Take acetaminophen as needed
- Talk to doctor or pharmacist before taking ibuprofen, naproxen or aspirin (may increase bleeding risk)
- Rest often and try light exercise

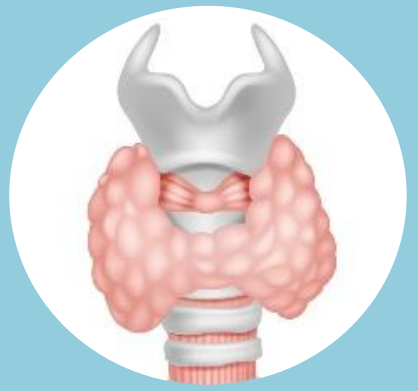
1. Cancer Care Ontario. https://www.cancercareontario.ca/en/node/57146
2. Cancer Care Ontario. https://www.cancercareontario.ca/en/node/44321
3. ERLEADA Product Monograph] 2021

Management of Side Effects of AR-Targeted Therapies – **Bone Health**

- Evaluate bone health and fracture risk prior to treatment and on a routine basis
  - DEXA screening
- Consider the use of bone-targeted agents
- Lifestyle modifications:
  - Recommendations for safe movement, adequate and safe exercise
  - Ensure adequate intake of protein, calcium, vitamin D
  - Caffeine and alcohol should be reduced

Hussain A, et al. Prostate Cancer Prostatic Dis 2021;24:290-300

Management of Side Effects of AR-Targeted Therapies – **Hypothyroidism** (Apalutamide)



- Common symptoms:
  - Fatigue/sluggishness, cold intolerance, constipation, hair loss, weight gain
- Monitor TSH at baseline and as clinically indicated.
  - If abnormal:
    - Test for total T3, free T4, total T4
    - Refer to PCP for thyroid hormone supplementation

PCP = Primary care physician
TSH = Thyroid-stimulating hormone

Dosage and Administration of the AR-Targeted Therapies

Apalutamide[1]

- 240 mg (four 60mg tablets) taken orally, **once daily**
- Swallow tablets whole with a glass of water
- Can be taken **with or without food**

Enzalutamide[2]

- 160 mg (four 40 mg capsules) taken orally, **once daily**
- Swallow tablets whole with a glass of water
- Can be taken **with or without food**

Darolutamide[3]

- 600 mg (two 300 mg film-coated tablets) taken orally, **twice daily**
- Swallow tablets whole **with food**

ERLEADA Product Monograph, 2021
XTANDI® Product Monograph, 2021
NUBEQA® (darolutamide) Product Monograph, 2021

Patients With Cancer Frequently Experience Comorbidities Requiring Multiple Medications

- Many patients with nmCRPC have comorbidities that require them to take multiple medications in addition to their cancer therapy:
  - Arthritis
  - Cardiac Disease
  - Depression
  - Diabetes
  - Dyslipidemia
  - Hypothyroidism
  - Hypertension
  - Obesity
  - Osteoporosis
  - Osteopenia

1. Pirschel C. ONSVoice. https://voice.ons.org/news-and-views/comorbidities-in-cancer-patient-care. January 30, 2017
2. Shore N, et al. Target Oncol 2019;14:527-39

Examples of Medications for Common Comorbidities in Patients With Cancer

Hypertension
- **Diltiazem** (CYP3A4 inhibitors)
- **Carvedilol, verapamil** (P-gp inhibitors)

Dyslipidemia
- **Lovastatin, simvastatin** (CYP3A4 substrates)
- **Rosuvastatin** (BCRP substrates)
- **Gemfibrozil** (CYP2C8 inhibitors)

Cardiac disease
- **Clopidogrel** (CYP2C8 inhibitors)
- **Amiodarone, carvedilol, verapamil** (P-gp inhibitors)
- **Amiodarone, diltiazem** (CYP3A4 inhibitors)
- **Digoxin** (P-gp substrates)

1. Pirschel C. ONSVoice. https://voice.ons.org/news-and-views/comorbidities-in-cancer-patient-care. Published January 30, 2017. Accessed May 14, 2019.
2. US Food and Drug Administration. Drug Development and Drug Interactions. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Potential Drug–Drug Interactions of AR-targeted Therapies

Drug category	Example[1,2]	Apalutamide Interactions[3]	Enzalutamide Interactions[4]	Darolutamide Interactions[5]
ACEI/ARBs	Losartan	X	x	
$Alpha_{1A}$-adrenergic receptor antagonists	Tamsulosin, Silodosin, Alfuzosin, Doxazosin	X	X	
Analgesics	Fentanyl, Oxycodone	X	X	
Antibiotics	Clarithromycin, Rifampin	X	X	X*†
Antifungals	Itraconazole	X	X	X*
Antithrombotics	Warfarin	X	X	
	Clopidogrel	X	X	
	Dabigatran	X	X	
	Apixaban, Rivaroxaban	X	X	
Beta-blockers	Bisoprolol	X	X	
PDE5 Inhibitors	Sildenafil, Tadalafil	x	X	

ACEI = Angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; PDE5 = Phosphodiesterase-5
*If P-gp and strong CYP3A4 inhibitors are used together, monitor patients more frequently for darolutamide adverse reactions. †Avoid concomitant use of P-gp and strong or moderate CPY3A4 inducers.

1. FDA. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm; 2. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, 2020; 3. ERLEADA Product Monograph, 2021; 4. XTANDI® Product Monograph, 2021; 5. NUBEQA® (darolutamide) Product Monograph, 2021

Potential Drug–Drug Interactions of AR-targeted Therapies (cont'd)

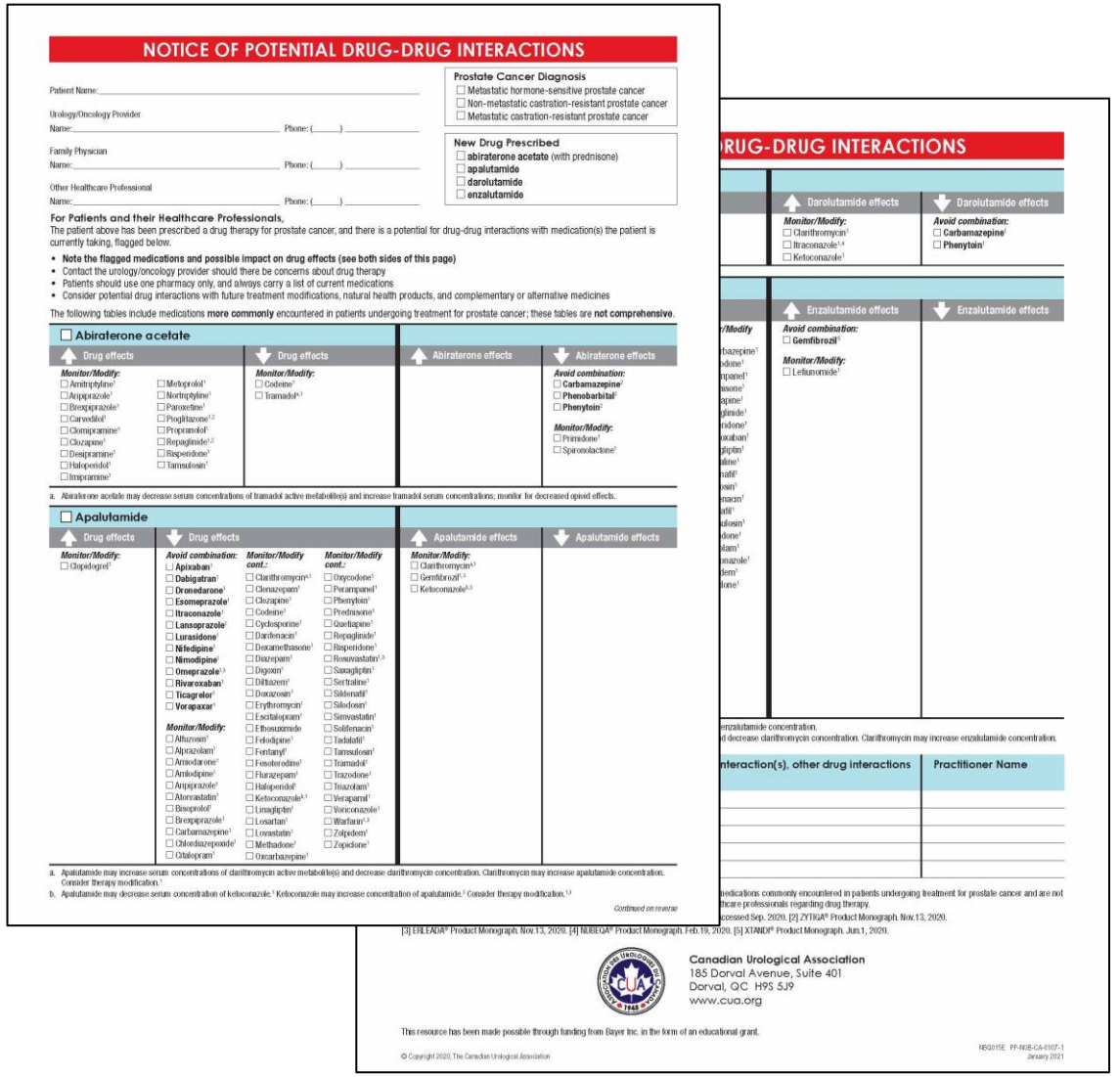
Drug category	Example[1,2]	Apalutamide Interactions[3]	Enzalutamide Interactions[4]	Darolutamide Interactions[5]
Calcium channel blockers	Amlodipine, Nifedipine, Felodipine	X	X	
	Diltiazem, Verapamil	X	X	
Cardiac glycosides	Digoxin	X	X	
Hypnotics	Alprazolam, Clonazepam, Diazepam	X	X	
Overactive Bladder	Darifenacin, Fesoterodine, Solifenacin, Tolterodine	X	X	
Proton pump inhibitors	Pantoprazole, Lansoprazole, Omeprazole	X	X	
Psychiatric medications	Citalopram, Escitalopram	X	X	
	Quetiapine, trazodone	X	X	
Statins	Rosuvastatin	X		X*
	Atorvastatin, simvastatin, lovastatin	X	X	

*If used together, monitor patients more frequently for adverse reactions and consider dose reduction of BCRP substrate drug.

1. FDA. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm; 2. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, 2020; 3. ERLEADA Product Monograph, 2021; 4. XTANDI® Product Monograph, 2021; 5. NUBEQA® (darolutamide) Product Monograph, 2021

Potential Drug–Drug Interactions of AR-targeted Therapies (cont'd)

- A DDI tool for AR-targeted therapies can be requested from the CUA or accessed digitally at the CUA website:
- cua.org/sites/default/files/Flipbooks/CPD/DDI/mobile/index.html#p=2



NOTICE OF POTENTIAL DRUG-DRUG INTERACTIONS

Patient Name:

Urology/Oncology Provider
Name: Phone: ( )

Family Physician
Name: Phone: ( )

Other Healthcare Professional
Name: Phone: ( )

Prostate Cancer Diagnosis
- ☐ Metastatic hormone-sensitive prostate cancer
- ☐ Non-metastatic castration-resistant prostate cancer
- ☐ Metastatic castration-resistant prostate cancer

New Drug Prescribed
- ☐ **abiraterone acetate** (with prednisone)
- ☐ **apalutamide**
- ☐ **darolutamide**
- ☐ **enzalutamide**

For Patients and their Healthcare Professionals,
The patient above has been prescribed a drug therapy for prostate cancer, and there is a potential for drug-drug interactions with medication(s) the patient is currently taking, flagged below.

- **Note the flagged medications and possible impact on drug effects (see both sides of this page)**
- Contact the urology/oncology provider should there be concerns about drug therapy
- Patients should use one pharmacy only, and always carry a list of current medications
- Consider potential drug interactions with future treatment modifications, natural health products, and complementary or alternative medicines

The following tables include medications **more commonly** encountered in patients undergoing treatment for prostate cancer; these tables are **not comprehensive.**

☐ **Abiraterone acetate**

Drug effects	Drug effects	Abiraterone effects	Abiraterone effects
Monitor/Modify: ☐ Amitriptyline[1] ☐ Aripiprazole[1] ☐ Bisoprolol[1] ☐ Carvedilol[1] ☐ Clomipramine[1] ☐ Clozapine[1] ☐ Desipramine[1] ☐ Haloperidol[1] ☐ Imipramine[1] ☐ Metoprolol[1] ☐ Nortriptyline[1] ☐ Paroxetine[1] ☐ Pioglitazone[1,2] ☐ Propranolol[1] ☐ Repaglinide[1,2] ☐ Risperidone[1] ☐ Tamsulosin[1]	***Monitor/Modify:*** ☐ Codeine[1] ☐ Tramadol[1,3]		***Avoid combination:*** ☐ **Carbamazepine**[1] ☐ **Phenobarbital**[1] ☐ **Phenytoin**[1] ***Monitor/Modify:*** ☐ Primidone[1] ☐ Spironolactone[1]

a. Abiraterone acetate may decrease serum concentrations of tramadol active metabolite(s) and increase tramadol serum concentrations; monitor for decreased opioid effects.

☐ **Apalutamide**

Drug effects	Drug effects		Apalutamide effects	Apalutamide effects
Monitor/Modify: ☐ Clopidogrel[1]	***Avoid combination:*** ☐ **Apixaban**[1] ☐ **Dabigatran**[1] ☐ **Dronedarone**[1] ☐ **Esomeprazole**[1] ☐ **Itraconazole**[1] ☐ **Lansoprazole**[1] ☐ **Lurasidone**[1] ☐ **Nifedipine**[1] ☐ **Nimodipine**[1] ☐ **Omeprazole**[1,3] ☐ **Rivaroxaban**[1] ☐ **Ticagrelor**[1] ☐ **Vorapaxar**[1] ***Monitor/Modify:*** ☐ Alfuzosin[1] ☐ Alprazolam[1] ☐ Amiodarone[1] ☐ Amlodipine[1] ☐ Aripiprazole[1] ☐ Atorvastatin[1] ☐ Bisoprolol[1] ☐ Bisoprazole[1] ☐ Carbamazepine[1] ☐ Chlordiazepoxide[1] ☐ Citalopram[1]	***Monitor/Modify cont.:*** ☐ Clarithromycin[1,2] ☐ Clonazepam[1] ☐ Clozapine[1] ☐ Codeine[1] ☐ Cyclosporine[1] ☐ Darifenacin[1] ☐ Dexamethasone[1] ☐ Diazepam[1] ☐ Digoxin[1] ☐ Diltiazem[1] ☐ Doxazosin[1] ☐ Erythromycin[1] ☐ Escitalopram[1] ☐ Ethosuximide ☐ Felodipine[1] ☐ Fentanyl[1] ☐ Fesoterodine[1] ☐ Flurazepam[1] ☐ Haloperidol[1] ☐ Ketoconazole[1,3] ☐ Linagliptin[1] ☐ Losartan[1] ☐ Lovastatin[1] ☐ Methadone[1] ☐ Oxcarbazepine[1]	***Monitor/Modify cont.:*** ☐ Oxycodone[1] ☐ Perampanel[1] ☐ Phenytoin[1] ☐ Prednisone[1] ☐ Quetiapine[1] ☐ Repaglinide[1] ☐ Risperidone[1] ☐ Rosuvastatin[1,3] ☐ Saxagliptin[1] ☐ Sertraline[1] ☐ Sildenafil[1] ☐ Silodosin[1] ☐ Simvastatin[1] ☐ Solifenacin[1] ☐ Tadalafil[1] ☐ Tamsulosin[1] ☐ Tramadol[1] ☐ Trazodone[1] ☐ Triazolam[1] ☐ Verapamil[1] ☐ Voriconazole[1] ☐ Warfarin[1,3] ☐ Zolpidem[1] ☐ Zopiclone[1]	***Monitor/Modify:*** ☐ Clarithromycin[a,1] ☐ Gemfibrozil[1,3] ☐ Ketoconazole[b,3]	***Avoid combination:*** ☐ **Gemfibrozil**[3] ***Monitor/Modify:*** ☐ Leflunomide[1]

a. Apalutamide may increase serum concentrations of clarithromycin active metabolite(s) and decrease clarithromycin concentration. Clarithromycin may increase apalutamide concentration. Consider therapy modification.[1]
b. Apalutamide may decrease serum concentration of ketoconazole.[1] Ketoconazole may increase concentration of apalutamide.[1] Consider therapy modification.[1,3]

Continued on reverse

RUG-DRUG INTERACTIONS

Darolutamide effects | Darolutamide effects
Monitor/Modify: ☐ Clarithromycin[1] ☐ Itraconazole[1,4] ☐ Ketoconazole[1]
Avoid combination: ☐ Carbamazepine[1] ☐ Phenytoin[1]

Enzalutamide effects | Enzalutamide effects
Avoid combination: ☐ Gemfibrozil[3]
Monitor/Modify: ☐ Leflunomide[1]

nteraction(s), other drug interactions | Practitioner Name

[3] ERLEADA® Product Monograph. Nov.13, 2020. [4] NUBEQA® Product Monograph. Feb.19, 2020. [5] XTANDI® Product Monograph. Jun.1, 2020.

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This resource has been made possible through funding from Bayer Inc. in the form of an educational grant.

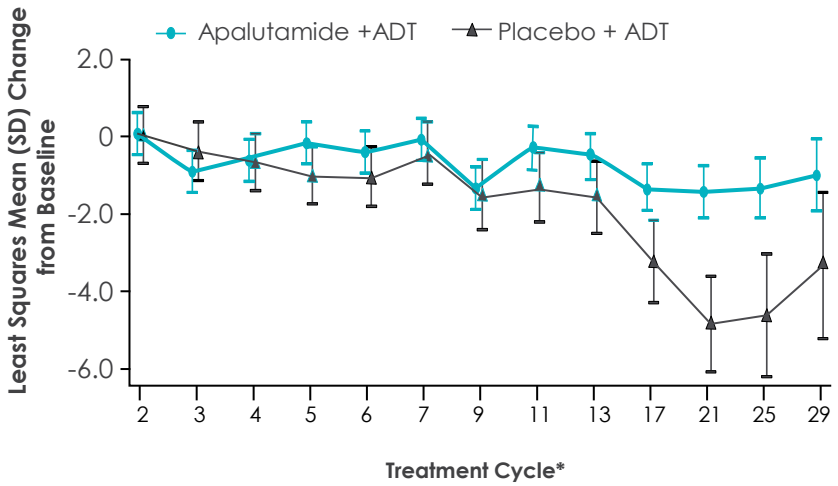
NBQ015E PP-NUB-CA-0107-1
January 2021

nmCRPC Trials – Health-related Quality of Life

- Men with nmCRPC generally have good QoL, and it is important to maintain that level of QoL
- In the nmCRPC AR inhibitor trials, HRQOL was maintained following treatment initiation

SPARTAN[1]

FACT-P total score (treatment difference in least squares mean change from baseline)

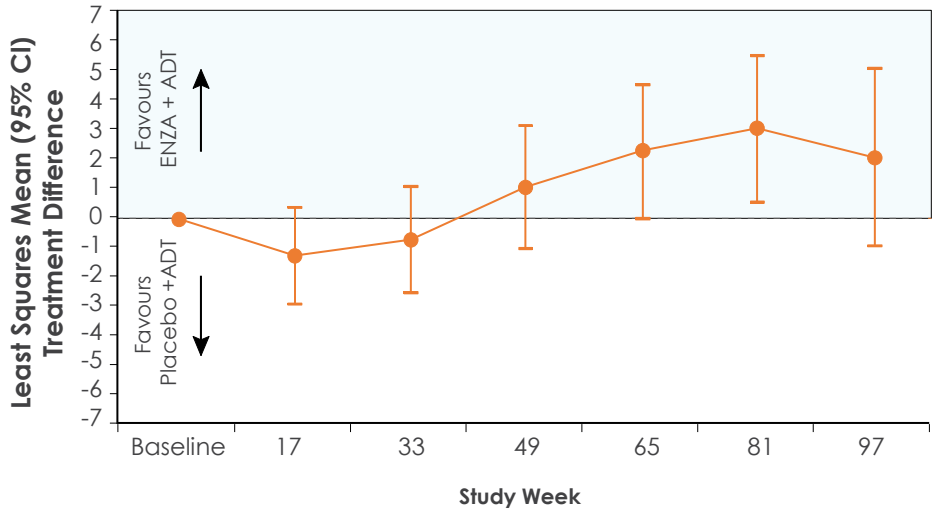


No. of patients in each cycle

APA + ADT	787	769	750	732	707	689	657	631	598	486	373	274	179
PBO + ADT	390	382	376	358	339	289	276	255	208	181	99	62	44

PROSPER[2]

FACT-P Total Score (treatment difference in least squares mean change from baseline)

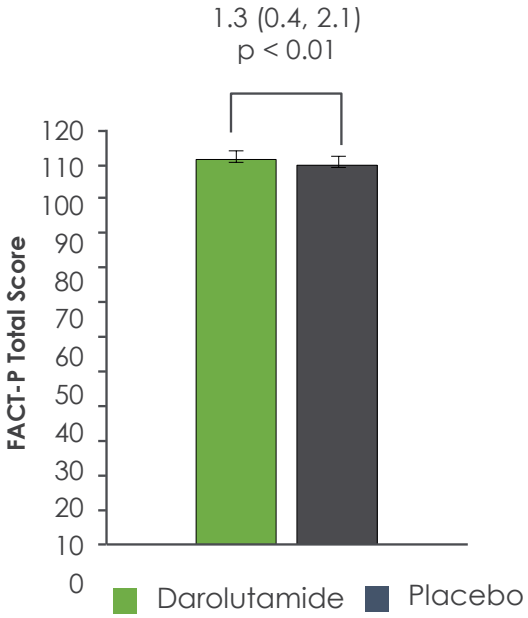


No. at risk

ENZA + ADT	...	815	718	621	522	427	354
PBO + ADT	...	403	329	239	183	139	90

ARAMIS[3]

FACT-P Total Score (difference vs. placebo)



*Cycle 29 is approximately 25.8 months from the start of treatment.

FACT-P = Functional Assessment of Cancer Therapy – Prostate
Minimum clinically important difference, 10 points
QoL = Quality of life

1. Saad F, et al. Lancet Oncol 2018;19:1404-16
2. Tombal B, et al. Lancet Oncol 2019;20:556-9
3. Fizazi K, et al. 2019;380:1235-46

Discussion Questions

- What quality-of-life considerations would you take into account when selecting a treatment for Brian?

Discussion Questions

- How would your management of Brian change if he were 52 years old with a PSADT of 11 months?

Discussion Questions

- How would your management of Brian change if he were 85 years old (PSADT 5 months)?

Provincial Support and Patient Assistance Programs [Province]

	Apalutamide	Darolutamide	Enzalutamide
Provincial coverage	X	X	X
Manufacturer Program name	○ Janssen BioAdvance Patient Assistance Program	○ Bayer DART Patient Assistance Program	○ Astellas Xtandi Patient Assistance Program
Available assistance	○ Compassionate supply may be available ○ Financial assistance for patients with or without private insurance may be available	○ Compassionate supply may be available ○ Financial assistance for patients with or without private insurance may be available	○ Compassionate supply may be available ○ Financial assistance for patients with or without private insurance may be available
Contact	P: 1.844.511.2616 F: 1.855.629.7100 E: erleada@bioadvancemail.ca	P: 1.833.955.3278 F: 1.877.2084393 E: info@dartsupport.ca	P: 1.855.982.6348 F: 1.855.982.6349 E: Info@XTANDIassistanceprogram.ca

Appropriate follow-up of patients with nmCRPC

Discussion Questions

- How do you monitor your patients with nmCRPC?
- If our patient "Brian" has castrate levels of testosterone and his PSA is still responding – would you test for radiologic progression?

Guidelines for Follow-up of Patients With CRPC Undergoing Hormonal Treatment – EAU Guidelines

- Evaluate patients 3–6 mos after initiation of treatment
- Minimum tests:
  - Serum PSA
  - Physical exam
  - Serum testosterone
  - Careful evaluation of symptoms
- Useful prognostic tests: hemoglobin, ALP, LDH
- Adapt/individualize follow-up in cases of disease progression or non-response to treatment
- If progression is suspected, assess testosterone

ALP = Alkaline phosphatase; LDH = Lactate dehydrogenase

Cornford P, et al. Eur Urol 2017;71:630-42.

Monitoring Considerations for Patients With nmCRPC on AR-Targeted Therapies – **Treatment-related Side Effects**

Clinical toxicity effects:

- Androgen withdrawal effects
- Fatigue
- Infection
- Active cardiac disease
- Seizures and other neuropsychiatric effects
- Dermatologic toxicity
- Fracture
- Falls
- Edema
- Diarrhea

Long-term side effects:

- BMD
- Cholesterol
- BP monitoring

BMD = Bone mineral density; BP = Blood pressure

ERLEADA Product Monograph, 2021
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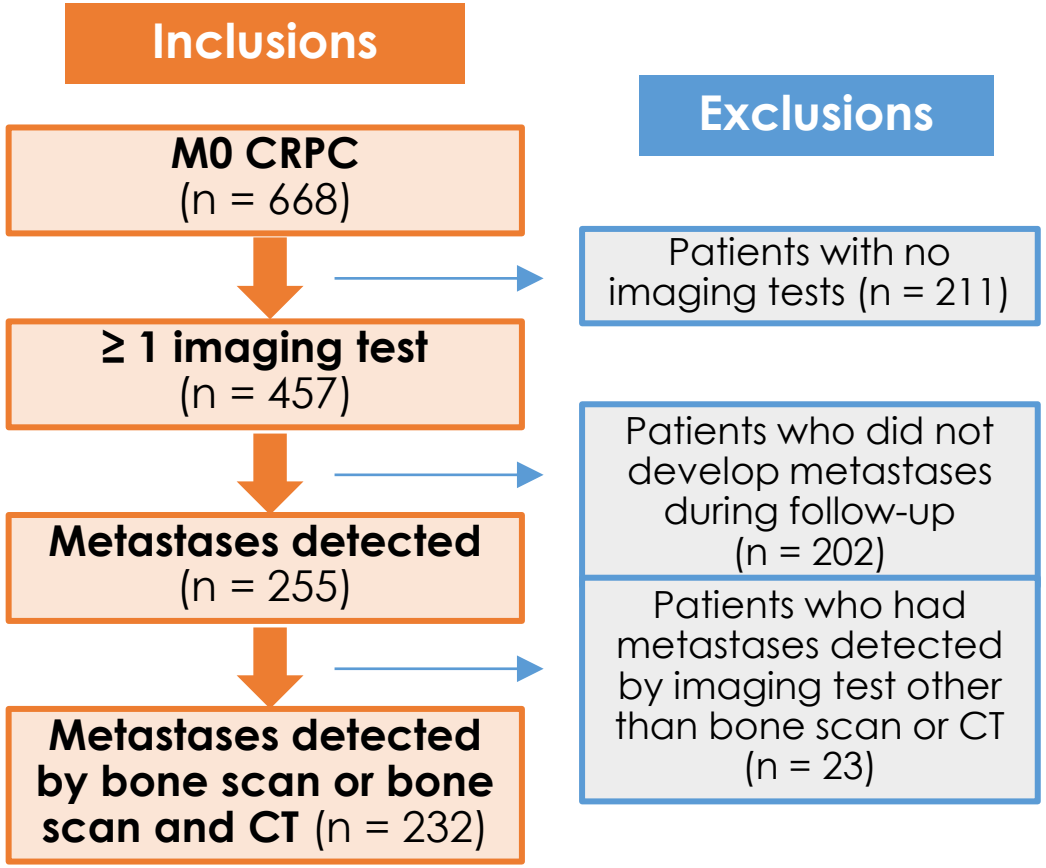
NUBEQA® (darolutamide) Product Monograph, 2021

Metastatic Sites at Conversion of M0 to M1 Disease in CRPC



Type of Imaging Test and Type of Metastasis		
	Bone scan only, No.	**CT ± Bone Scan, No. (%)**
Soft-tissue metastases	-	36 (30)
Bone metastases	Unknowable	66 (56)
Both soft-tissue and bone metastases	Unknowable	16 (14)
Total	**114**	**118**

- Foregoing CT during a metastatic evaluation may lead to an underdiagnosis of soft-tissue metastases and an underdiagnosis of metastases in general.

Hanyok BT, et al. Cancer 2016;122:222-9

Monitoring Considerations for Patients With nmCRPC on AR-Targeted Therapies – **Disease Progression**

- In addition to PSA, monitor radiographically
  - Distant metastasis without PSA progression occurred in the nmCRPC trials
    - > 40% of patients had bone or soft-tissue mets without "PSA Progression"
- Useful prognostic tests:
  - Hemoglobin
  - ALP
  - LDH
- Monitor symptoms at each visit

BMD = Bone mineral density; BP = Blood pressure

ERLEADA Product Monograph, 2021
XTANDI® Product Monograph, 2021
NUBEQA® (darolutamide) Product Monograph, 2021

Discussion Question

- What would you do if a patient had a rising PSA while on treatment and imaging (CT and bone scan) were negative?

- This patient should continue with treatment until there is evidence of clinical progression

Drug-Specific Monitoring Requirements for the AR-Targeted Therapies

Apalutamide[1]

Monitor for laboratory or clinical parameters as per routine practice, **PLUS**

- **TSH** at baseline and as clinically indicated
- **ECG** at baseline and as clinically indicated for patients at risk for QTc prolongation
- **INR** for patients on warfarin, at baseline and at each visit

Enzalutamide[2]

Monitor for laboratory or clinical parameters as per routine practice, **PLUS**

- **Blood pressure** at baseline and at each visit
- **ECG and electrolytes** baseline and at each visit for patients at risk for electrolyte abnormality and QTc prolongation
- **INR** for patients on warfarin, at baseline and at each visit

Darolutamide[3]

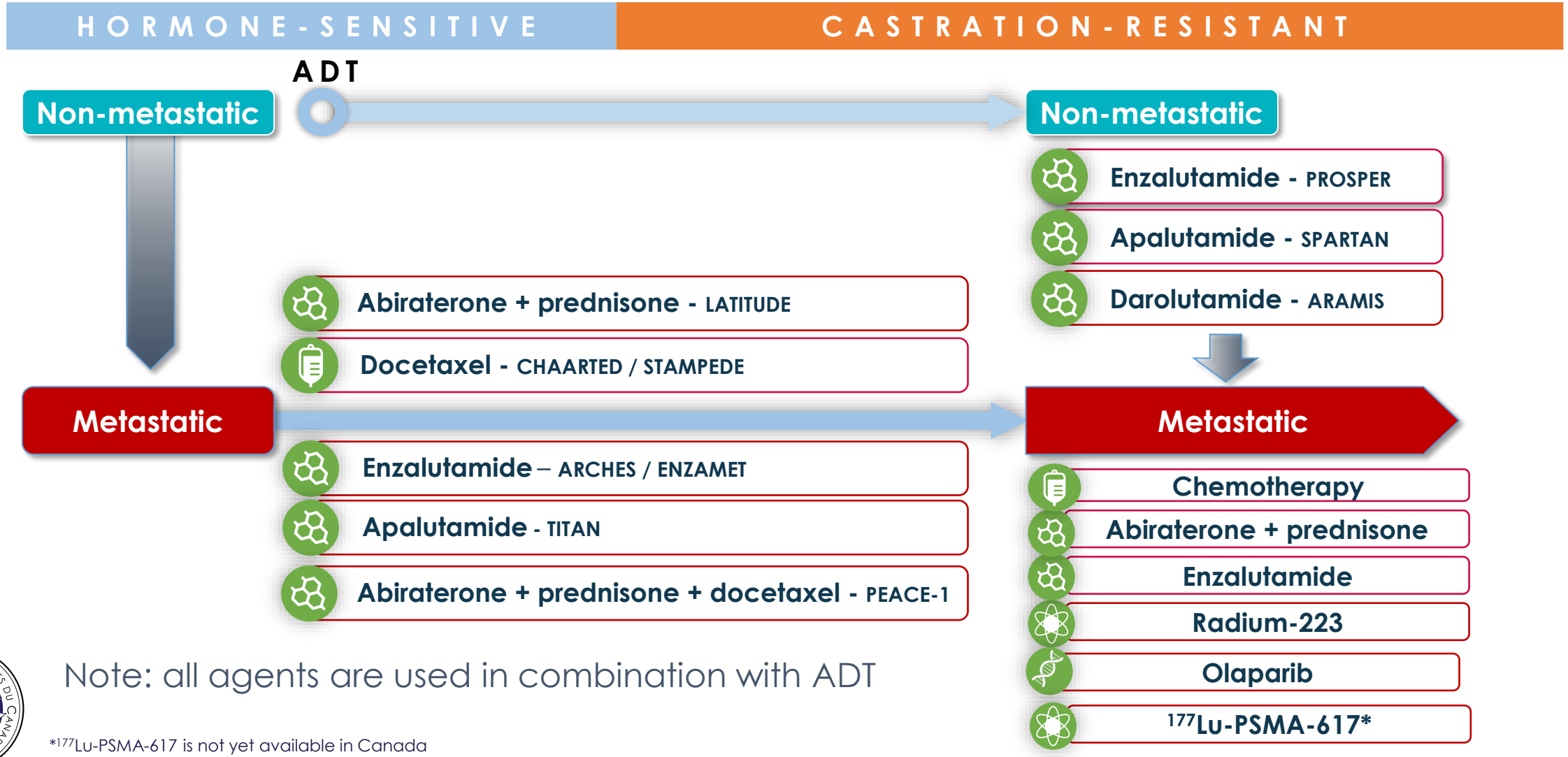
Monitor for laboratory or clinical parameters as per routine practice

ECG = Electrocardiogram; INR = International normalized ratio

1. ERLEADA Product Monograph, 2021
2. XTANDI® Product Monograph, 2021
3. NUBEQA® (darolutamide) Product Monograph, 2021

What to do when patients progress to mCRPC?

The New Reality in Systemic Therapy



Note: all agents are used in combination with ADT

*^{177}Lu-PSMA-617 is not yet available in Canada

Sequential Treatment with ARATs Associated with Limited Clinical Benefit in mCRPC – Randomized Trials

Study Treatment sequence	Median PFS (mos)	Median TTPP (mos)	≥ 50% PSA response	Median OS (months)
PLATO[1]				
Enzalutamide → Abiraterone + enzalutamide (n = 126)				NR
Enzalutar				NR
Khalaf et c				
Abiratero				ached
Enzalutar				4.3
CARD[4]				
Docetaxel + ARAT* → ARAT* (n = 126)	3.7†	NR	13.5	11.6
Docetaxel + ARAT* → Cabazitaxel (n = 129)	8.0†	NR	35.7	13.6
PROFOUND[5]				
ARAT* → ARAT* (n = 83)	3.55†	NR	NR	15.11‡
ARAT* → Olaparib (n = 162)	7.39†	NR	NR	18.5

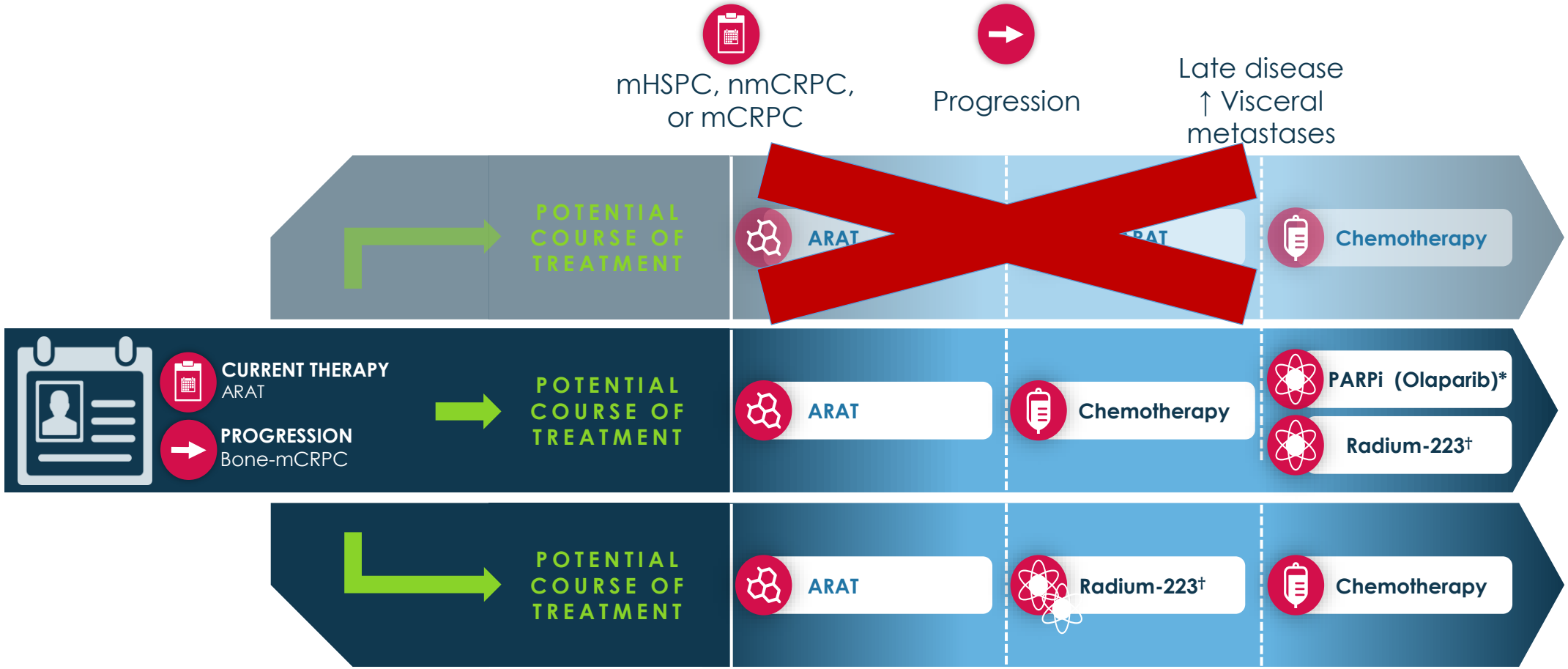
Given the lack of benefit shown in studies of switching from one ARAT to another in mCRPC, would you expect a similar lack of benefit if the first ARAT were used in nmCRPC and the second in mCRPC?

*Physician choice of abiraterone + prednisone or enzalutamide; †rPFS; ‡Interim OS

NR = Not reported;
rPFS = Radiographic PFS; TTPP = Time to PSA progression

1. Attard G, et al. J Clin Oncol 2018;36:2639-46; 2. Khalaf D, et al. ASCO 2018. Abstr 5015;
3. Khalaf D, et al. Lancet Oncol 2019;20:1730-9;3.
4. de Wit R, et al. N Engl J Med 2019;381:2506-18; 5. Hussain M, et al. Ann Oncol 2019;30(suppl_5): v851-v934

Prostate Cancer Disease Progression: Potential Treatment Sequencing Options



*Indicated for *ATM*- or *BCRA*1/2-mutated mCRPC
† *Indicated for patients with CRPC, symptomatic bone metastases, and no known visceral metastases.

mHSPC = Metastatic hormone-sensitive prostate cancer

Multidisciplinary Management of Men with nmCRPC

Discussion Questions

- At what point do you refer a patient with CRPC to the medical oncologist?
- What factors do you consider?
  - Symptoms?
  - PSA?
  - Imaging?

nmCRPC Conclusions

- Treatment of patients with high risk nmCRPC results in improved overall survival, despite high rate of active therapy in the placebo + ADT groups.
  - Patients do not “catch-up” if treatment is delayed

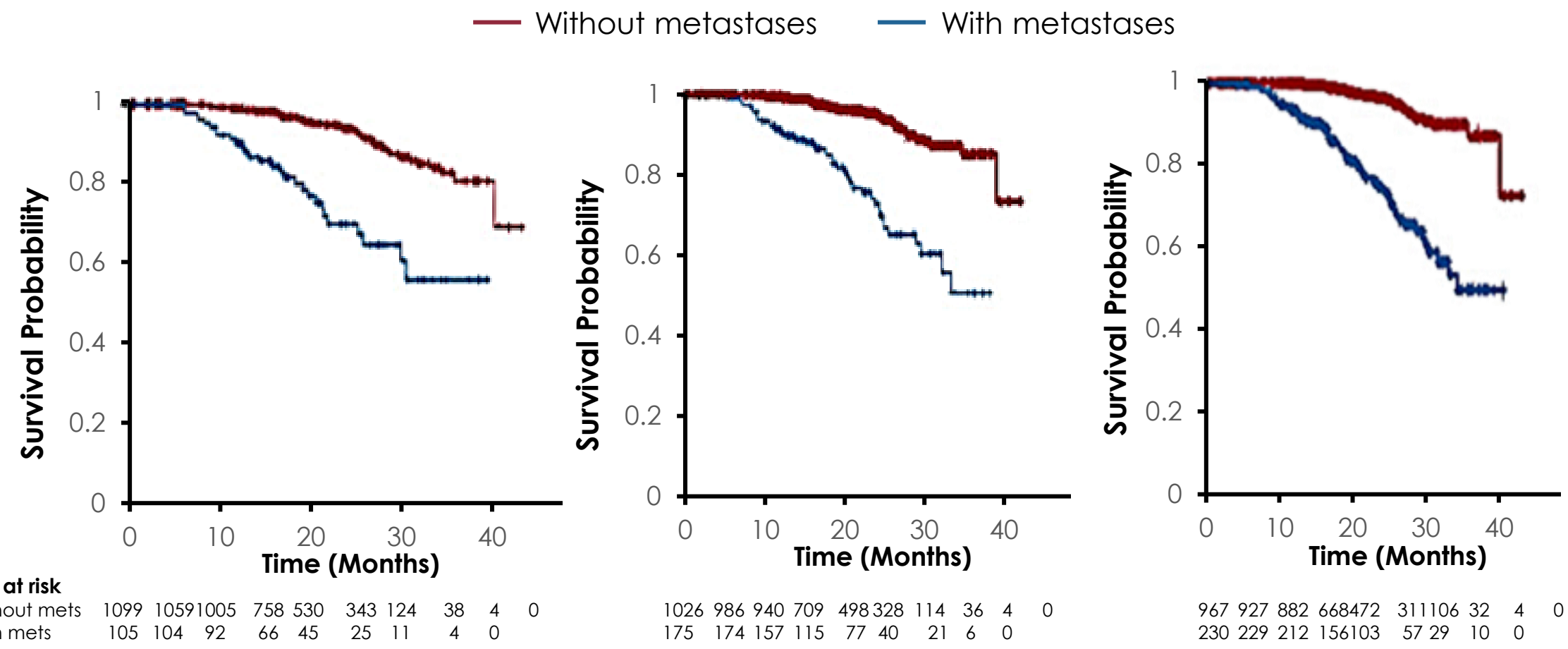
SECTION 3 SELF-ASSESSMENT PROGRAM IS ALSO AVAILABLE:

www.cua.org/uropedia

UROpedia CANADA

Backup Slides

Metastasis-free Survival as a Surrogate of Overall Survival in nmCRPC



Smith MR, et al. Clin Genitourin Cancer 2020;18:e180-9

Relationship Between PSADT and Risk for Bone Metastasis

Population	Intervention	Median time to BMFS (mos)	Median delay to BMFS (mos)	HR	p
All patients (n = 1,432)	Denosumab	29.5	4.2	0.85	0.028
	Placebo	25.2			
PSADT					
≤ 10 mos (n = 1,554)	Denosumab	28.4	6.0	8.4	0.042
	Placebo	22.4			
≤ 6 mos (n = 846)	Denosumab	25.9	7.2	0.77	0.006
	Placebo	18.7			
≤ 4 mos (n = 552)	Denosumab	25.8	7.5	0.71	0.004
	Placebo	18.3			

BMFS = Bone metastases-free survival

Smith M, et al. J Clin Oncol 2013;31:3800-6

Redefining Metastatic Risk in Recurrent Prostate Cancer

Study of castration-naïve PCa after radical prostatectomy

- 193 men
- Median PSA at bone scan conversion to metastatic disease was 31
- PSA at bone scans conversion (% patients)
  - < 10 = 25.8%
  - 10-100 = 50.8%
  - > 100 = 23.3%
- Risk factor for low PSA (< 10) at bone mets conversion
  - Low PSA at diagnosis
  - Higher Gleason score
  - Shorter time to metastasis

- Because metastasis may occur at a low PSA, patients with biochemical progression managed expectantly need regular bone scans even if PSA is low in order to detect metastasis before symptoms.

Loeb S, et al. J Urology 2010;184:157-61

nmCRPC Phase 3 Trials: Inclusion Criteria

	ARAMIS[1–4]			SPARTAN[5,6]			PROSPER[7,8]		
Intervention	Darolutamide vs. Placebo			Apalutamide vs. Placebo			Enzalutamide vs. Placebo		
Study design	Randomized (2:1); PSADT (≤ 6 vs. > 6 mos) and use of osteoclast-targeted therapy			Randomized (2:1); stratified based on PSADT (≤ 6 mos vs. > 6 mos), use of osteoclast-targeted therapy, and presence of locoregional disease			Randomized (2:1); stratified by PSADT (< 6 mos vs. ≥ 6 mo) and use of osteoclast-targeted therapy		
Accrual (targeted/actual)	1500/1509			1200/1207			1560/1401		
Dates	Start date	PCD	Final completion	Start date	PCD	Final completion	Start date	PCD	Final completion
	Sep 2014	Sep 2018	Jun 2020	Oct 2013	May 2017	Nov 2021	Oct 2013	Jun 2017	May 2020
Primary endpoints	MFS, time to metastasis or death								
Secondary endpoints	OS, time to pain progression, time to use of CT, time to first SSE, safety			Time to metastasis, PFS, time to symptomatic progression, OS, time to use of CT, PFS, safety, PK			Time to PSA progression, time to first use of new antineoplastic therapy, OS, time to first use of CT, HRQoL, time to CT-free disease specific survival, time to CT-free survival, time to pain progression, safety, PSA response rate		
Additional endpoints	PFS, time to first PC-related invasive procedure, initiation of subsequent antineoplastic therapy, PSA progression, PSA response, ECOG status, and HRQoL			Time to PSA progression, PSA response rate, HRQoL, PFS2			NA		
HRQoL	FACT-P, EORTC-QLQ-PR25, EQ-5D-3L			FACT-P and EQ-5D			FACT-P, EQ-5D-5L and QLQ-PR25		
Neuro-condition exclusions	None			History of seizure or any condition that may predispose to seizure					
Eligibility criteria	nmCRPC with PSADT ≤ 10 mo								
	screening PSA ≥ 2 ng/mL			screening PSA > 2 ng/mL			screening PSA ≥ 2 ng/mL		

1. ClinicalTrials.gov Identifier: NCT02200614. 2. Fizazi K, et al. J Clin Oncol. 2015;33:(suppl; abstr TPS5080). 3. Fizazi K, et al. Expert Rev Anticancer Ther. 2015;15:1007–17. 4. Fizazi K, et al. N Engl J Med. 2019;380:1235–46.. 5. ClinicalTrials.gov Identifier: NCT01946204. 6. Smith MR, et al. N Engl J Med 2018;378:1408–18. 7. ClinicalTrials.gov Identifier: NCT02003924. 8. Hussain M, et al. N Engl J Med 2018;378:2465–74

nmCRPC Trials: Safety Meta-analysis

Adverse event (AE)	Safety Ranking				Odds Ratio		
	Rank 1	Rank 2	Rank 3	Rank 4	APA vs. ENZA	DARO vs. ENZA	APA vs. DARO
Serious AEs	PBO	APA	DARO	ENZ	0.76	0.92	0.83
Falls, severe*	PBO	DARO	ENZA	APA	0.86	0.58	0.50
Fatigue (all grades)*	PBO	DARO	APA	ENZA	0.61	0.59	0.97
Fatigue, severe*	DARO	PBO	APA	ENZA	0.76	0.10	0.13
Hypertension*	PBO	DARO	APA	ENZA	0.53	0.51	0.96
Mental impairment*	DARO	PBO	APA	ENZA	0.63	0.15	0.24
Nausea	DARO	PBO	APA	ENZA	0.86	0.63	0.74
Diarrhea	PBO	ENZA	DARO	APA	0.71	0.81	0.87
Rash	PBO	DARO	APA	/	/	/	0.62
Seizure	PBO	DARO	APA	ENZA	0.71	0.33	0.47
Fractures	PBO	DARO	APA	/	/	/	0.62

*Significant heterogeneity in the effect found among AR inhibitors for these AEs. Differences were not significant for other AEs
4,104 patients were included in the safety analysis
/ = Not reported; APA = Apalutamide; DARO = Darolutamide; ENZA = Enzalutamide; PBO = Placebo

Atlavilla A, et al. ESMO 2019. (Abstr868P)