Treatment of non-metastatic CRPC

THE AR-TARGETED THERAPIES

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Three androgen-receptor (AR)-targeted therapies have been approved in Canada for the treatment of non-metastatic castrate-resistant prostate cancer (nmCRPC) – apalutamide, enzalutamide, and darolutamide. These treatments may be prescribed for patients diagnosed with high-risk nmCRPC who have the following characteristics:

- Prostate-specific antigen doubling time (PSADT) ≤ 10 months
- CT and bone scan negative for metastases
- Castrate testosterone levels (< 1.7 nmol/L)

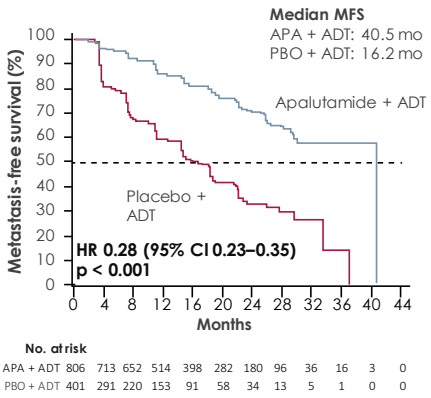
Each of the phase 3 clinical trials for the three AR-targeted therapies had similar inclusion criteria, and similar positive results for the primary endpoint of metastasis-free survival (MFS).

Overview of the nmCRPC phase 3 trials:

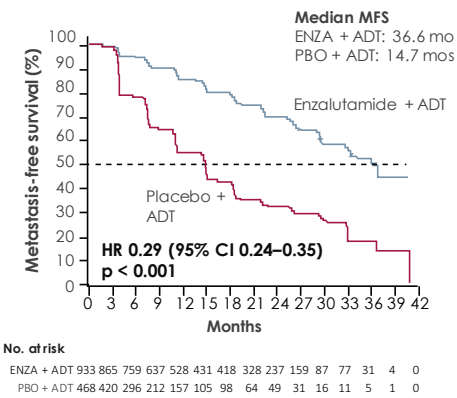
	SPARTAN[1,2]	PROSPER[3]	ARAMIS[4]
Intervention	**Apalutamide vs. Placebo**	**Enzalutamide vs. Placebo**	**Darolutamide vs. Placebo**
Sample size	1,207	1,401	1,509
Primary endpoint	MFS (time to metastasis or death)		
Eligibility criteria	nmCRPC with PSA > 2 ng/mL and PSADT ≤ 10 months		
Neuro-condition exclusions	History of seizure or any condition that may predispose to seizure		None

MFS Results for the AR-targeted Therapies in the Phase 3 Trials:

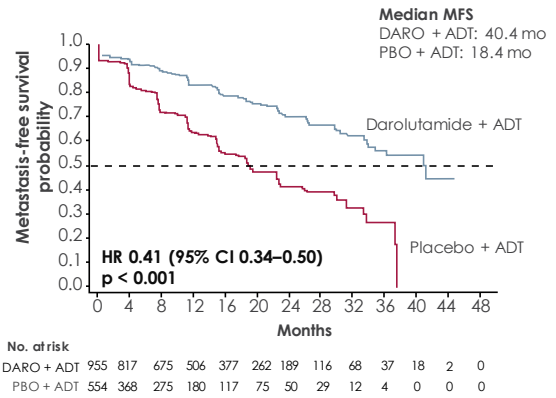
Apalutamide (SPARTAN)[2]



Enzalutamide (PROSPER)[3]



Darolutamide (ARAMIS)[4]



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

All three of the phase 3 clinical trials for the AR-targeted therapies have shown a statistically significant overall survival benefit for men with nmCRPC.[5,7,9]

Survival Endpoints for the AR-targeted Therapies in the Phase 3 Trials:

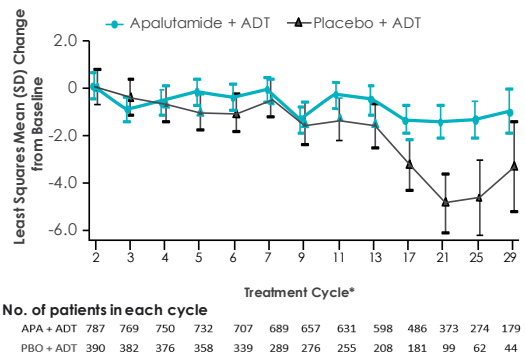
End Points (median)	ARAMIS (DARO vs. PBO)[4,5] n = 1,508	SPARTAN (APA vs. PBO)[2,6,7] n = 1,207	PROSPER (ENZA vs. PBO)[8,9] n = 1,401
OS	NR vs. NR (HR = 0.69; p = 0.003)	73.9 vs. 59.9 mos (HR = 0.784; p = 0.0161)	67.0 vs. 56.3 mos (HR = 0.73; p = 0.0011)
PFS	36.8 mos vs. 14.8 mos (HR = 0.38, p < 0.001)	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)	—

APA = Apalutamide; DARO = Darolutamide; ENZA = Enzalutamide; HR = Hazard ratio; NR = Not reached; OS = Overall survival; PBO = Placebo; PFS = Progression-free survival; PFS2 = Second-progression-free survival

Men with nmCRPC generally have good quality of life (QoL), and it is important that they be able to maintain that level of QoL for as long as possible. In each of the nmCRPC AR-targeted therapy trials, health-related QoL was maintained following treatment initiation:

SPARTAN[10]

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

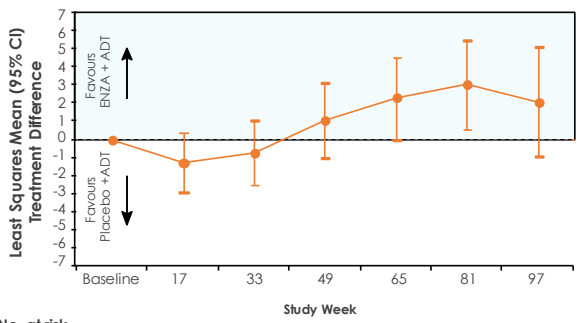


No. of patients in each cycle

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[11]

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

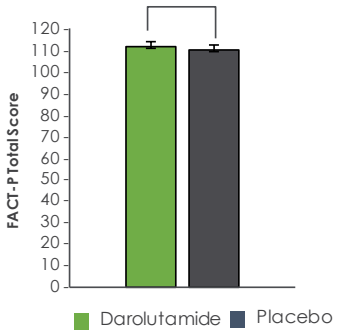


No. at risk

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

ARAMIS[4]

FACT-P Total Score
(difference vs. placebo)
1.3 (0.4, 2.1)
$p < 0.01$



*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

Each of the AR-targeted therapies is associated with a different adverse event (AE) profile:

Adverse events (AEs) in the phase 3 trials of AR-targeted therapies (not meant for cross-trial comparisons):

	SPARTAN[2]		PROSPER[3]		ARAMIS[4]	
	All Grades (%)		All Grades (%)		All Grades (%)	
	Apalutamide	Placebo	Enzalutamide	Placebo	Darolutamide	Placebo
AE leading to discontinuation	10.6	7.0	9.4	6.0	8.9	8.7
Hypertension	24.8	19.8	12	5.2	6.6	5.2
Rash	23.8	5.5	NR	NR	2.9	0.9
Fatigue	30.4	21.1	32.6	13.8	12.1	8.7
Fracture	11.7	6.5	9.8	4.9	4.2	3.6
Fall	15.6	9.0	11.4	4.1	4.2	4.7
Seizure	0.2	0	0.3	0	0.2	0.2
Dizziness	9.3	6.3	9.8	4.3	4.5	4.0
Hypothyroidism	8.1	2.0	NR	NR	0.2	0

NR = Not reported

Dosing and monitoring requirements differ slightly among the three AR-targeted therapies:

Dosage and administration:

Apalutamide[12]

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

Enzalutamide[13]

- 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[14]

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

Patient Monitoring

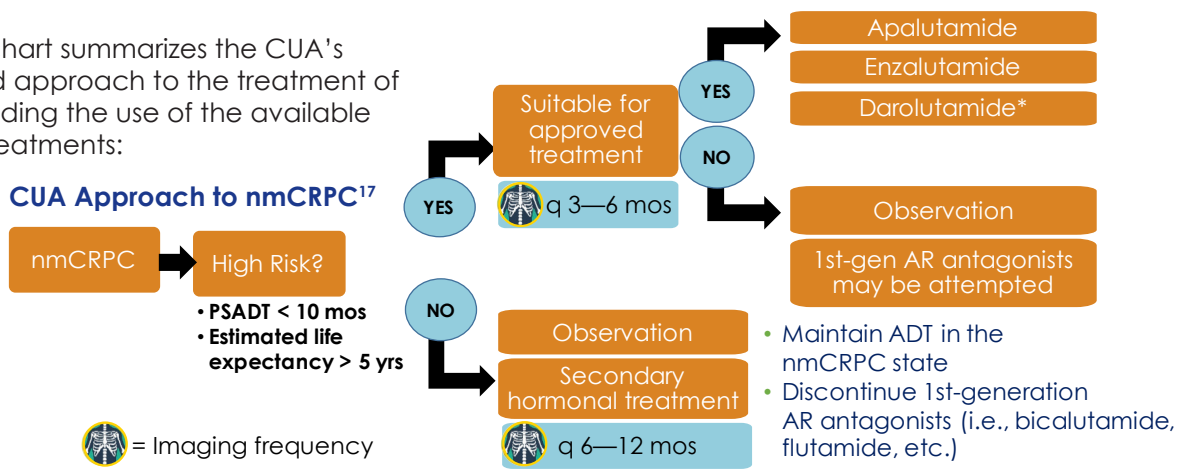
In general, AR-targeted therapies require minimal monitoring. All patients should undergo monitoring for laboratory or clinical parameters as per routine clinical practice.[12-14] Patients on apalutamide should also have their thyroid-stimulating hormone levels measured at baseline and as clinically indicated.[12] Patients on enzalutamide should have their blood pressure measured at baseline and periodically during treatment.[13] For patients on apalutamide or enzalutamide, electrocardiogram monitoring at baseline and during treatment should be considered for patients at risk for QTc prolongation.[12,13] Patients who are on apalutamide or enzalutamide and also taking warfarin should have their international normalized ratio measured at baseline and at each visit.

Drug Interactions

Patients with nmCRPC often have comorbidities requiring several drug treatments. AR-targeted treatments are associated with drug-drug interactions.[12-16] Please consult a pharmacist for specific interactions.

The following chart summarizes the CUA's recommended approach to the treatment of nmCRPC, including the use of the available AR-targeted treatments:

CUA Approach to nmCRPC[17]



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

* At the time of the guidelines publication, darolutamide was not yet approved in Canada; however, it was acknowledged that darolutamide was tested in a similar patient population of high-risk nmCRPC with positive results.

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