



Treatment of Non-Metastatic Castration-Resistant Prostate Cancer

Maha Hussain, MD, FACP, FASCO
Genevieve Teuton Professor of Medicine
Deputy Director
Robert H. Lurie Comprehensive Cancer Center



Disclosures

Consulting	AstraZeneca, Pfizer Inc, Bayer
Other (lectures)	Genentech, Sanofi Genzyme, Research to Practice, Aptitude Health, Epics, Astellas, PER
Contracted Research with Northwestern U. or U of Michigan	AstraZeneca, Bayer, Genentech, Pfizer Inc

PROS



CONS

Non Metastatic Castration-Resistant Prostate Cancer (nmCRPC) Background & History

Till early 2018 nmCRPC was an area of unmet need with no approved therapies.

- **2011** FDA convened an Oncologic Drugs Advisory Committee (ODAC) meeting:

Focus - Clinical trials end points & trial designs to support drug approval

- **ODAC: Transition from nmCRPC to M1 is a clinically relevant event & metastasis-free survival (MFS) is a reasonable end point**

- Clinical benefit of a drug would require a substantial magnitude of improvement and a favorable benefit–risk evaluation.

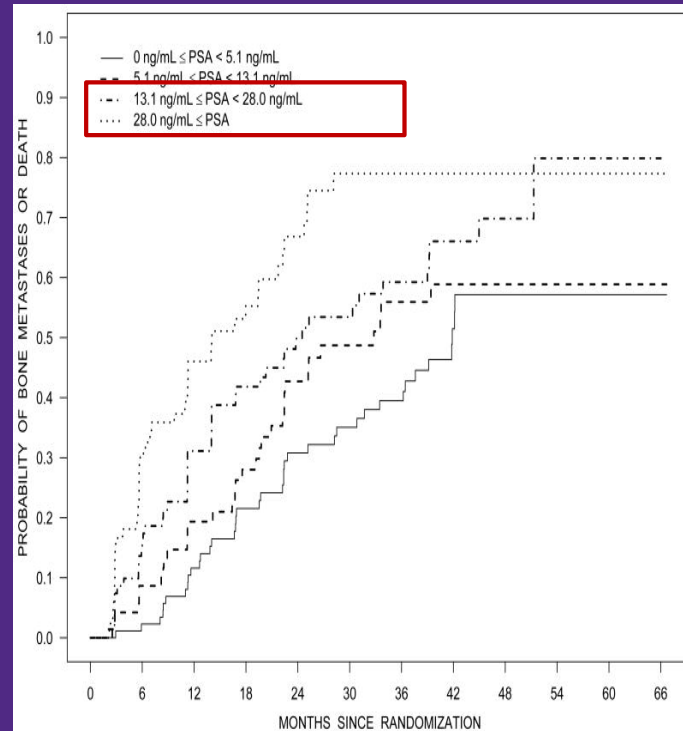
- **2012** another ODAC examined the results **Denosumab in nmCRPC**: Estimated median improvement of only 4 months in bone-only metastasis-free survival.

- **ODAC: Benefit/Risk not favorable.**

Time to Bone Metastases or Death by Baseline PSA Quartiles

nmCRPC:

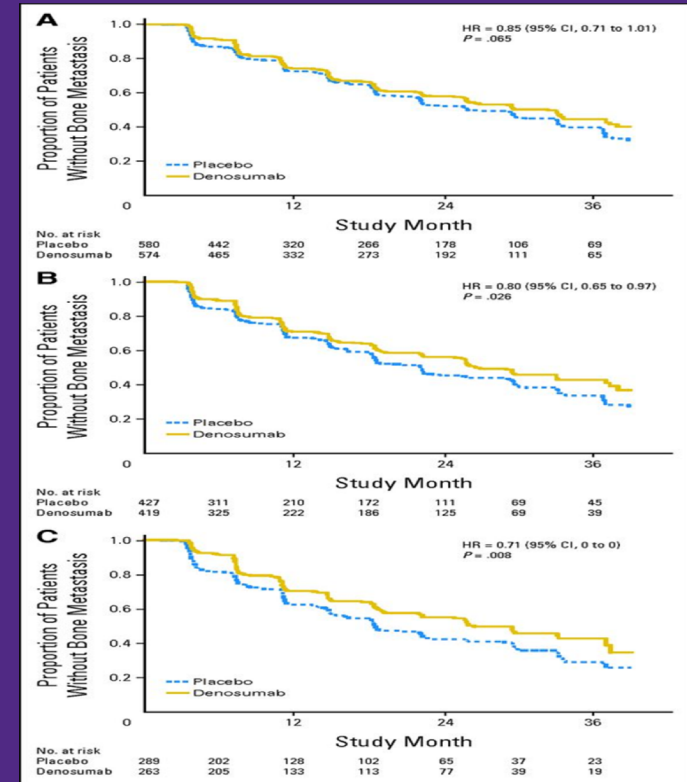
- Development of metastases is predictable & is associated with increasing baseline PSA & PSA doubling time < 10 months
- Median bone MFS is 25-30 months



Control arm: Atrasentan vs Placebo
At 2 years, 46% of pts developed bone metastases, and 20% died

Nelson JB, et al. Cancer 2008, Smith MR, et al. Cancer. 2011

Denosumab in nmCRPC Time to first bone metastasis by PSA Doubling Time (A) ≤ 10, (B) ≤ 6, and (C) ≤ 4 months



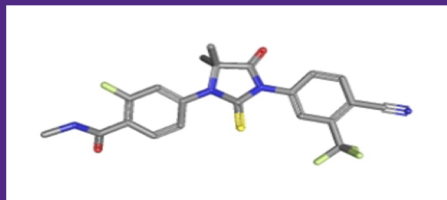
Smith M R et al. JCO 2013

Why Focus on nmCRPC?

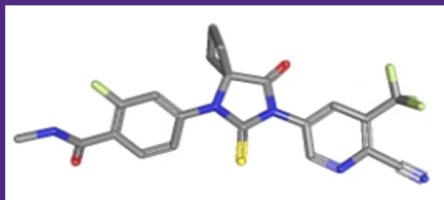
“Window of Opportunity”

1. Lower tumor burden may portend for better & more durable response
2. Advancing effective systemic therapy earlier has **greater “ROI”**:
Enzalutamide: mCRPC post docetaxel vs Pre-docetaxel vs mHSPC
3. M1 CRPC is Deadly disease: Delaying time to all metastases is clinically relevant, with potential to delay cancer-related morbidity & prolong overall survival

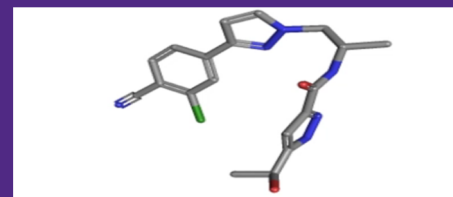
Enzalutamide, Apalutamide, Darolutamide



Enzalutamide



Apalutamide



Darolutamide

Enzalutamide & Apalutamide:

- Second-generation anti-androgens; target androgen receptors (AR) at 3 key points to inhibit its function:
 - Prevent the binding of androgens to the AR.
 - Inhibit the translocation of the AR into the nucleus.
 - Interfere with the binding of the AR to the DNA.
- **Darolutamide:** structurally distinct from apalutamide & enzalutamide, characterized by low blood–brain barrier penetration & may have improved tolerability (1,2)

Demographic & Disease Characteristics at Baseline

SPARTAN: Apalutamide

PROSPER: Enzalutamide

ARAMIS: Darolutamide

Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Apalutamide (N = 806)	Placebo (N = 401)
Age — yr		
Median	74	74
Range	48–94	52–97
Median time from initial diagnosis to randomization — yr	7.95	7.85
Prostate-specific antigen doubling time		
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 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Previous prostate-cancer treatment — no. (%)		
Prostatectomy or radiation therapy	617 (76.6)	307 (76.6)
Gonadotropin-releasing hormone analogue agonist	780 (96.8)	387 (96.5)
First-generation antiandrogen agent†	592 (73.4)	290 (72.3)

* There were no significant differences between groups in the demographic and disease characteristics at baseline.

† First-generation antiandrogen agents are flutamide, bicalutamide, and nilutamide.

Characteristic	Enzalutamide + ADT (n = 933)	Placebo + 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 doubling time (range), mo	3.8 (0.4-37.4)	3.6 (0.5-71.8)
PSA doubling time category, no. (%)		
< 6 mo	715 (77%)	361 (77%)
≥ 6 mo	217 (23%)	107 (23%)
Baseline use of bone targeting agent, no. (%)		
No	828 (89%)	420 (90%)
Yes	105 (11%)	48 (10%)

Table 1. Patient Demographic and Clinical Characteristics at Baseline.*

Characteristic	Darolutamide (N = 955)	Placebo (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 the world†	728 (76)	411 (74)
Median time from initial diagnosis (range) — mo	86.2 (2.6–337.5)	84.2 (0.5–344.7)
Presence of lymph nodes 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 doubling time		
Median (range) — mo	4.4 (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/L‡	0.6 (0.2–25.9)	0.6 (0.2–7.3)
ECOG performance status — no. (%)§		
0	650 (68)	391 (71)
1	305 (32)	163 (29)
Use of bone-sparing agent — no. (%)		
Yes	31 (3)	32 (6)
No	924 (97)	522 (94)
Previous hormonal therapy agents received — no. (%)¶		
One	177 (19)	103 (19)
Two or more	727 (76)	420 (76)
Not applicable‖	51 (5)	31 (6)

* Percentages may not total 100 because of rounding. PSA denotes prostate-specific antigen.

† This category predominantly includes European countries (15% of these patients came from non-European countries).

‡ Testosterone levels from screening or day 1 could be used for eligibility, and all patients met the inclusion criterion of having a testosterone level lower than 1.7 nmol per liter.

§ Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher scores reflecting greater disability.

¶ Common previous hormonal therapies for prostate cancer (received by ≥10% of all patients) included leuprolide (52%), goserelin (32%), triptorelin (29%), bicalutamide (66%), flutamide (13%), and cyproterone (11%).

‖ This category includes patients who underwent surgical castration.

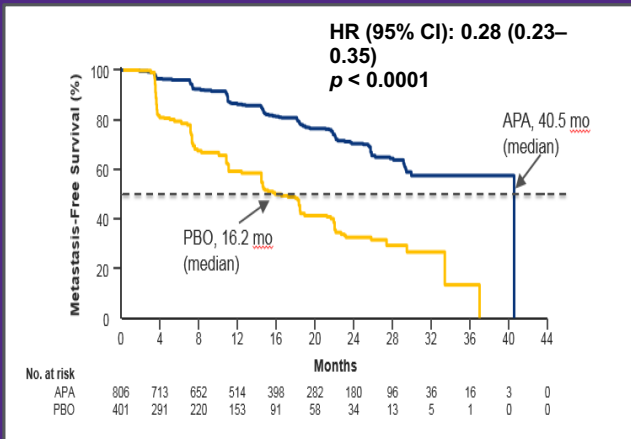
Smith et al. NEJM 2018

Hussain et al. NEJM 2018

Fizazi et al. NEJM 2019

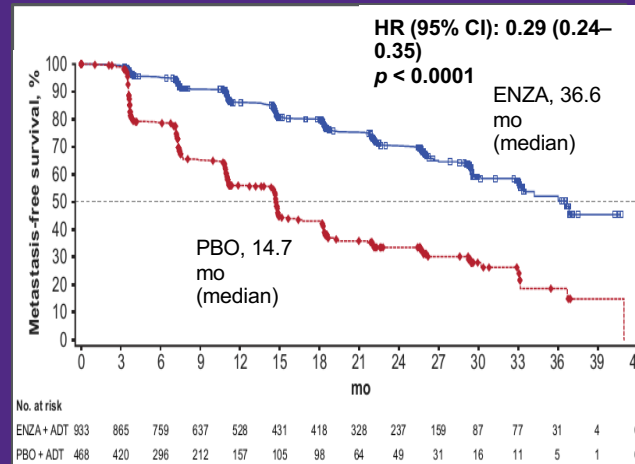
Metastasis-Free Survival (MFS)

Apalutamide: SPARTAN ¹



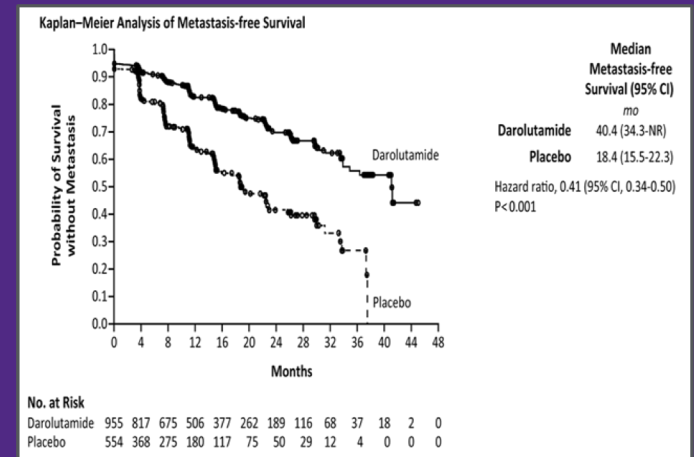
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 months vs PBO 16.2
- 24-month increase in MFS

Enzalutamide: PROSPER ²



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

Darolutamide: ARAMIS ³



- 59% reduction of distant mets or death
- Median MFS: DARO 40.4 months vs PBO 18.4 (22 m)
- 22-month increase in MFS

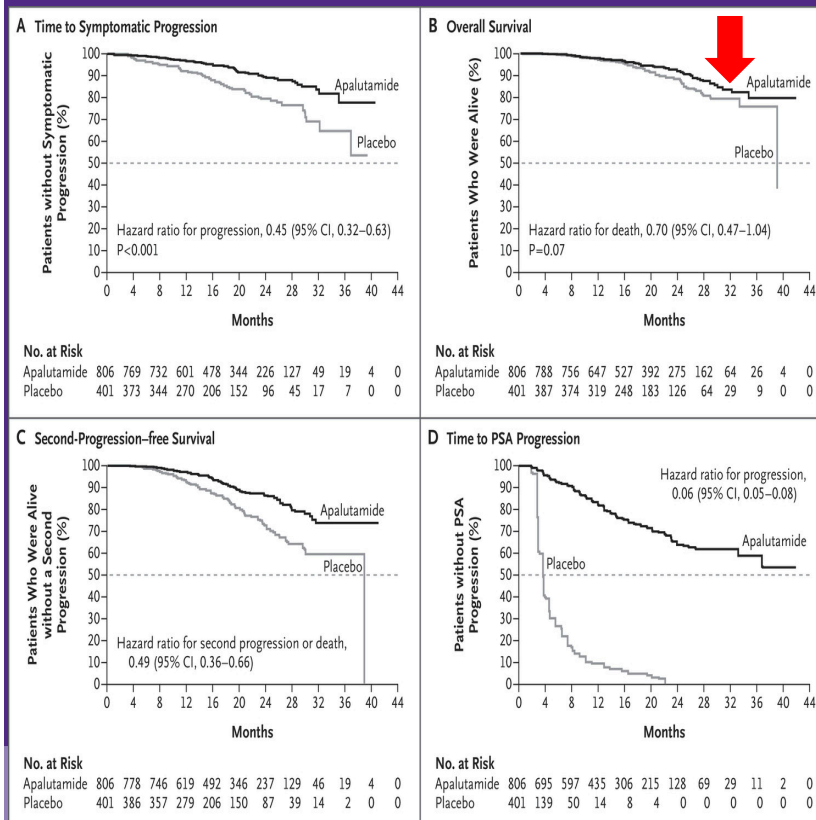
1. Smith MR, et al. NEJM 2018.

2. Hussain M, et al. NEJM 2018

3. Fizazi K, et al. NEJM 2019

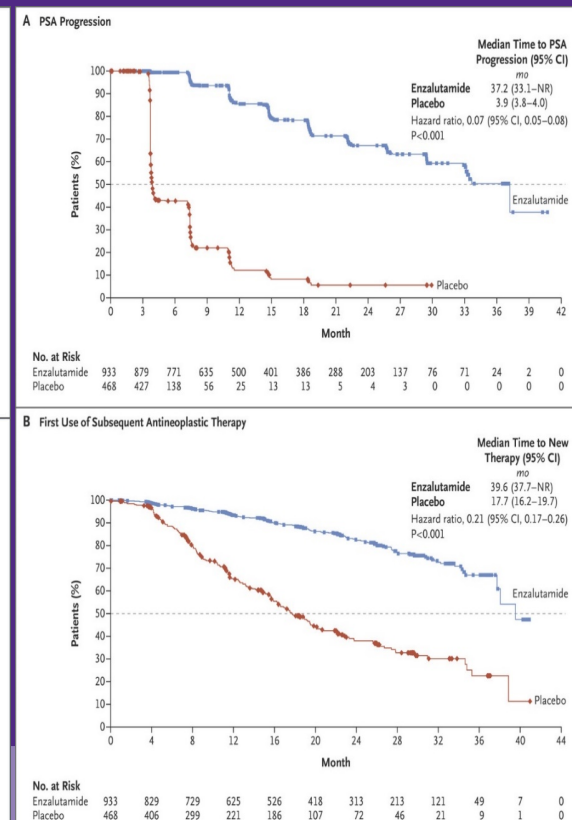
Prespecified Secondary and Exploratory Efficacy End Points

Apalutamide vs Placebo

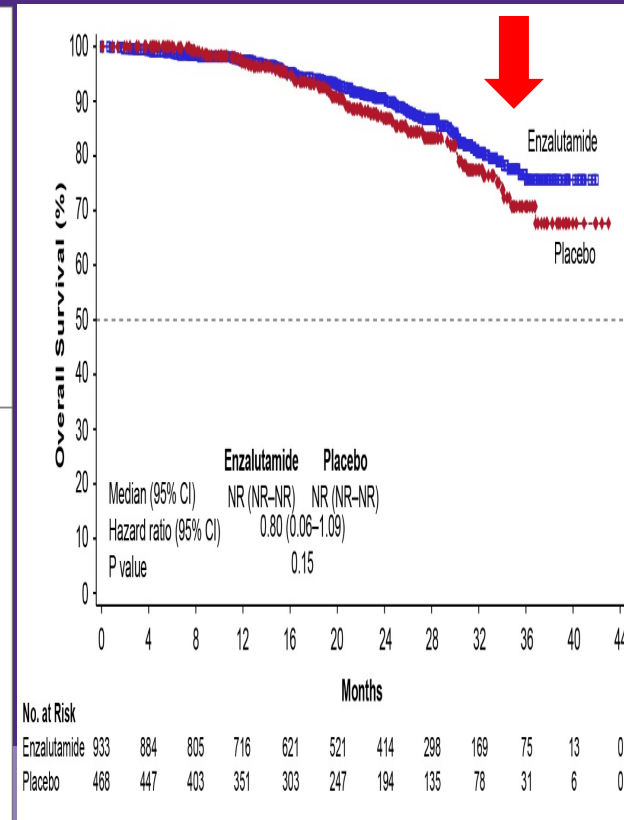


Smith et al. NEJM, 2018

Enzalutamide vs Placebo: Time to PSA Progression & Time to First Use of Subsequent Antineoplastic Therapy



Estimate of First Interim Analysis of Overall Survival



Hussain et al. NEJM 2018

ARAMIS: Darolutamide in nmCRPC

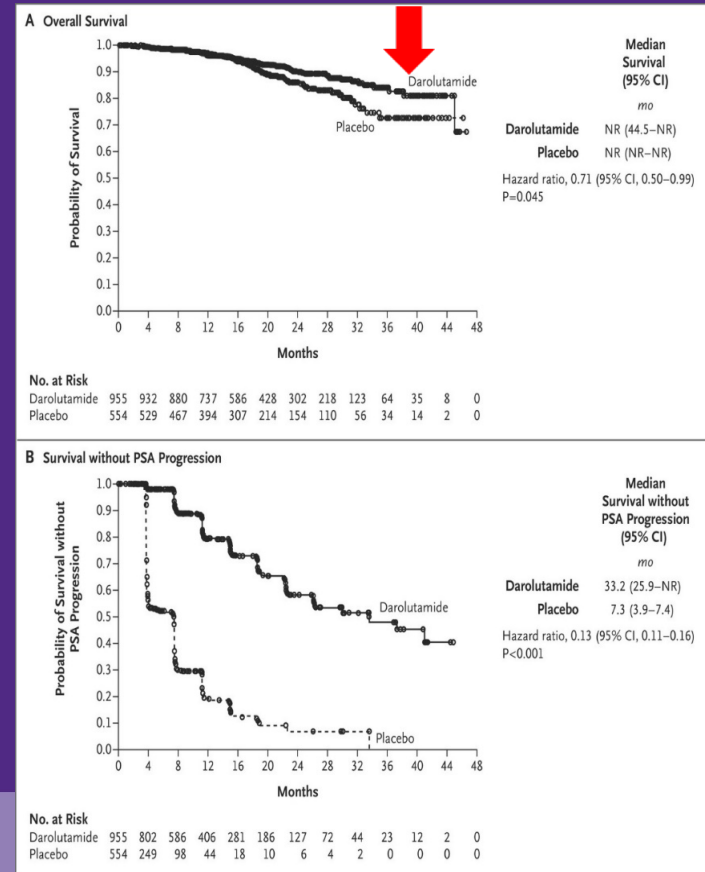
Prespecified Secondary & Exploratory Efficacy End Points

Table 2. Prespecified Secondary and Exploratory Efficacy End Points (Intention-To-Treat Population).*

End Point	Darolutamide (N=955)		Placebo (N=554)		Hazard Ratio (95% CI)	P Value
	Median Duration	No. of Events	Median Duration	No. of Events		
	mo		mo			
Secondary end points						
Overall survival	NR	78	NR	58	0.71 (0.50–0.99)	0.045
Time to pain progression	40.3	251	25.4	178	0.65 (0.53–0.79)	<0.001
Time to cytotoxic chemotherapy	NR	73	38.2	79	0.43 (0.31–0.60)	<0.001
Time to first symptomatic skeletal event	NR	16	NR	18	0.43 (0.22–0.84)	0.01
Time-to-event exploratory end points						
Progression-free survival	36.8	255	14.8	258	0.38 (0.32–0.45)	<0.001
Time to PSA progression	33.2	226	7.3	368	0.13 (0.11–0.16)	<0.001
Time to first prostate cancer–related invasive procedure	NR	34	NR	44	0.39 (0.25–0.61)	<0.001
Time to initiation of subsequent anti-neoplastic therapy	NR	48	NR	70	0.33 (0.23–0.47)	<0.001

* A total of 798 patients (84%) in the darolutamide group and 45 (8%) in the placebo group had a PSA response of 50% or greater. NR denotes not reached.

Kaplan–Meier Estimates of Overall Survival & Time to PSA Progression



K Fizazi et al. NEJM 2019.

Apalutamide vs Placebo

Table 3. Adverse Events.

Adverse Event ^a	Apalutamide (N=803)		Placebo (N=398)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	—	92 (23.1)	—
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	—	28 (7.0)	—
Adverse event associated with death	10 (1.2)	—	1 (0.3)	—
Adverse events that occurred in ≥15% of patients in either group [†]				
Fatigue‡	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash‡	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Falls‡	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other adverse events of interest				
Fracture‡	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism‡	65 (8.1)	0	8 (2.0)	0
Mental-impairment disorder‡	41 (5.1)	0	12 (3.0)	0
Seizure‡	2 (0.2)	0	0	0

* The incidences of the following adverse events in the apalutamide group versus the placebo group were adjusted for exposure (events per 100 patient-years): fatigue (incidence, 32.3 vs. 27.2), hypertension (36.3 vs. 38.7), rash (29.6 vs. 8.3), diarrhea (21.6 vs. 22.6), nausea (15.8 vs. 20.4), weight loss (18.3 vs. 10.5), arthralgia (14.7 vs. 8.0), falls (13.6 vs. 10.0), fracture (10.5 vs. 7.8), dizziness (7.7 vs. 6.6), hypothyroidism (7.6 vs. 2.2), mental-impairment disorder (3.9 vs. 3.4), and seizure (0.2 vs. 0).

† This category includes adverse events that occurred up to 28 days after the last dose of the trial regimen was administered.

‡ These adverse events were considered by the investigators to be related to the trial regimen.

§ Mental-impairment disorders included the following adverse events: disturbance in attention, memory impairment, cognitive disorder, and amnesia.

Enzalutamide vs Placebo

Table 3. Adverse Events.

Event	Enzalutamide Group (N=930)		Placebo Group (N=465)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	808 (87)	292 (31)	360 (77)	109 (23)
Any serious adverse event*	226 (24)	—	85 (18)	—
Adverse event leading to discontinuation of trial regimen	87 (9)	—	28 (6)	—
Adverse event leading to death	32 (3)	—	3 (1)	—
Most common adverse events, occurring in ≥5% of patients [†]				
Fatigue	303 (33)	27 (3)	64 (14)	3 (1)
Hot flush	121 (13)	1 (<1)	36 (8)	0
Nausea	106 (11)	3 (<1)	40 (9)	0
Diarrhea	91 (10)	3 (<1)	45 (10)	2 (<1)
Hypertension	111 (12)	43 (5)	24 (5)	10 (2)
Fall	106 (11)	12 (1)	19 (4)	3 (1)
Constipation	85 (9)	2 (<1)	32 (7)	2 (<1)
Dizziness	91 (10)	4 (<1)	20 (4)	0
Arthralgia	78 (8)	1 (<1)	32 (7)	1 (<1)
Asthenia	82 (9)	11 (1)	28 (6)	1 (<1)
Decreased appetite	89 (10)	2 (<1)	18 (4)	1 (<1)
Back pain	73 (8)	2 (<1)	33 (7)	1 (<1)
Headache	85 (9)	2 (<1)	21 (5)	0
Hematuria	62 (7)	16 (2)	36 (8)	13 (3)
Urinary tract infection	38 (4)	7 (1)	30 (6)	3 (1)
Weight loss	55 (6)	2 (<1)	7 (2)	0
Urinary retention	20 (2)	4 (<1)	28 (6)	5 (1)
Adverse events of special interest				
Hypertension‡	114 (12)	43 (5)	25 (5)	11 (2)
Major adverse cardiovascular events§	48 (5)	34 (4)	13 (3)	8 (2)
Mental impairment disorders¶	48 (5)	1 (<1)	9 (2)	0
Hepatic impairment	11 (1)	5 (1)	9 (2)	2 (<1)
Neutropenia	9 (1)	5 (1)	1 (<1)	1 (<1)
Convulsion	3 (<1)	2 (<1)	0	0
Posterior reversible encephalopathy syndrome	0	0	0	0

* Serious adverse events were events that resulted in death, were life-threatening, resulted in or prolonged hospitalization, resulted in inability to conduct normal life functions, or led to a congenital anomaly or birth defect. A full definition is provided in the protocol.

† Listed in descending order are the adverse events that were reported in at least 5% of the patients in either group.

‡ This adverse event includes increased blood pressure.

§ This adverse event includes acute myocardial infarction, hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions, and heart failure.

¶ This adverse event includes memory impairment, disturbance in attention, cognitive disorders, amnesia, Alzheimer's disease, senile dementia, mental impairment, and vascular dementia.

Darolutamide vs Placebo

Table 3. Adverse Events.

Adverse Event ^a	Darolutamide (N=954)		Placebo (N=554)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious adverse event	237 (24.8)	151 (15.8)	111 (20.0)	70 (12.6)
Grade 5 adverse event	37 (3.9)	—	18 (3.2)	—
Adverse event leading to discontinuation of the trial regimen	85 (8.9)	32 (3.4)	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	31 (5.6)	1 (0.2)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Constipation	60 (6.3)	0	34 (6.1)	0
Pain in an extremity	55 (5.8)	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	23 (4.2)	0
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	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)
Adverse events of interest				
Fatigue or asthenic conditions†	151 (15.8)	6 (0.6)	63 (11.4)	6 (1.1)
Bone fracture‡	40 (4.2)	9 (0.9)	20 (3.6)	5 (0.9)
Falls, including accident§	40 (4.2)	8 (0.8)	26 (4.7)	4 (0.7)
Seizure, any event	2 (0.2)	0	1 (0.2)	0
Rash¶	28 (2.9)	1 (0.1)	5 (0.9)	0
Weight decrease, any event	34 (3.6)	0	12 (2.2)	0
Dizziness, including vertigo	43 (4.5)	2 (0.2)	22 (4.0)	1 (0.2)
Cognitive disorder	4 (0.4)	0	1 (0.2)	0
Memory impairment	5 (0.5)	0	7 (1.3)	0
Change in mental status	0	0	1 (0.2)	0
Hypothyroidism	2 (0.2)	0	0	0
Cerebral ischemia	13 (1.4)	7 (0.7)	8 (1.4)	4 (0.7)
Coronary-artery disorder**	31 (3.2)	16 (1.7)	14 (2.5)	2 (0.4)
Heart failure††	18 (1.9)	5 (0.5)	5 (0.9)	0

* Exposure-adjusted incidences of adverse events in the darolutamide group and the placebo group were as follows: fatigue or asthenic conditions (11.3 patients per 100 years of exposure and 11.1 patients per 100 years of exposure, respectively), back pain (6.3 and 8.8), arthralgia (5.8 and 9.0), diarrhea (4.9 and 5.5), hypertension (4.7 and 5.1), constipation (4.5 and 6.0), pain in extremity (4.1 and 3.2), anemia (4.0 and 4.4), hot flush (3.7 and 4.1), nausea (3.6 and 5.6), weight loss (2.5 and 2.1), falls (2.7 and 4.1), bone fracture (3.0 and 3.5), memory impairment (0.4 and 1.2), cognitive disorder (0.3 and 0.2), and seizure (0.2 and 0.2).

† This category combines the following MedDRA terms: asthenic conditions, disturbances in consciousness, decreased strength and energy, malaise, lethargy, asthenia, and fatigue.

‡ This category combines the following MedDRA terms: any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.

§ All events that had been recorded under the MedDRA term "accident" were determined to have been accidental falls and are included in this category.

¶ This category combines the following MedDRA terms: dermatitis, erythema, rash, macular rash, maculopapular rash, papular rash, and pustular rash.

|| This category combines the following MedDRA terms: cerebral infarction, cerebral ischemia, cerebrovascular accident, ischemic stroke, and transient ischemic attack. Grade 5 events occurred in one patient receiving darolutamide and three patients receiving placebo.

** This MedDRA High Level Group Term includes coronary-artery disorders not elsewhere classified, coronary-artery arteriosclerosis, coronary artery disease, coronary-artery occlusion, and coronary-artery stenosis. Grade 5 events occurred in three patients receiving darolutamide and one patient receiving placebo.

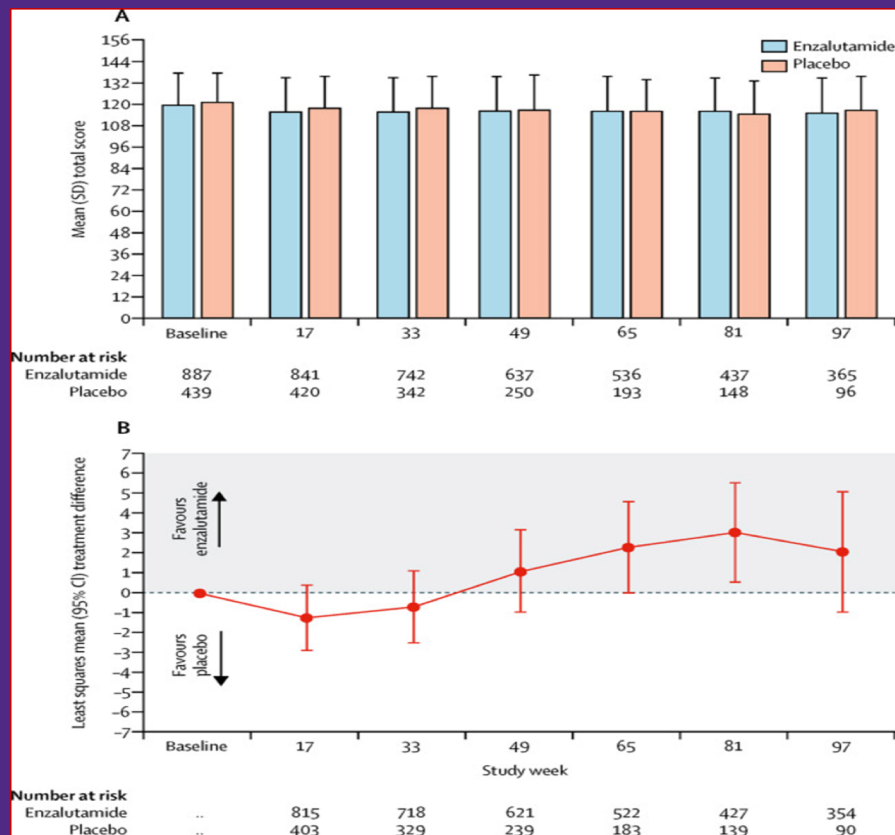
†† This MedDRA High Level Group Term includes heart failure not elsewhere classified, cardiac failure, acute cardiac failure, chronic cardiac failure, congestive cardiac failure, and cardiogenic shock. Grade 5 events occurred in four patients receiving darolutamide and three patients receiving placebo.

Smith et al. NEJM 2018

Hussain et al. NEJM 2018

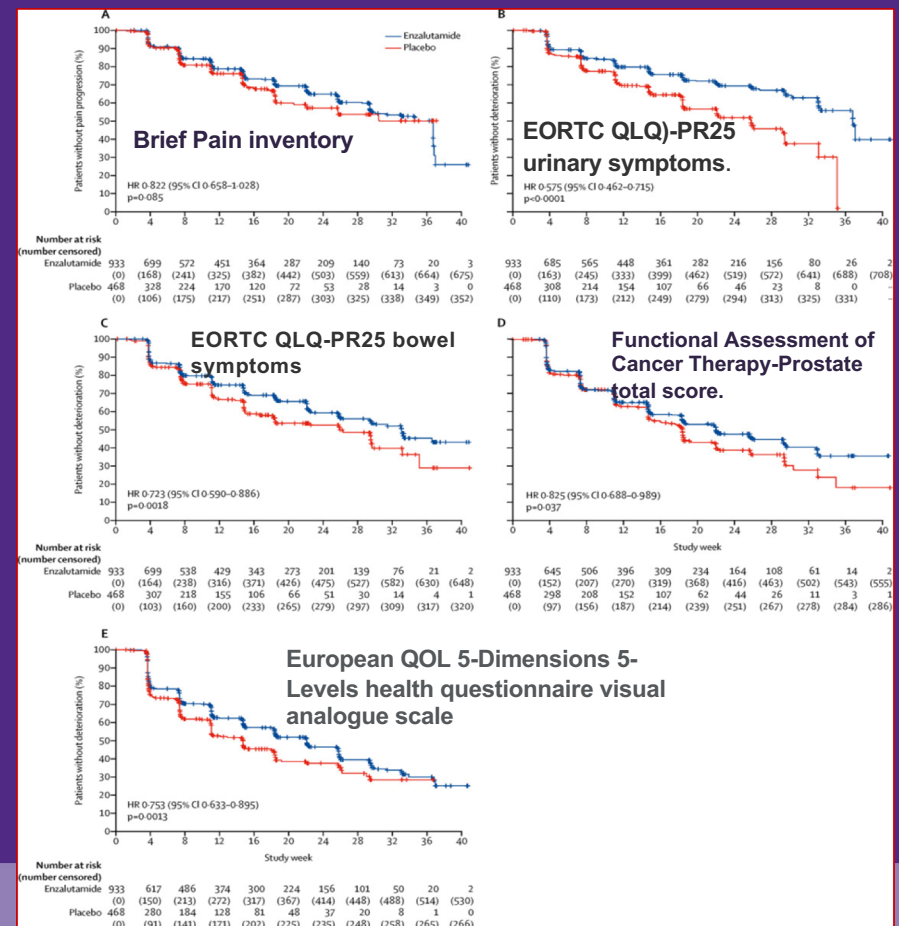
Fizazi et al. NEJM 2019.

Patient-reported Changes in FACT-P Total Score



Scores are for study visit (A) and treatment difference in least square mean change from baseline (B). FACT-P=Functional Assessment of Cancer Therapy-Prostate.

Time to Confirmed Pain Progression & HRQOL Deterioration



Tombal et al, Lancet Oncol 2019

Conclusion

- In men with nmCRPC & rapid PSA doubling time:
 - Enzalutamide, Apalutamide & Darolutamide resulted in a clinically meaningful & statistically significant reduction in the relative risk of developing M1 CRPC
 - Therapy was overall well tolerated
 - **The FDA approval for all 3 agents is not restricted by PSA doubling time**
 - Therapy decision should take into account disease risks, comorbidities, life expectancy and potential for toxicities (Shared Decision):

Balancing risks & benefits

- **Future directions:**
 - Role of better imaging
 - Novel multi-targeted combination therapy

Thank You

