2023 ASCO/ESMO Updates in Prostate Cancer: Combination Therapy becoming the best approach?

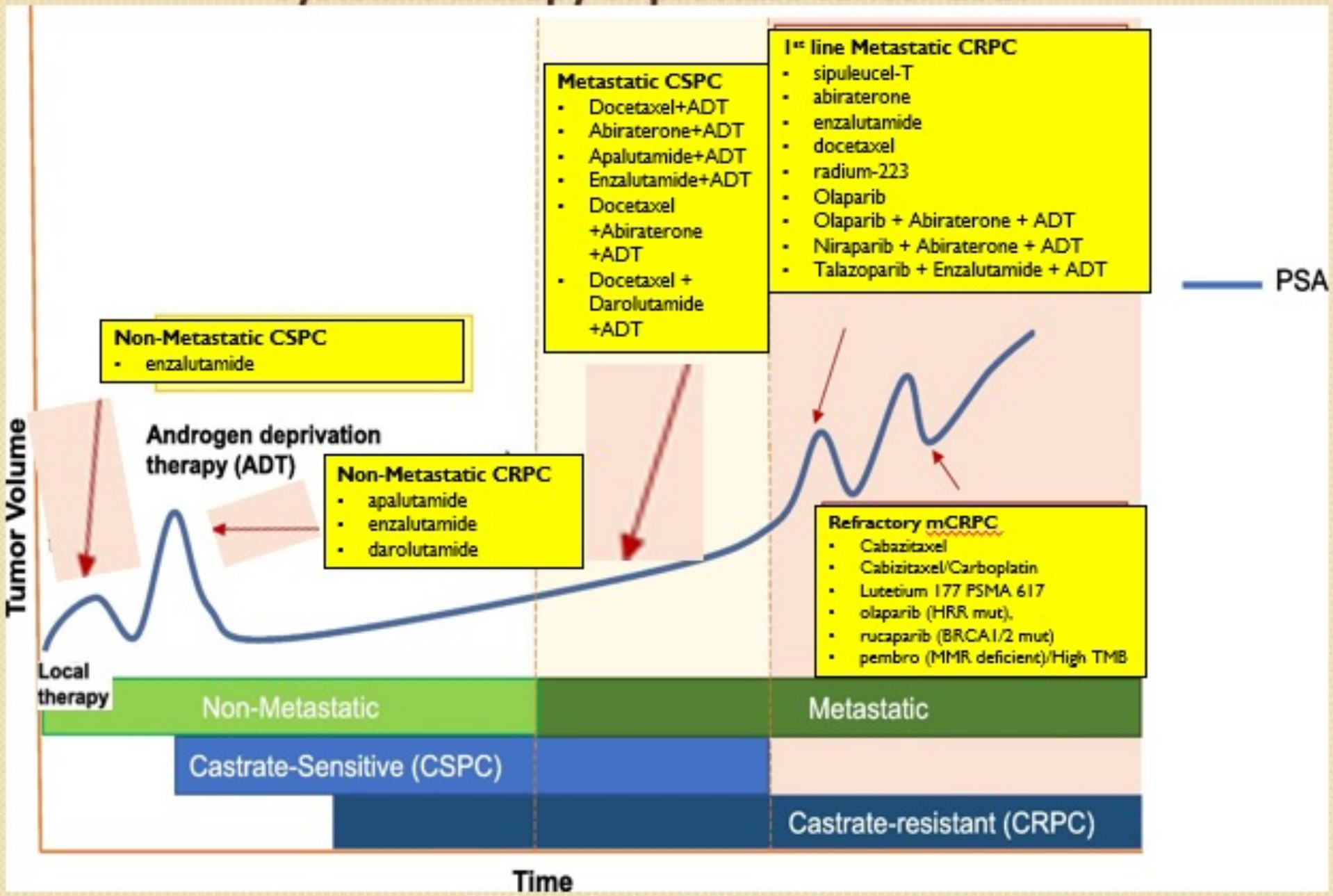
Chandler Park , MD FACP
Co-Director GU Clinical Trials
Norton Cancer Institute
Advisory Dean, Clinical Professor
University of Louisville School of Medicine
Faculty, ASCO University

NORTON CANCER INSTITUTE

doximity ChandlerParkMD
Twitter: @CParkMD
LinkedIn ChandlerParkMD

Program Directors
Luis E. Raez, MD, FACP, FCCP
Edgardo S. Santos, MD, FACP

Systemic therapy of prostate cancer 2023

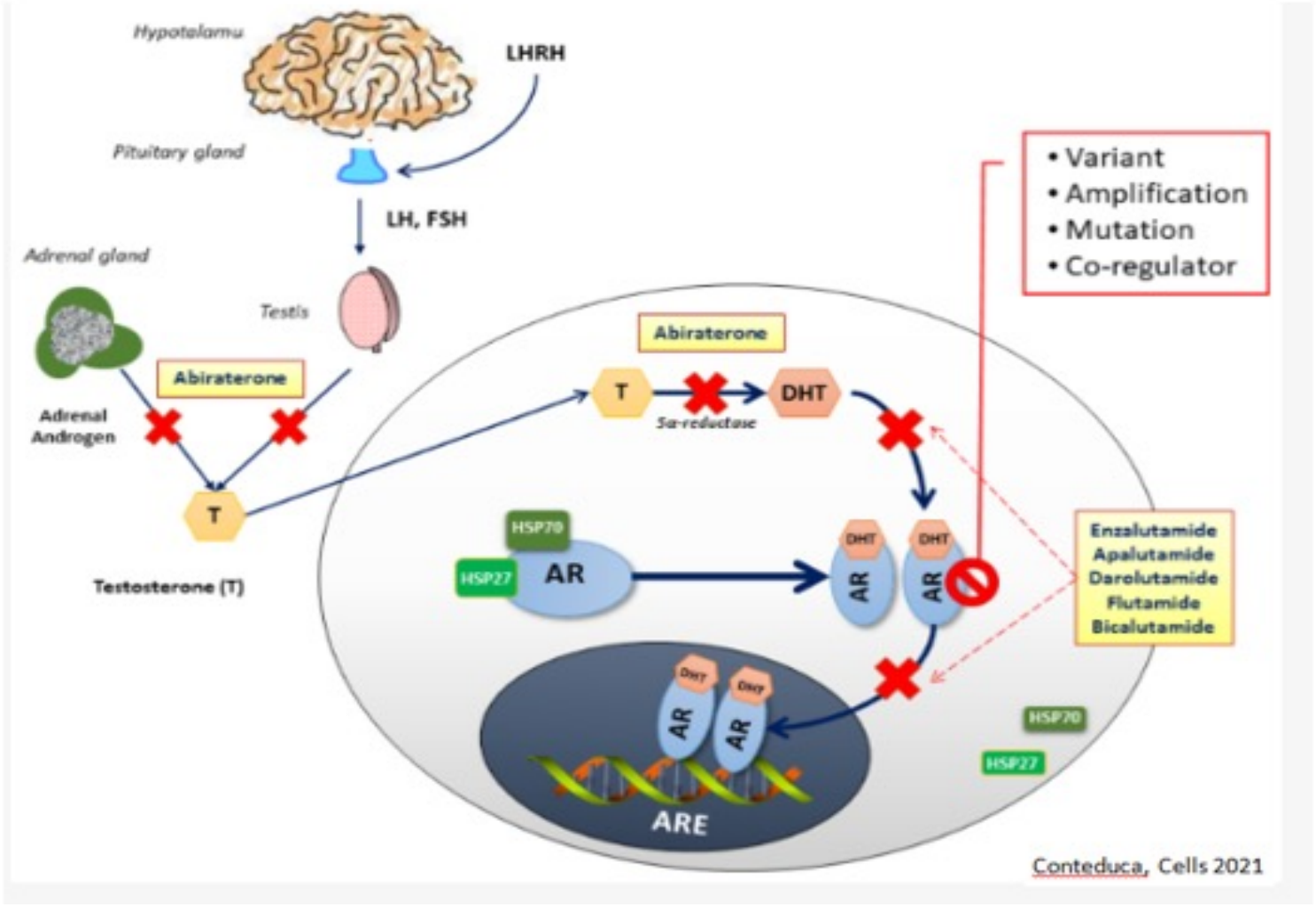


Alkhudair NA. *Saudi Pharm J.* 2019 Mar;27(3):368-372.

Today's Agenda

- Metastatic Castrate(Hormone) Sensitive Prostate Cancer (mCSP)
  - (Triplet vs Doublet)
- Metastatic Castrate Resistant Prostate Cancer (Monotherapy PARP vs PARP with Androgen Receptor Pathway Inhibitor)

Pathophysiology



mCSPC: Updated NCCN

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Prostate Cancer

NCCN Guidelines Index
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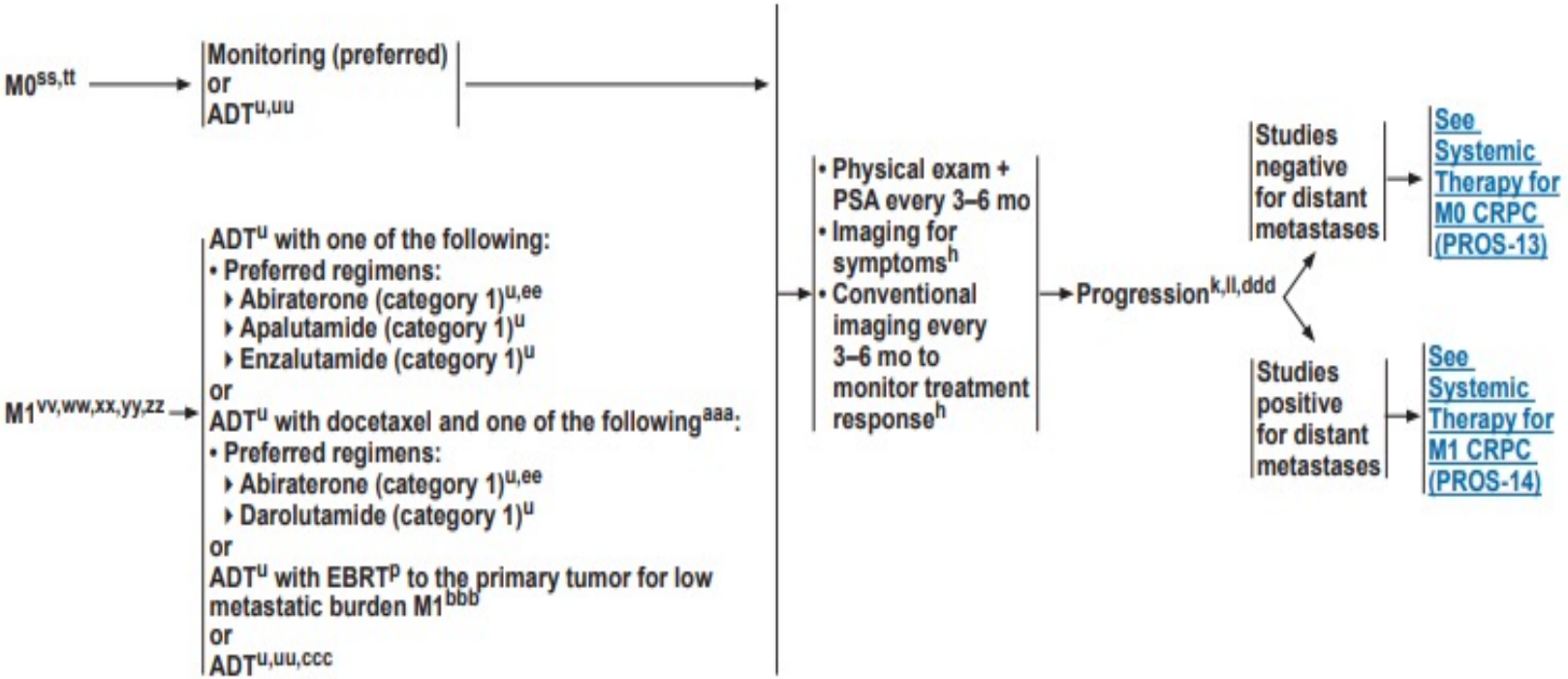
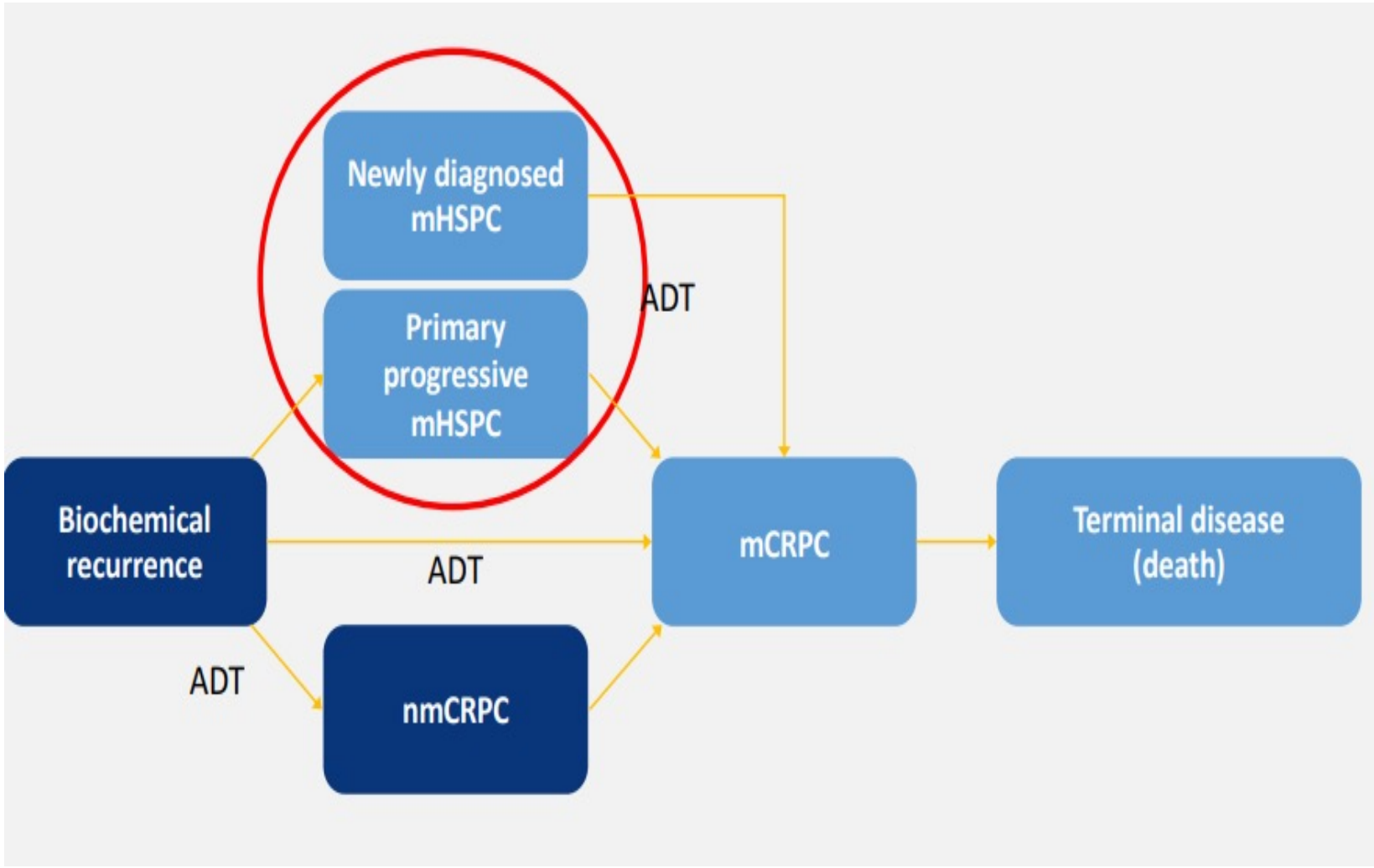
Discussion

SYSTEMIC THERAPY FOR CASTRATION-SENSITIVE PROSTATE CANCER[rr]

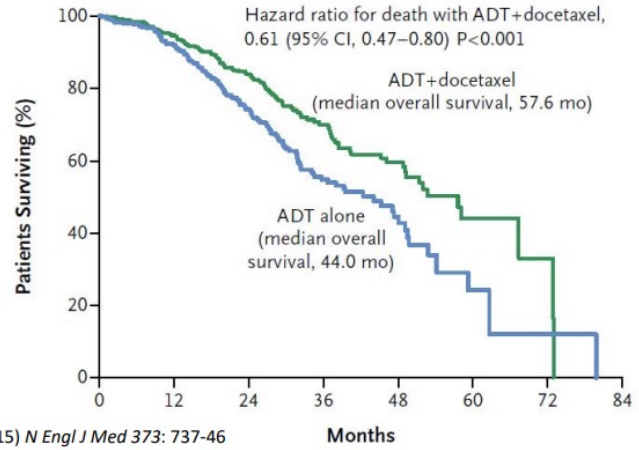


Version 4.2023 — September 7, 2023

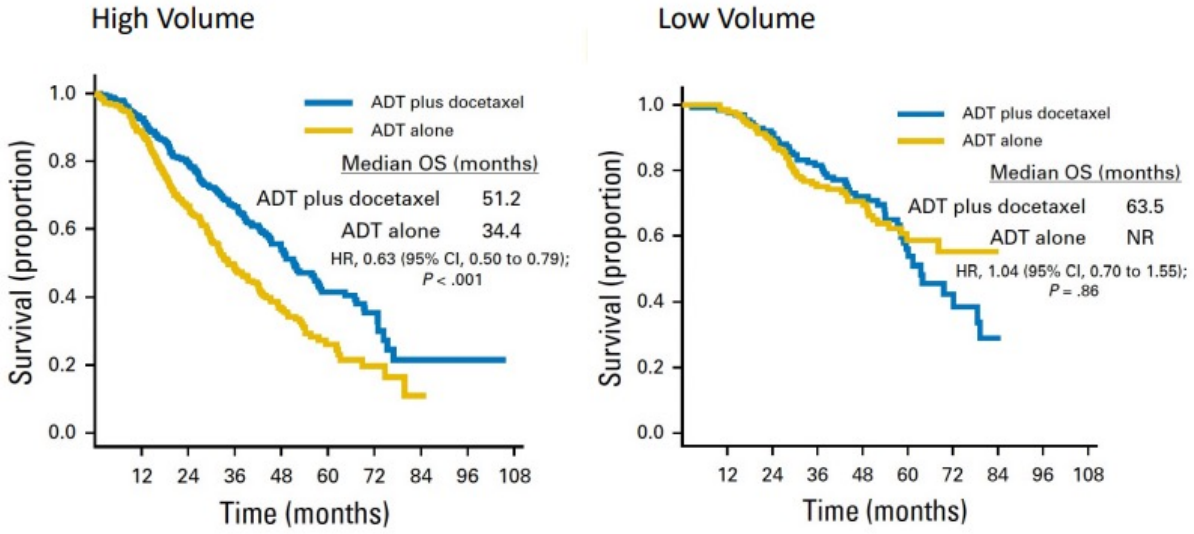
Metastatic Hormone Sensitive



Historical Data: CHAARTED Study



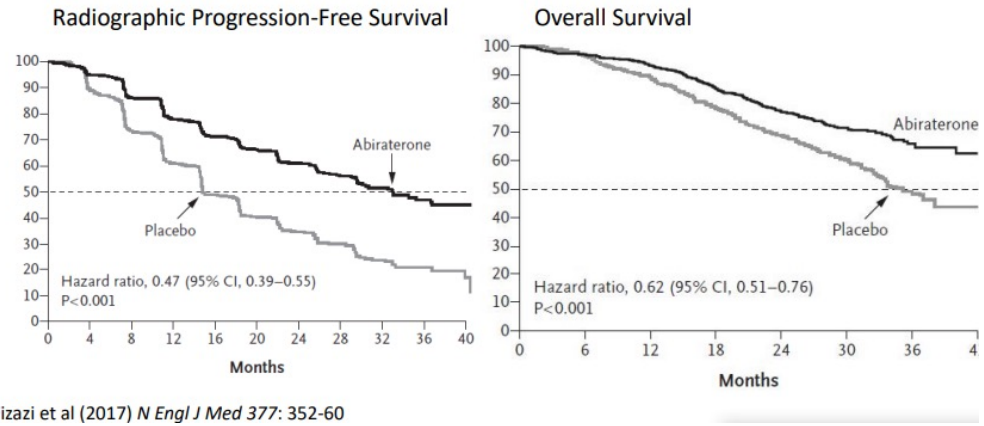
Sweeney et al (2015) *N Engl J Med 373*: 737-46



Kyriakopoulos et al (2018) *J Clin Oncol 36*: 1080-0187

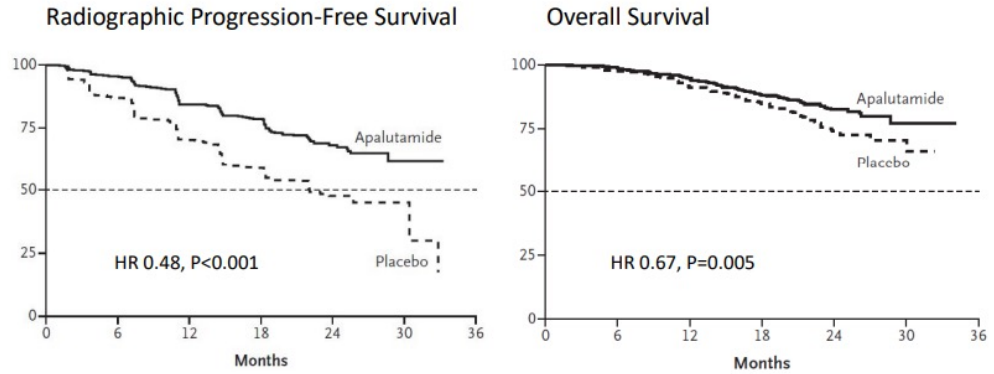
Androgen Pathway Inhibitors

LATITUDE: Abiraterone Acetate for mHSPC



Fizazi et al (2017) *N Engl J Med 377*: 352-60

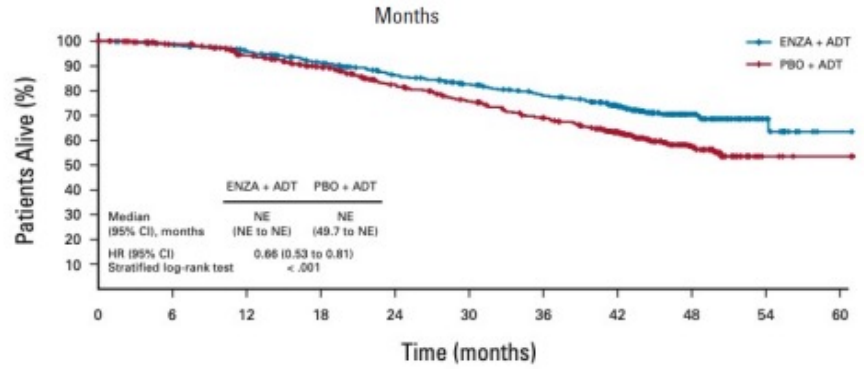
TITAN: Apalutamide for mHSPC



Chi et al (2019) *N Engl J Med 381*: 13-24

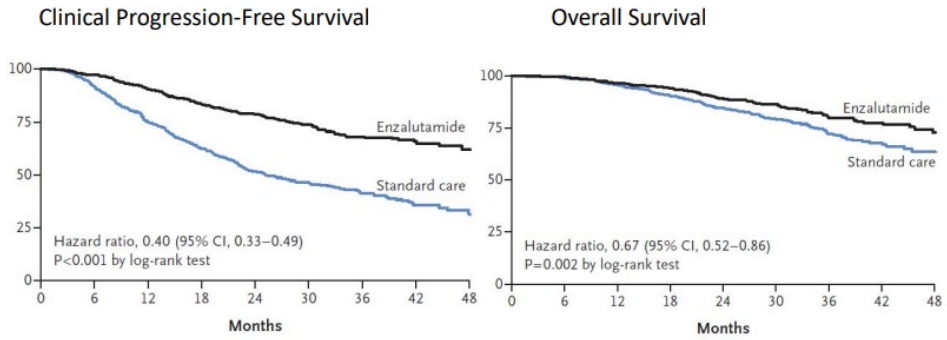
ARCHES and ENZAMET

OS



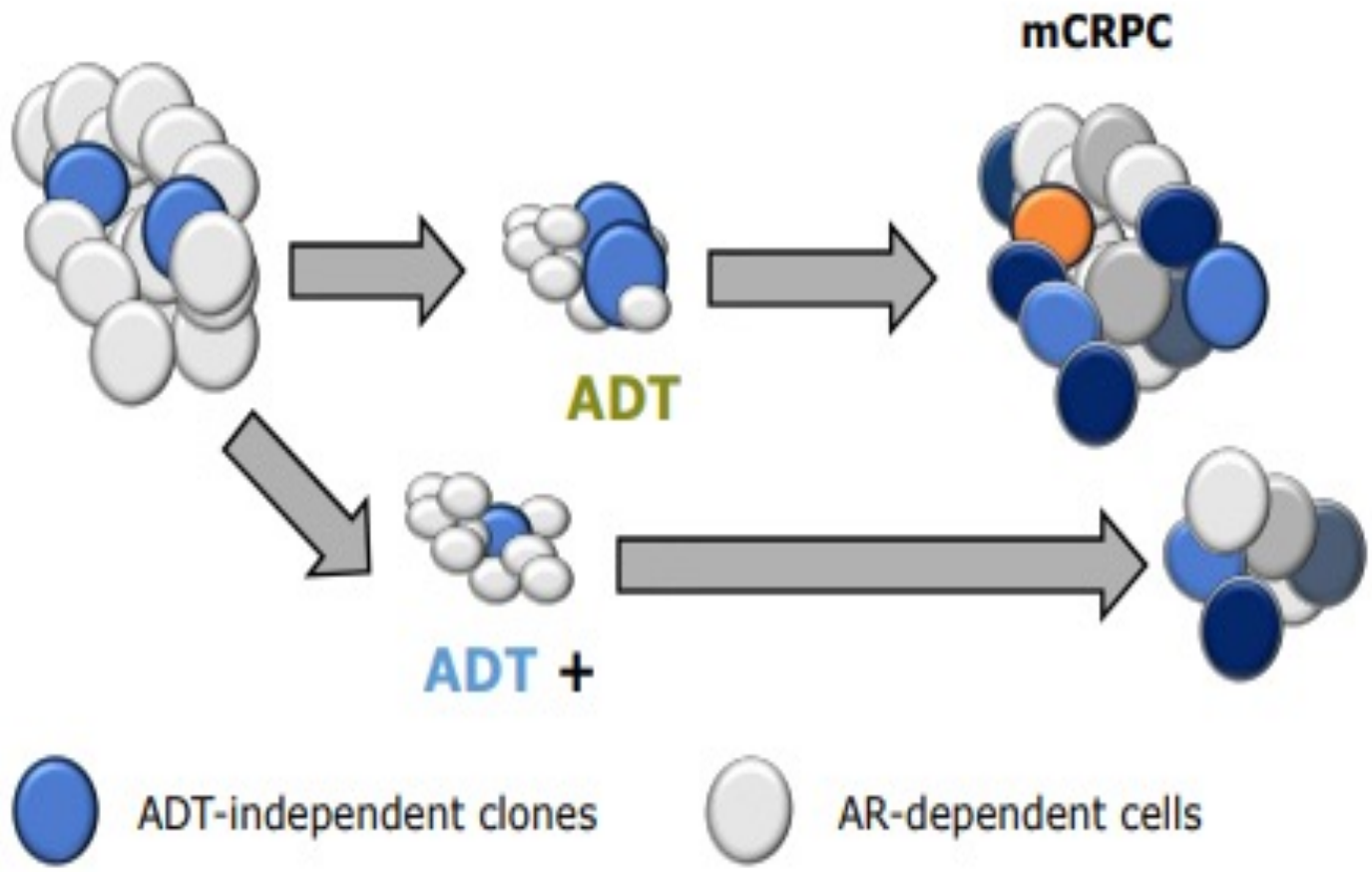
Armstrong et al (2019) *J Clin Oncol 37:* 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JCO.22.00193

ENZAMET: Enzalutamide for mHSPC



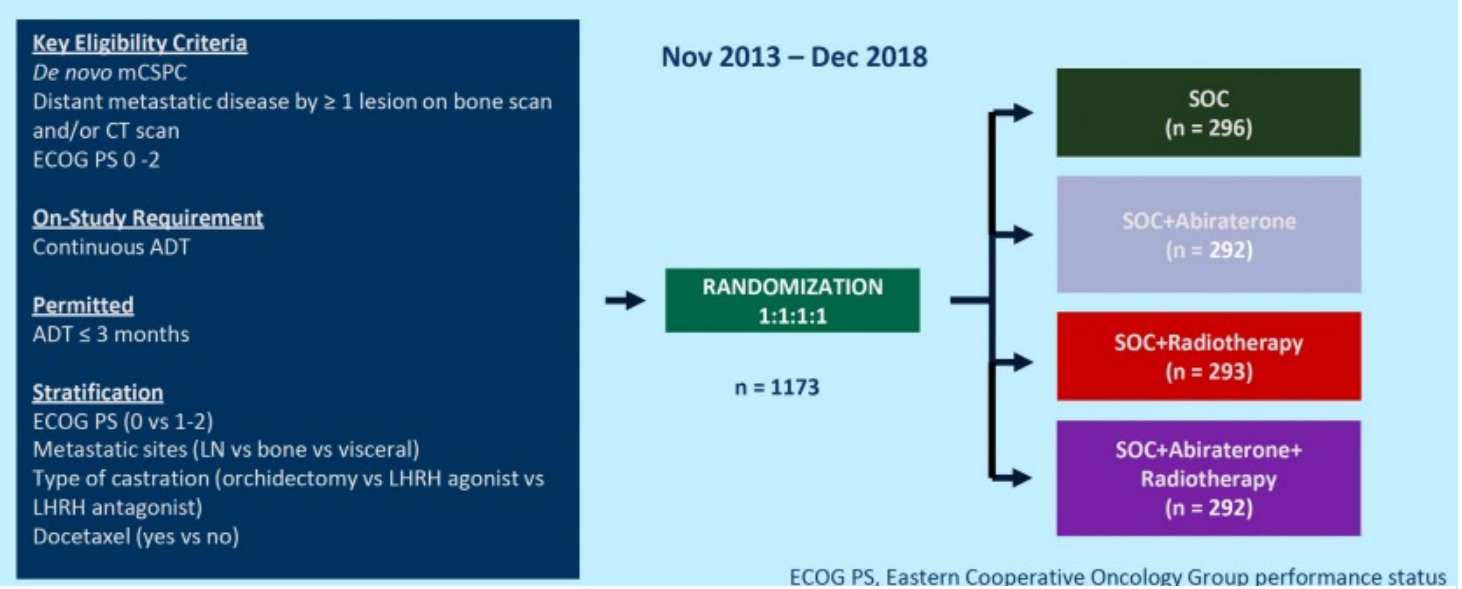
Davis et al (2019) *N Engl J Med 381*: 121-131

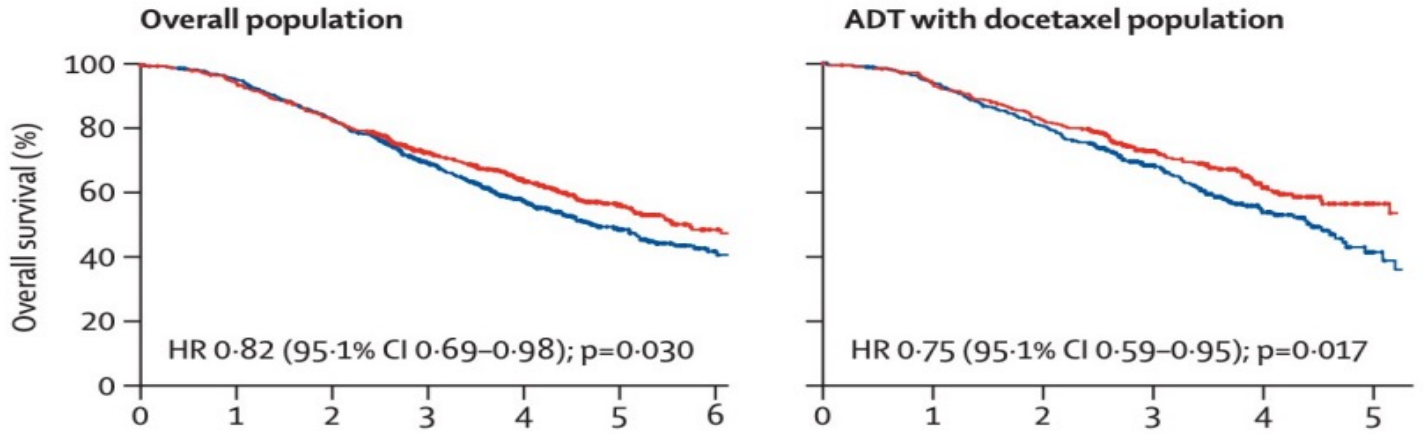
Doublet vs Triplet?
Prostate Adenocarcinoma is Heterogenous



Conteduca, Cells 2021

PEACE -1



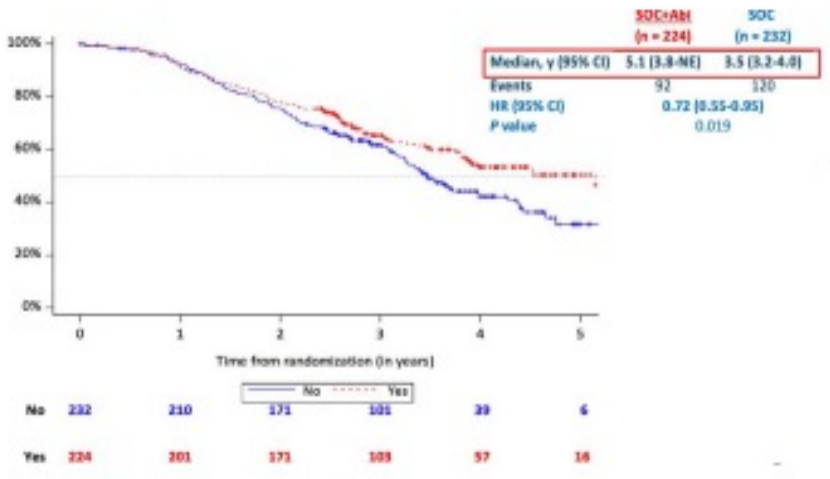


Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

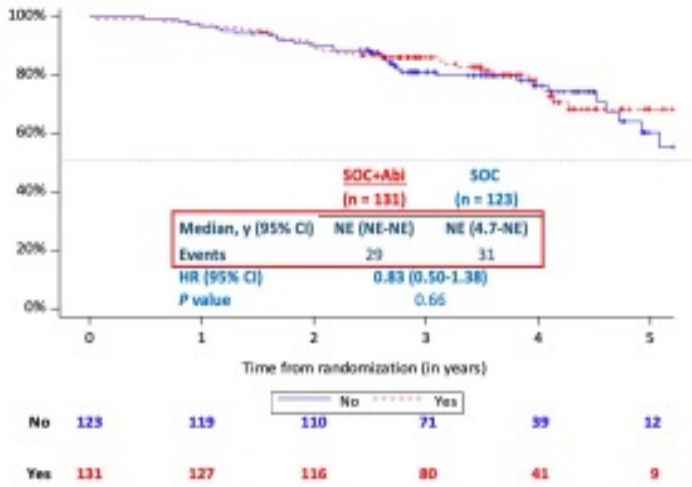
PEACE-1

ADT/docetaxel +/- abiraterone population

High-volume patients



Low-volume patients



Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

March 24, 2022
N Engl J Med 2022; 386:1132-1142
DOI: 10.1056/NEJMoa2119115

ARASENS: Darolutamide vs Placebo in Combination With ADT + Docetaxel in mCSPC

- International, randomized, double-blind phase III trial in 286 sites across 23 countries

Stratified by metastasis stage (M1a vs M1b vs M1c), alkaline phosphatase level (< vs ≥ ULN)

Patients with newly diagnosed metastatic CSPC; ECOG PS 0/1 (N = 1306)

- **Darolutamide** 600 mg PO BID + **ADT** + **Docetaxel** 75 mg/m² on D1 x six 28-day cycles (n = 651)
- **Placebo** PO BID + **ADT** + **Docetaxel** 75 mg/m² on D1 x six 28-day cycles (n = 655)

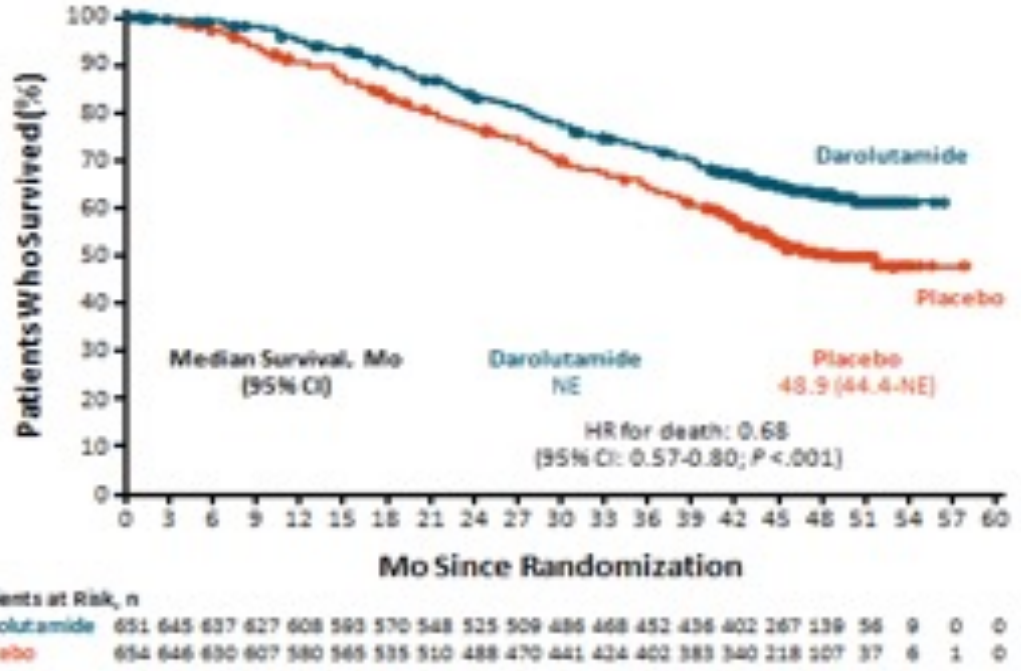
Until symptomatic PD, change in neoplastic tx, unacceptable toxicity, patient–physician decision, or nonadherence

ARASENS

- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, tir SSE-free survival, time to first SSE, time to initiation of subsequent antica

OS (Primary Endpoint)

- Addition of darolutamide to ADT + docetaxel significantly reduced risk of death by 32.5% vs placebo (*P* <.001)
  - 75.6% of patients in placebo arm received subsequent life-prolonging systemic tx
- OS benefit observed across most subgroups
  - HR (95%) for those stratified by metastatic stage at initial dx: M1, 0.707 (0.590-0.848); M0, 0.605 (0.348-1.052)



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Adverse Events

Selected Grade 3/4 AE, n (%)	Darolutamide + ADT + Docetaxel (n = 652)	Placebo + ADT + Docetaxel (n = 650)
Neutropenia	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT	18 (2.8)	11 (1.7)
Increased AST	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
UTI	13 (2.0)	12 (1.8)

Safety Outcome, n (%)	Darolutamide + ADT + Docetaxel (n = 652)	Placebo + ADT + Docetaxel (n = 650)
Any AE	649 (99.5)	643 (98.9)
Serious AE	292 (44.8)	275 (42.3)
AE leading to permanent d/c of trial agent		
▪ Darolutamide or placebo	88 (13.5)	69 (10.6)
▪ Docetaxel	52 (8.0)	67 (10.3)

Smith. NEJM. March 2023

ASCO Genitourinary Cancers Symposium

Definition of Disease Volume and Risk Subgroups

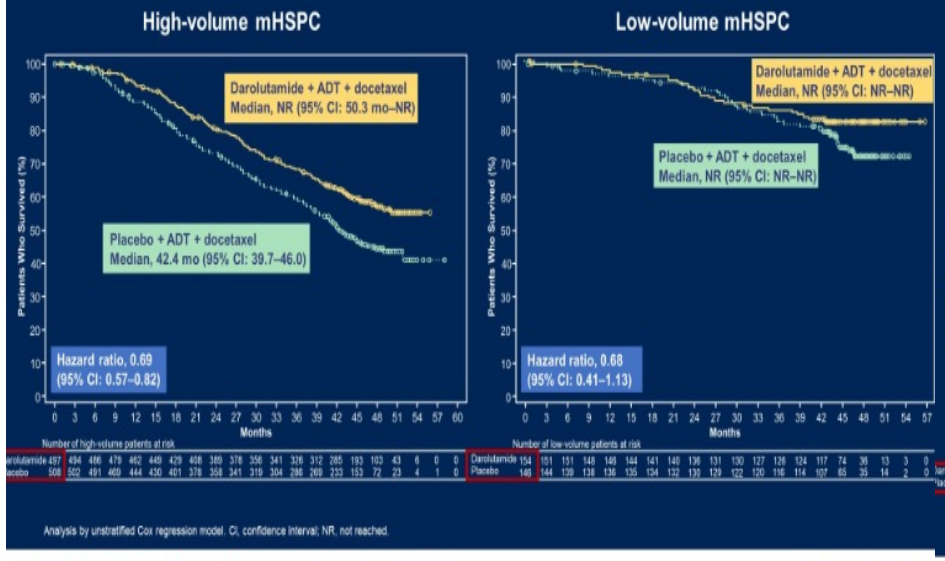
High-Volume Disease: CHAARTED Criteria[1]	High-Risk Disease: LATITUDE Criteria[2]
• Visceral metastases • ≥4 bone metastases with ≥1 beyond the vertebral column/pelvis[a]	• ≥2 risk factors: ▪ Gleason score ≥8 ▪ ≥3 bone metastases[a] ▪ Visceral metastases

Low-volume and low-risk disease were defined as not meeting the respective high-volume and high-risk criteria
[a]Including those with diffusely increased skeletal metastases with superscan[3]

- Of 1305 patients in the ARASENS full analysis set
  - **1005 (77%) had high-volume disease and 300 (23%) had low-volume disease**
  - **912 (70%) had high-risk disease and 393 (30%) had low-risk disease**

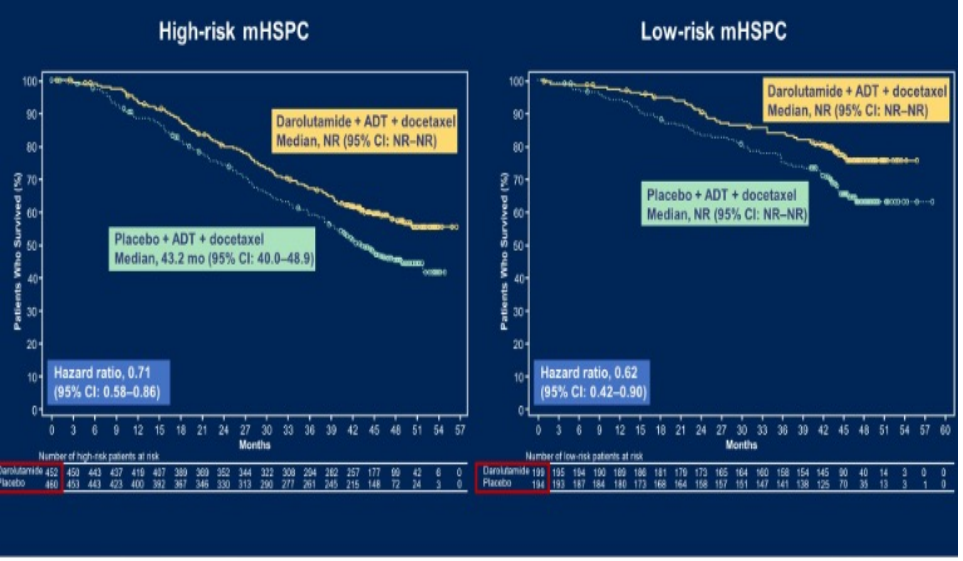
1. Sweeney CJ, et al. *N Engl J Med*. 2015; 373:737-746; 2. Fizazi K, et al. *N Engl J Med*. 2017;377:352-360; 3. Manohar PR, et al. *World J Nucl Med*. 2017;16:39-44.

ARASENS VOLUME Subgroups: Overall Survival



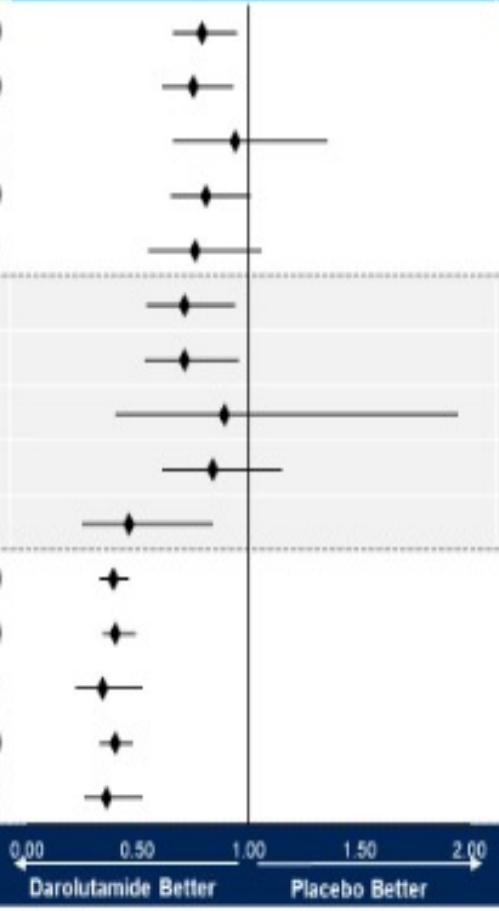
Analysis by unstratified Cox regression model. CI, confidence interval; NR, not reached.

ARASENS RISK Subgroups: Overall Survival



ARASENS VOLUME and RISK Subgroups: Other Key Secondary Efficacy Endpoints

Secondary endpoint	Patient subgroups	Number of events/ Number of patients		Median (95% CI), months		HR (95% CI)[a]
		DARO	PBO	DARO	PBO	
Time to pain progression	All patients[b]	222/651	248/654	NE (30.5–NE)	27.5 (22.0–36.1)	0.79 (0.66–0.95)
	High volume	161/497	192/508	NE (26.7–NE)	24.4 (16.8–33.3)	0.75 (0.61–0.93)
	Low volume	61/154	56/146	46.1 (25.0–NE)	39.5 (24.6–NE)	0.94 (0.66–1.36)
	High risk	155/452	173/460	35.4 (25.0–NE)	25.0 (18.2–36.9)	0.81 (0.65–1.01)
	Low risk	67/199	75/194	NE (39.2–NE)	28.8 (19.3–NE)	0.76 (0.55–1.06)
Time to first symptomatic skeletal event	All patients[b]	95/651	108/654	NE (NE–NE)	NE (NE–NE)	0.71 (0.54–0.94)
	High volume	82/497	96/508	NE (NE–NE)	NE (NE–NE)	0.71 (0.53–0.96)
	Low volume	13/154	12/146	NE (NE–NE)	NE (NE–NE)	0.89 (0.40–1.95)
	High risk	78/452	79/460	NE (NE–NE)	NE (NE–NE)	0.84 (0.61–1.15)
	Low risk	17/199	29/194	NE (51.2–NE)	NE (NE–NE)	0.46 (0.25–0.84)
Time to initiation of subsequent systemic antineoplastic therapy	All patients[b]	219/651	395/654	NE (NE–NE)	25.3 (23.1–28.8)	0.39 (0.33–0.46)
	High volume	187/497	324/508	NE (49.6–NE)	22.7 (19.6–25.1)	0.40 (0.34–0.49)
	Low volume	32/154	71/146	NE (NE–NE)	42.5 (34.0–NE)	0.34 (0.22–0.52)
	High risk	173/452	299/460	NE (49.6–NE)	21.3 (19.2–24.0)	0.40 (0.33–0.48)
	Low risk	46/199	96/194	NE (NE–NE)	39.0 (31.8–NE)	0.36 (0.26–0.52)

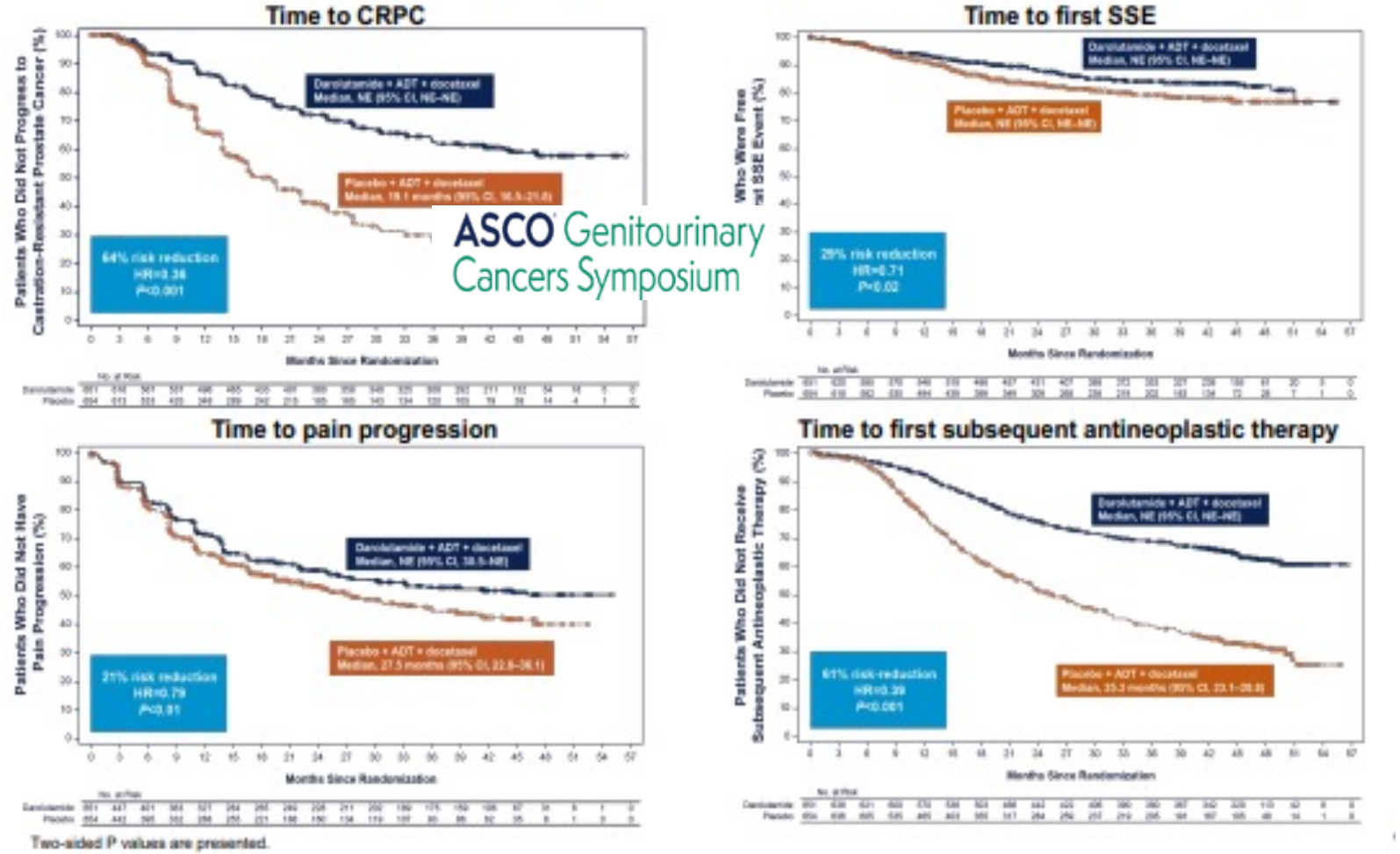


[a]Based on unstratified Cox regression model.
[b]Includes all randomized patients according to planned treatment.

ASCO Genitourinary Cancers Symposium

February 16-18, 2023
Moscone West Building
San Francisco, CA

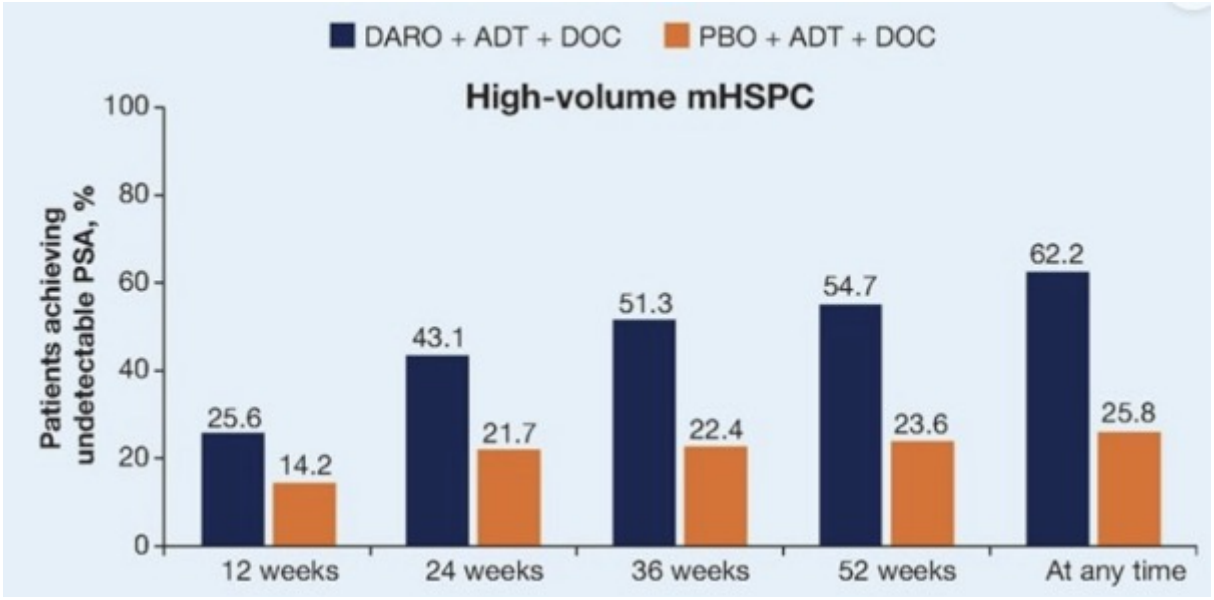
Darolutamide significantly improved key secondary efficacy endpoints

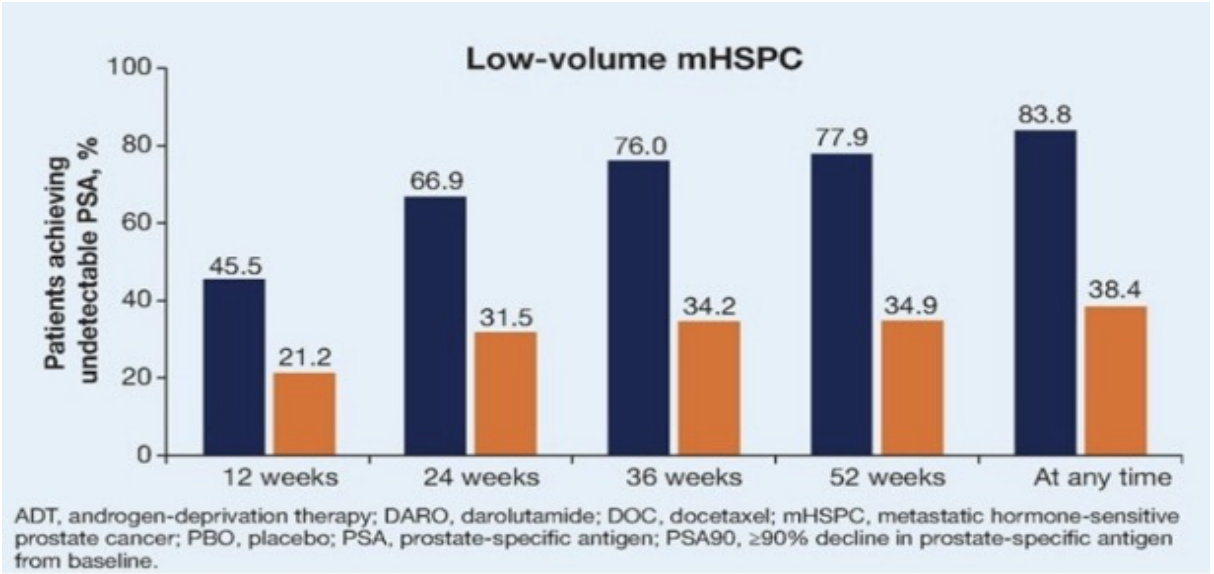


ASCO Genitourinary Cancers Symposium

Two-sided P values are presented.

Objective: Undetectable (≤0.2) PSA Levels





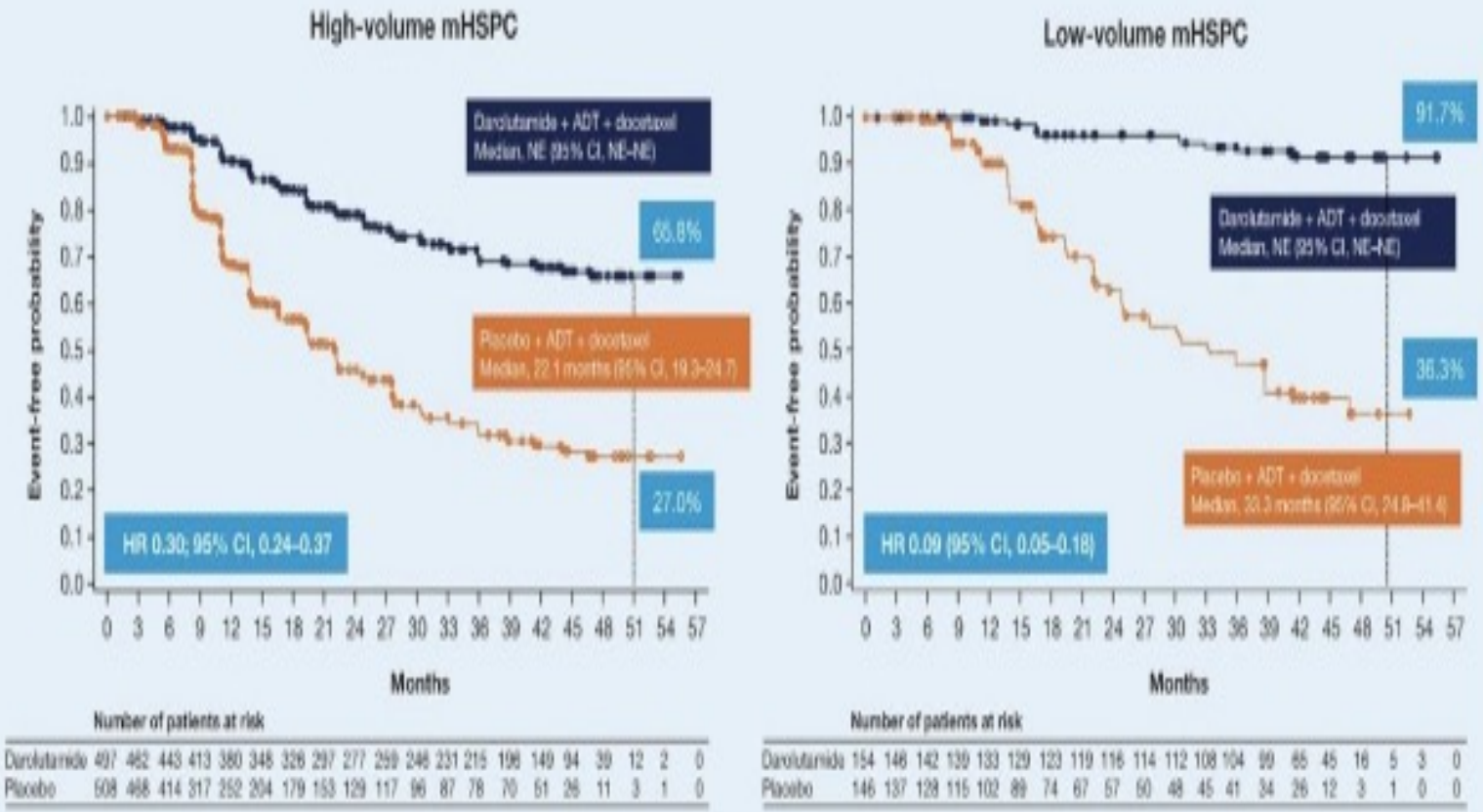
ADT, androgen-deprivation therapy; DARO, darolutamide; DOC, docetaxel; mHSPC, metastatic hormone-sensitive prostate cancer; PBO, placebo; PSA, prostate-specific antigen; PSA90, ≥90% decline in prostate-specific antigen from baseline.

ARASENS Update

Time to PSA progression was prolonged in patients receiving darolutamide versus placebo

- high volume (HR: 0.30; 95% CI: 0.24–0.37)
- low volume subgroups (HR: 0.09; 95% CI 0.05–0.18).

Figure 3. Time to PSA progression by disease volume subgroups



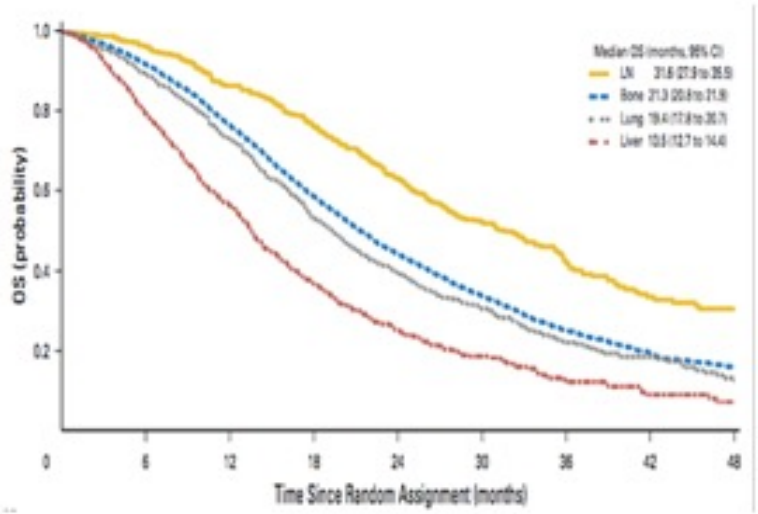
ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NE, not estimable; PSA, prostate-specific antigen.

What do I consider in my Practice?

High Volume vs Low Volume

Synchronous vs Metachronous

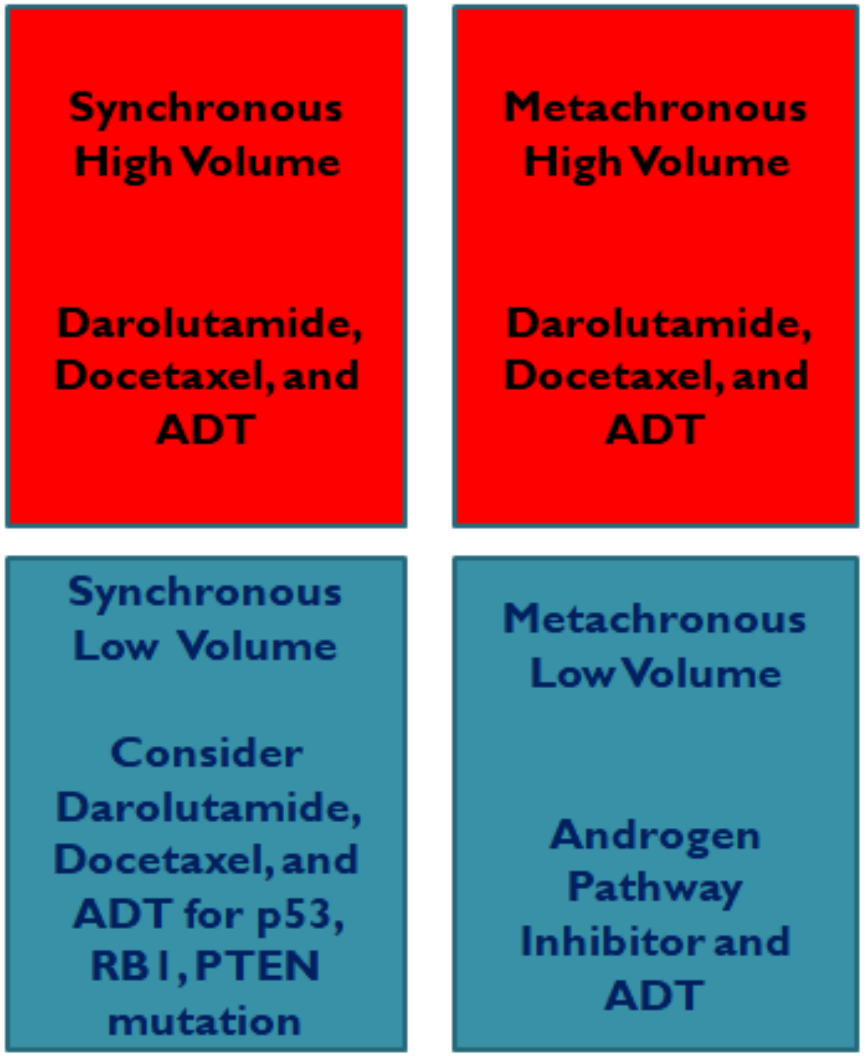
Staging in prognostication



ADT Alone (using CHAARTED and GETUG)	Median OS
Relapsed Low Volume	~8 y
Relapsed High Volume	4.5
De Novo Low Volume	4.5
De Novo High Volume	3

Halabi, JCO, 2016; Gravis Eur Urol 2018; Kyriakopoulos JCO 2018

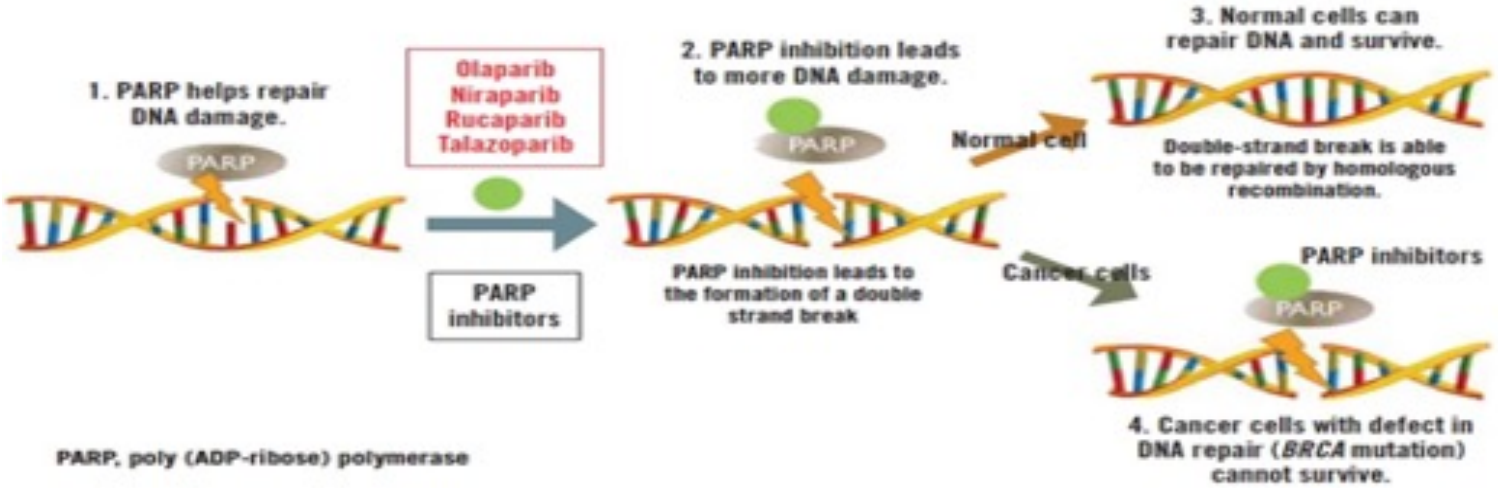
My Practice


Synchronous High Volume
Darolutamide, Docetaxel, and ADT
Metachronous High Volume
Darolutamide, Docetaxel, and ADT
Synchronous Low Volume
Consider Darolutamide, Docetaxel, and ADT for p53, RB1, PTEN mutation
Metachronous Low Volume
Androgen Pathway Inhibitor and ADT

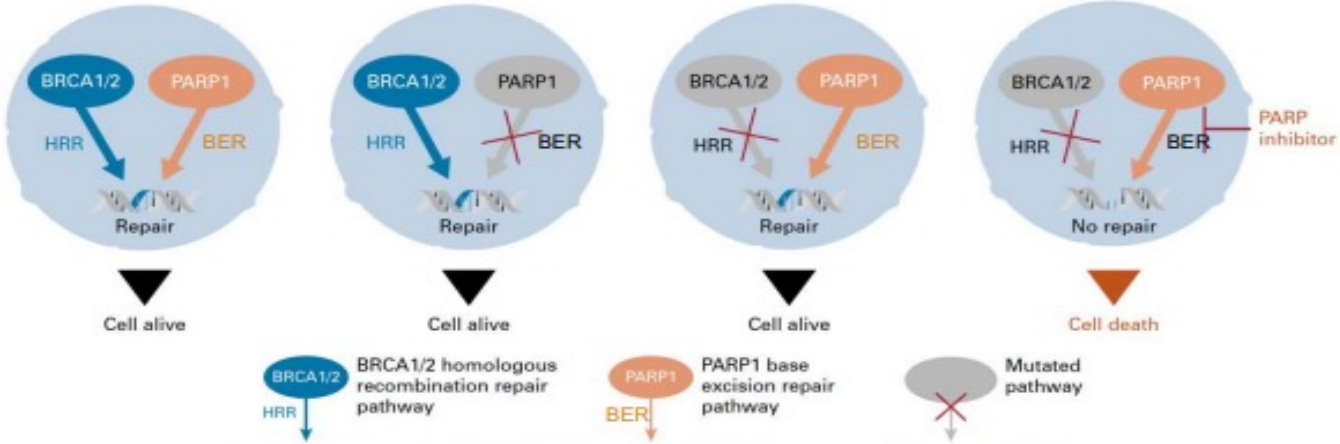
Metastatic Castrate Resistant Prostate Cancer (Monotherapy PARP vs PARP with Androgen Receptor Pathway Inhibitor)

PARP Inhibitor

Mechanism of Action



PARP, poly (ADP-ribose) polymerase



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

Jacob et al. UCC December 2020, Volume 09, Issue 04

Monotherapy PARP summary

Properties of PARP Inhibitors

	Olaparib	Talazoparib	Niraparib	Rucaparib
Mol. Weight	434.5	380.8	320.4	323.4
PARP1 IC_{50}	5 nM	0.56 nM	3.8 nM	0.65 nM
PARP2 IC_{50}	1 nM	0.15 nM	2.1 nM	0.08 nM
Trapping	++	++++	+++	++

Carney B, et al. *Nat Commun* 2018; 9: 176.

Summary of PARPi *Monotherapy* Trials in mCRPC

Study and treatment	Prior therapy	HRR status criteria; Sample type	Primary endpoint	Results
TOPARP-A[1] **Olaparib** 400 mg BID (N=50)	1–2 taxane CT regimens; 98% had prior NHT	Deficiency not required; tumor	Composite response rate	**33%** overall; 88% (14 of 16) with DDR gene alterations
TOPARP-B[2] **Olaparib** 300 mg or 400 mg BID, randomized 1:1 (N=98)	1–2 taxane CT regimens; 88%–92% had prior NHT	Deleterious germline or somatic DDR gene alterations; tumor	Composite response rate	**39.1%** 300-mg cohort; **54.3%** 400-mg cohort
TRITON2[3] **Rucaparib** 600 mg BID (N=115)	1 taxane and 1–2 NHT	Deleterious germline or somatic *BRCA1/2* alteration; tumor or plasma	ORR by blinded independent radiology review	**43.5%** (27 of 62)
GALAHAD[4] **Niraparib** 300 mg QD (N=289)	≥1 taxane and ≥1 NHT	Deleterious germline or somatic alteration in ≥1 of 8 prespecified DDR genes; tumor or plasma	ORR in patients with *BRCA* mutation and measurable disease	**34.2%** (26 of 76 measurable *BRCA* cohort) 10.6% (5 of 47 measurable non-*BRCA* cohort)
TALAPRO-1[5] **Talazoparib** 1 mg QD (N=128)	1–2 CT regimens (≥1 taxane) and ≥1 NHT	Deleterious germline or somatic alterations in ≥1 of 11 prespecified DDR-HRR genes; tumor or plasma	ORR by blinded independent review	**29.8%** (31 of 104)

1. Mateo J et al. *N Engl J Med.* 2015;373:1697-708; **2.** Mateo J et al. *Lancet Oncol.* 2020;21:162-174; **3.** Abida W et al. *J Clin Oncol.* 2020;38:3763-3772; **4.** Smith MR et al. *Lancet Oncol.* 2022;23:362-373; **5.** de Bono JS et al. *Lancet Oncol.* 2021;22:1250-1264.

Olaparib: PROfound, Randomized Phase 3 Study

Key Eligibility Criteria
- mCRPC with disease progression on prior NHA (eg, abiraterone or enzalutamide)
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

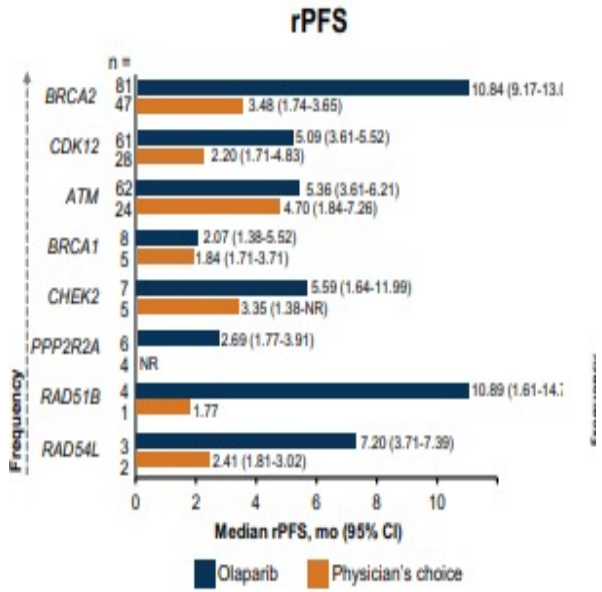
Stratification Factors
- Previous taxane
- Measurable disease

2:1 R Open-label

Cohort A *BRCA1*, *BRCA2*, or *ATM* n = 245
- **Olaparib** 300 mg BID n = 162
- **Physician's choice** n = 83

Cohort B Other alterations n = 142
- **Olaparib** 300 mg BID n = 94
- **Physician's choice** n = 48

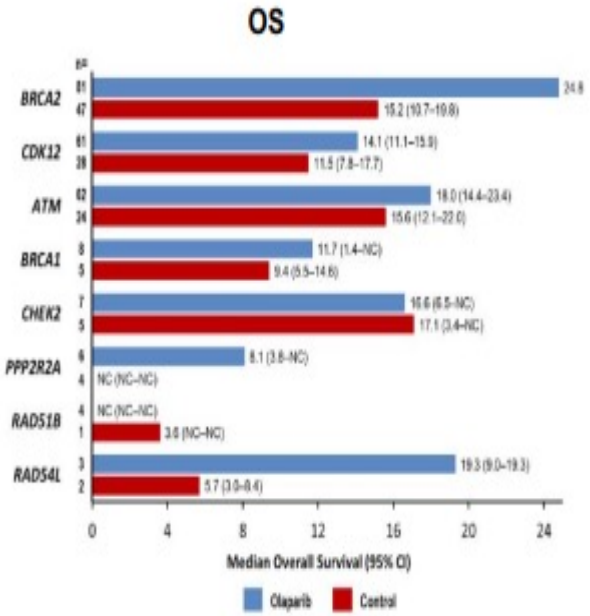
Upon BICR progression, physician's choice patients were allowed to cross over to olaparib

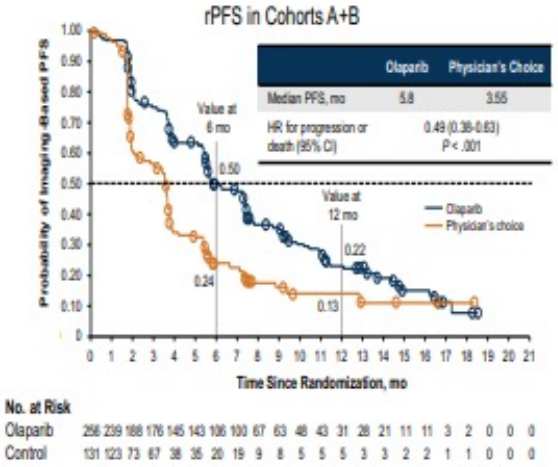


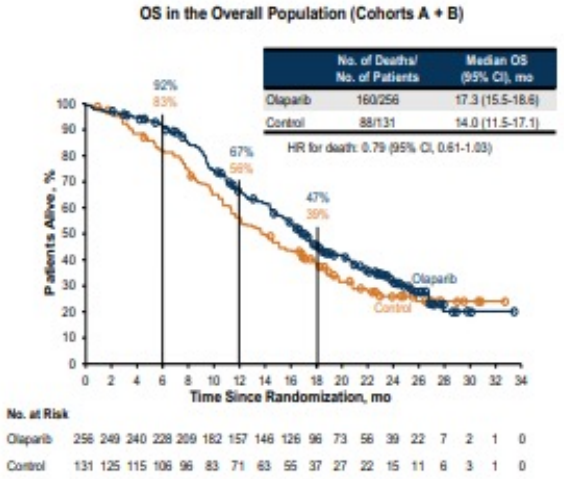
- Primary endpoint: rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- Key secondary endpoints: rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound: rPFS and OS in Whole Population (A+B)







1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

TRITON3: Randomized Phase III Trial

Patient population

- mCRPC with progression after 1 prior AR signaling-directed therapy (abiraterone, enzalutamide, or investigational agent)
- Deleterious germline or somatic alteration in ***BRCA1, BRCA2,*** or ***ATM****
- No prior PARP inhibitor
- No prior chemotherapy for mCRPC

Planned enrollment: 400

Open-label → R 2:1

- **Rucaparib** 600 mg BID (n=267)
- **Physician's choice** (**Docetaxel**, or **Abi**, or **Enza**) (n=133)

Crossover upon progression may be considered

Primary endpoint

rPFS
(RECIST 1.1 and PCWG3 by IRR)

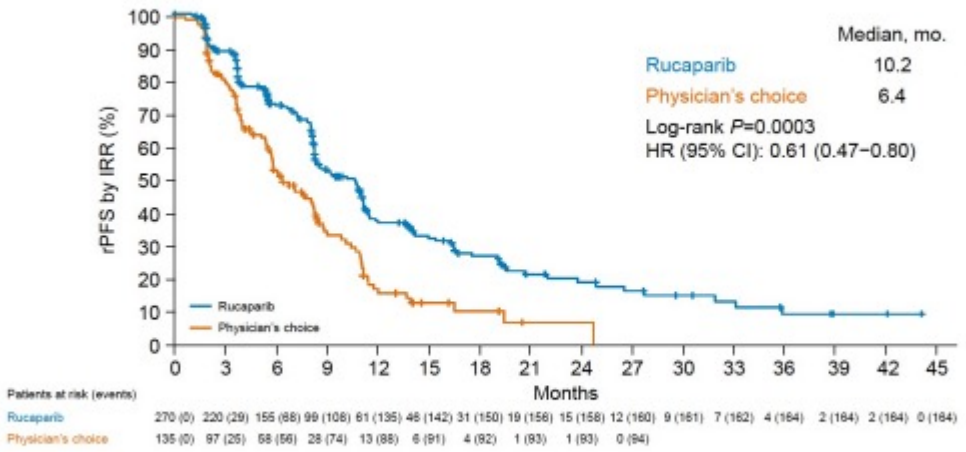
Key secondary endpoints

- ORR and DOR by modified RECIST criteria in patients with measurable nodal/visceral disease
- OS
- Clinical benefit rate
- PSA response of ≥50% and ≥90%
- Time to PSA progression
- Patient-reported outcomes
- Safety and tolerability

*Mutations identified in blood, archival tissue, or screening tumor tissue

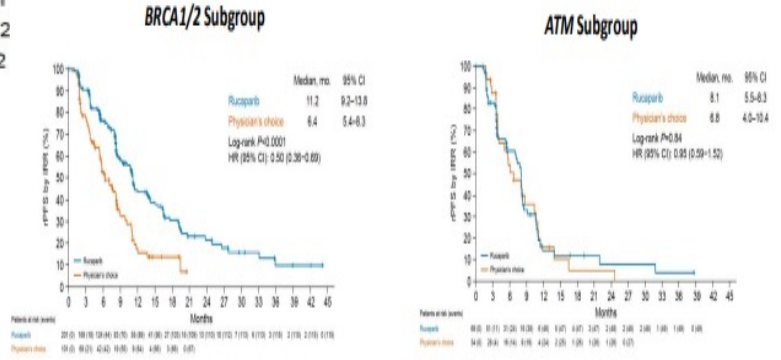
Bryce A et al NEJM 2023; 388; 719-32. **NCT02975934**.

TRITON3: rPFS in ITT Population



Bryce A et al NEJM 2023; 388; 719-32.

TRITON3: rPFS in *BRCA1/2* and *ATM* Subgroups



Bryce A et al NEJM 2023; 388; 719-32.

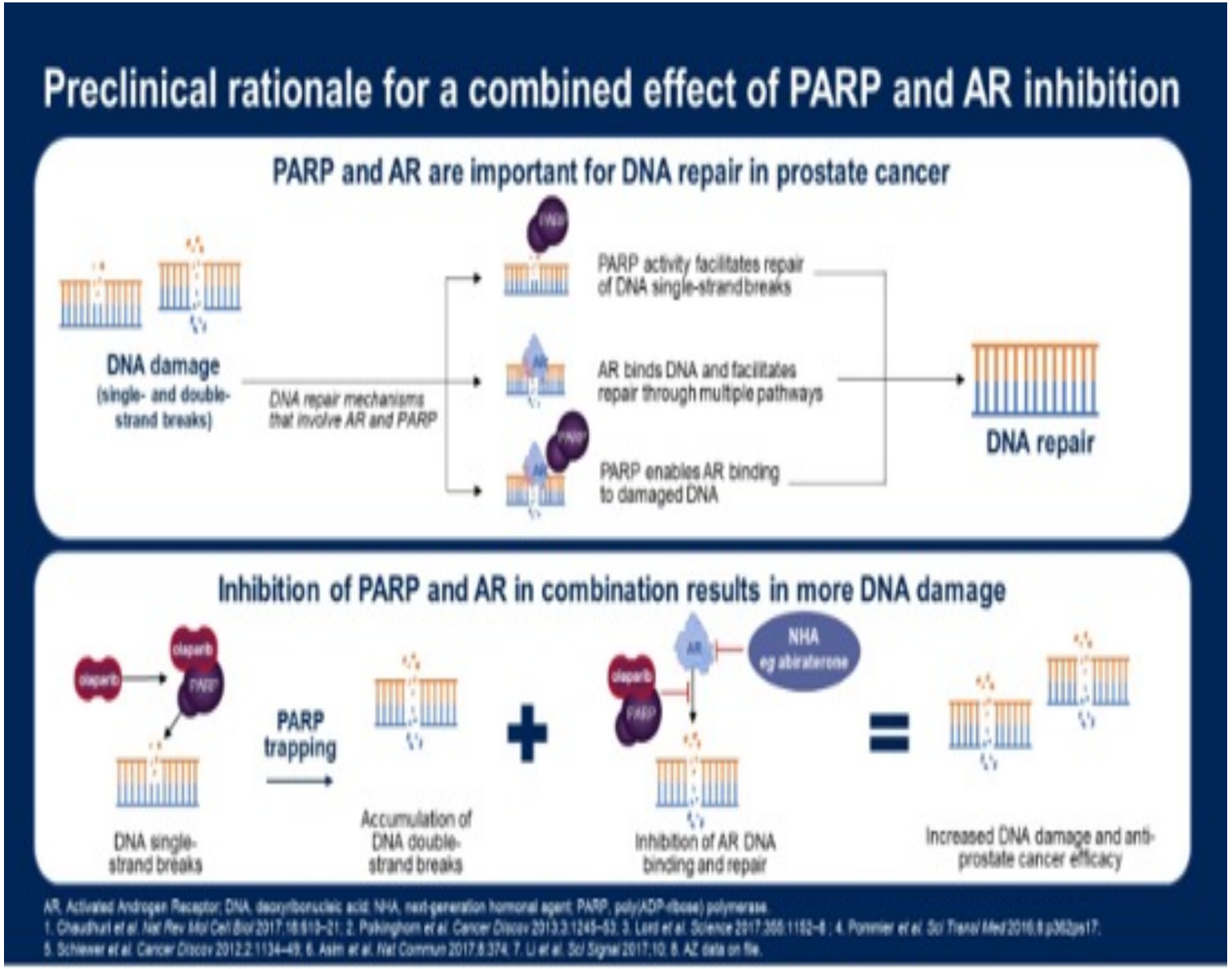
Three FDA Approved PARP Combinations in 2023 (PROpel, Magnitude, Talapro2)

- What are the differences?

PROpel: Phase III Trial of Abiraterone +/– Olaparib

MAGNITUDE: Phase III Trial of Abi +/– Niraparib

TALAPRO-2: Phase III Trial of Enza +/– Talazoparib


Preclinical rationale for a combined effect of PARP and AR inhibition
PARP and AR are important for DNA repair in prostate cancer
DNA damage
(single- and double-strand breaks)
DNA repair mechanisms that involve AR and PARP
PARP activity facilitates repair of DNA single-strand breaks
AR binds DNA and facilitates repair through multiple pathways
PARP enables AR binding to damaged DNA
DNA repair
Inhibition of PARP and AR in combination results in more DNA damage
olaparib
PARP
PARP trapping
DNA single-strand breaks
Accumulation of DNA double-strand breaks
AR
NHA
eg abiraterone
Inhibition of AR DNA binding and repair
Increased DNA damage and anti-prostate cancer efficacy
AR, Activated Androgen Receptor; DNA, deoxyribonucleic acid; NHA, next-generation hormonal agent; PARP, poly(ADP-ribose) polymerase.
1. Chaudhuri et al. Nat Rev Mol Cell Biol 2017;18:610–21; 2. Pilonghorn et al. Cancer Discov 2013;3:1245–53; 3. Lord et al. Science 2017;355:1152–8; 4. Pommier et al. Sci Transl Med 2016;8:362ps17;
5. Schiewer et al. Cancer Discov 2012;2:1134–49; 6. Asim et al. Nat Commun 2017;8:374; 7. Li et al. Sci Signal 2017;10; 8. AZ data on file.
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PROpel: Phase III Trial of Abiraterone +/– Olaparib

Patient population

- mCRPC
- Docetaxel for mCSPC allowed
- No prior abiraterone
- Other NHT allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG PS 0–1

Stratification factors

- Site of distant metastases (bone only vs visceral vs other)
- Prior taxane for mCSPC

R 1:1

Olaparib 300 mg BID + **Abiraterone*** 1000 mg QD (n=399)

Placebo + **Abiraterone*** 1000 mg QD (n=397)

Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

- OS

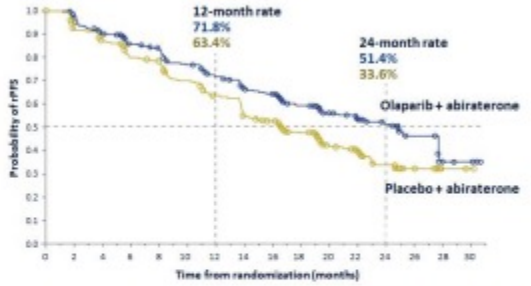
Additional endpoints

- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

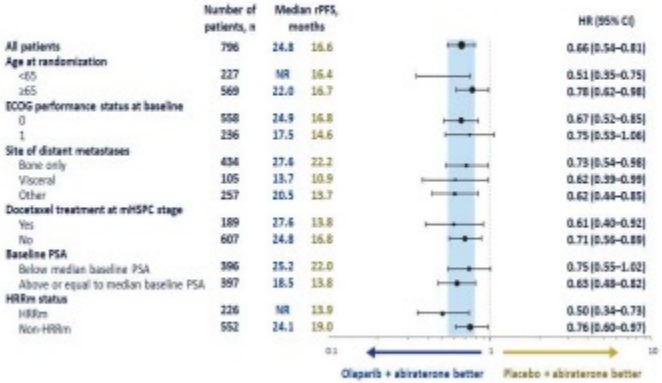
*Plus prednisone or prednisolone 5 mg BID

Saad F et al. *ASCO GU 2022*; abstr 11; **NCT03732820**.

PROpel: Radiographic Progression-Free Survival



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	



Clarke NW et al. *NEJM Evidence*; 2022.

MAGNITUDE: Phase III Trial of Abi +/– Niraparib

Patient population

- mCRPC
- ≤4 months prior abiraterone for mCRPC allowed
- ECOG PS 0–1
- BPI-SF worst pain score ≤3

Stratification factors

- Prior taxane for mCSPC
- Prior NHT for nmCRPC or mCSPC
- Prior abiraterone for mCRPC
- *BRCA1/2* vs other HRR gene alterations (HRR biomarker+ cohort only)

Prescreening for HRR biomarker status*

HRR Biomarker + (Planned N=400)
R 1:1
- **Niraparib 200 mg QD + Abiraterone† 1000 mg QD**
- **Placebo + Abiraterone† 1000 mg QD**

HRR Biomarker – (Planned N=600)
R 1:1
- **Niraparib 200 mg QD + Abiraterone† 1000 mg QD**
- **Placebo + Abiraterone† 1000 mg QD**

Patients could request to be unblinded and change to subsequent therapy of investigator's choice

Primary endpoint

rPFS by central review

Key secondary endpoints

- Time to cytotoxic chemotherapy
- Time to symptomatic progression
- OS

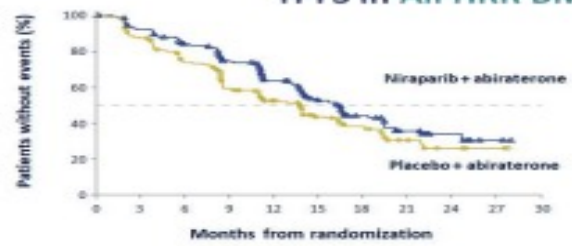
Other prespecified endpoints

- Time to PSA progression
- ORR
- PFS2
- Time to pain progression
- Patient-reported outcomes

*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***
†Plus prednisone 10 mg daily

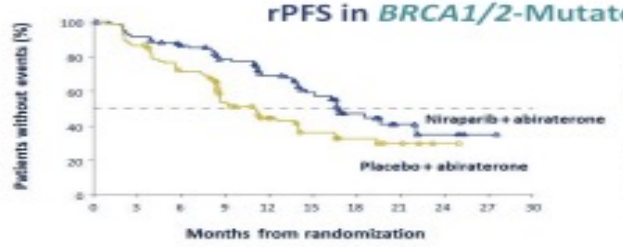
MAGNITUDE: Radiographic Progression-Free Survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

rPFS in *BRCA1/2*-Mutated Group



	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

Chi KN et al. *ASCO GU 2022*; abstr 12.

TALAPRO-2: Phase III Trial of Enza +/– Talazoparib

Patient population

- mCRPC with progression (PSA, bone, and/or soft tissue)
- Prior docetaxel and/or abiraterone in CSPC setting allowed
- Ongoing ADT or bilateral orchiectomy
- ECOG PS 0–1

Stratification factors

- Previous treatment with abiraterone or taxane-based chemotherapy for CSPC
- DDR[#] alteration status (deficient vs nondeficient/unknown)

R 1:1

Talazoparib 0.5 mg QD* + **Enzalutamide** 160 mg QD

Planned enrollment: 1018

Placebo + **Enzalutamide** 160 mg QD

Co-primary endpoints

- rPFS by BICR per RECIST 1.1 and PCWG3 in **All-comers (Cohort 1), n=804**
- rPFS by BICR in patients with **DDR[#] alterations (Cohort 2), n=214**

Key secondary endpoints (analyzed for both cohorts separately)

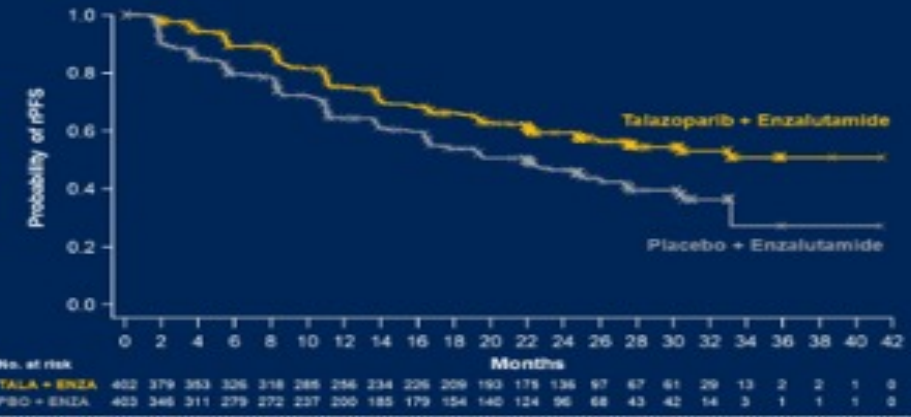
- OS
- OR per RESIST 1.1 (measurable disease)
- PSA response ≥50%
- Time to PSA progression
- Time to initiation of cytotoxic CT or antineoplastic therapy
- Time to first symptomatic skeletal event
- PFS2
- Safety
- Patient-reported outcomes

*0.35 mg QD if moderate renal impairment

[#] DDR alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*).

TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); $P < 0.001$	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); $P < 0.001$

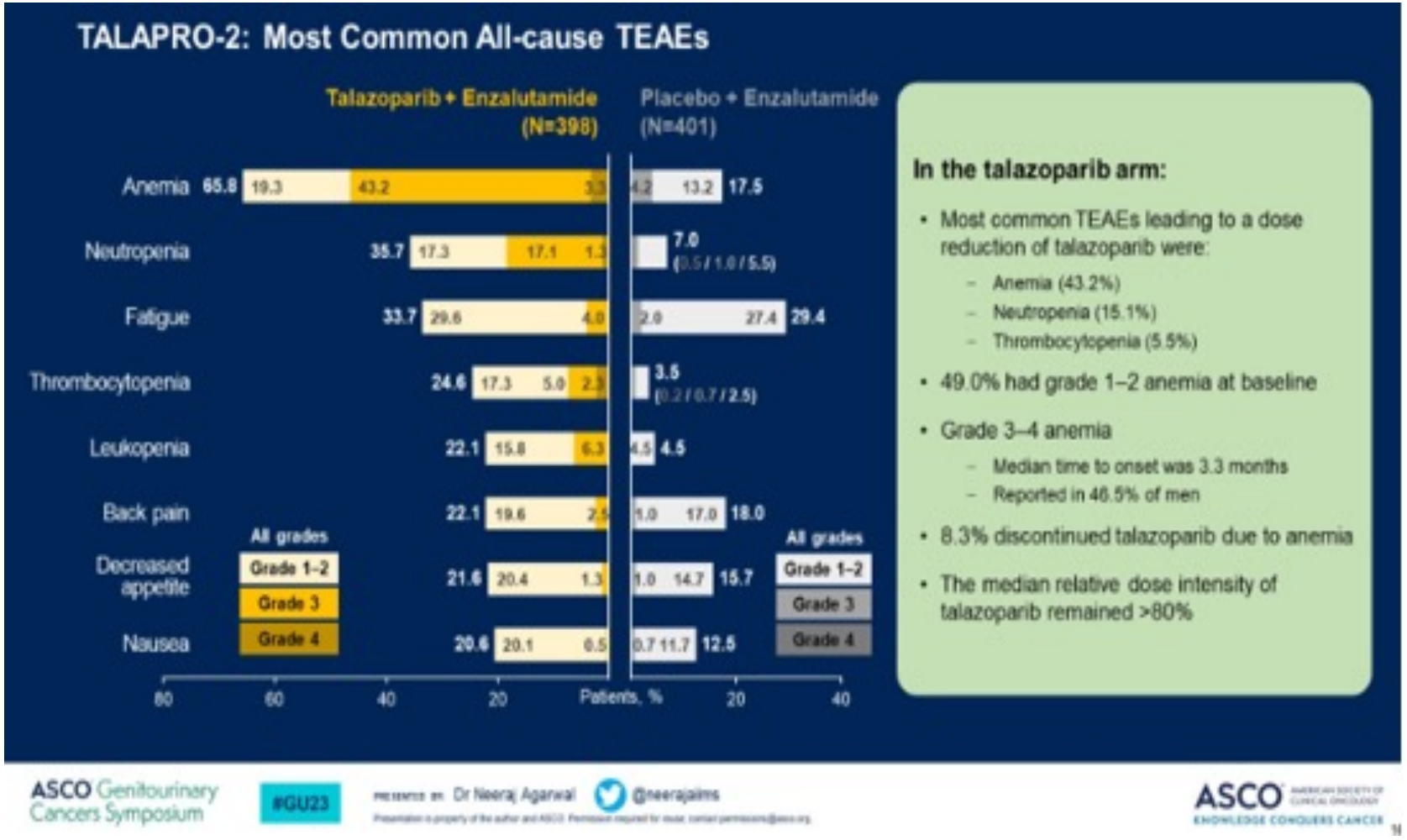
Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

ASCO Genitourinary Cancers Symposium #GU23

Presented by: Dr Neeraj Agarwal

Agarwal N et al. *Future Oncol.* 2022;18:425-436; NCT03395197.

What about Adverse Events?



What do I do in my Practice?

- Patients with metastatic castrate resistant prostate cancer (mCRPC) with BRCA1 and BRCA2 have a poor prognosis (19 months vs 37 months)
- In my practice, patients with mCRPC with BRCA1 and BRCA2 mutation I will treat with PARP inhibitor, AR pathway inhibitor, and ADT.

How do I choose between 3 combinations

- 1. Co-morbidities(Uncontrolled diabetes, recent coronary artery disease).
- 2. Have they previously received androgen receptor pathway inhibitor? (Abiraterone and ADT in high risk early stage?)
- 3. Do they have a fall risk/cognitive difficulty/mental status changes?
- 4. Do they have a low baseline anemia?

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