Prostate Cancer Updates

University of Colorado Cancer Center

Presented by: Dr. Laura S. Graham, MD

Assistant Professor, Division of Medical Oncology

University of Colorado

October 14, 2023

OUTLINE

Triplet Therapy in First-Line Hormone Sensitive Prostate Cancer

PARPi combination therapy in Castration Resistant Prostate Cancer

Androgen Deprivation Therapy (ADT) is the Mainstay of Treatment in HSPC

There is an **Overall Survival** Benefit to Treatment Intensification With:

Abiraterone/Prednisone (CYP17 inhibitor)

Enzalutamide or Apalutamide (AR Antagonist)

Docetaxel Chemotherapy

Radiation to the prostate in low volume disease

Triplet Therapy in HSPC

Docetaxel + Darolutamide + ADT

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*

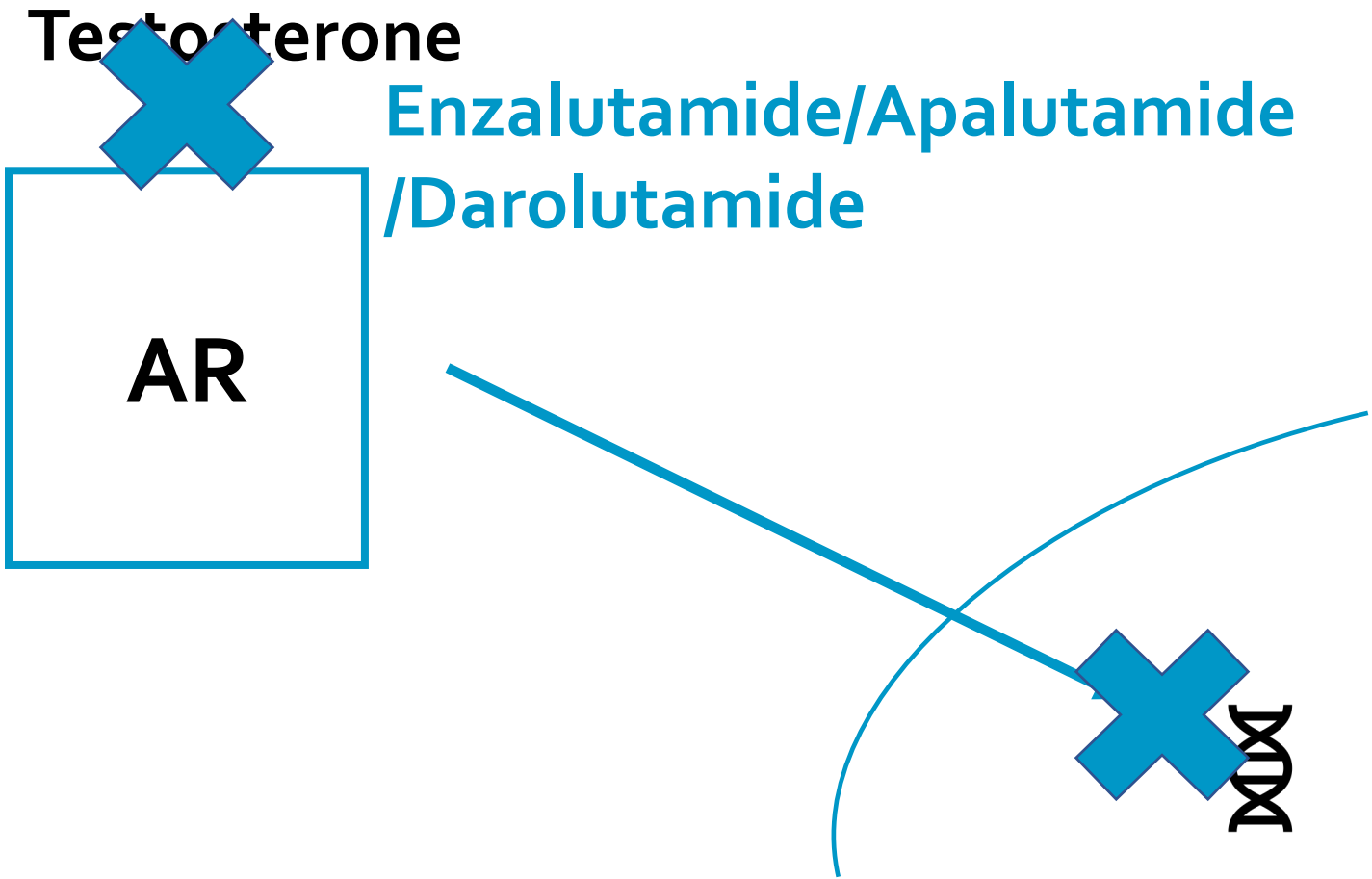
ARASENS

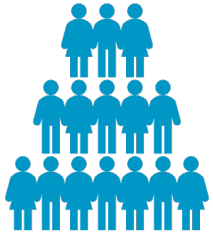
Docetaxel + Abiraterone + ADT

Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

*Karim Fizazi, Stéphanie Foulon, Joan Carles, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Loic Mourey, Brigitte Laguerre, Sophie Abadie-Lacourtoisie, Etienne Martin, Claude El Kouri, Anne Escande, Alvar Rosello, Nicolas Magne, Friederike Schlurmann, Frank Priou, Marie-Eve Chand-Fouche, Salvador Villà Freixa, Muhammad Jamaluddin, Isabelle Rieger, Alberto Bossi, on behalf of the PEACE-1 investigators**

PEACE-1


Testosterone
Enzalutamide/Apalutamide
/Darolutamide
AR
DNA



1306 patients
Metastatic
Treatment Naive

ADT

Docetaxel
75mg/m2 x 6
cycles

Placebo

ADT

Docetaxel
75mg/m2 x 6
cycles

Darolutamide
600mg BID

Smith et al. NEJM 2022

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

Characteristic	Darolutamide–ADT–Docetaxel (N=651)†	Placebo–ADT–Docetaxel (N=654)†
Median age (range) — yr	67 (41–89)	67 (42–86)
Age group — no. (%)		
<65 yr	243 (37.3)	234 (35.8)
65–74 yr	303 (46.5)	306 (46.8)
75–84 yr	102 (15.7)	110 (16.8)
≥85 yr	3 (0.5)	4 (0.6)
ECOG performance-status score — no. (%)‡		
0	466 (71.6)	462 (70.6)
1	185 (28.4)	190 (29.1)
Race — no. (%)§		
White	345 (53.0)	333 (50.9)
Asian	230 (35.3)	245 (37.5)
Black	26 (4.0)	28 (4.3)
Other	7 (1.1)	2 (0.3)
Not reported	43 (6.6)	46 (7.0)
Region — no. (%)		
North America	125 (19.2)	119 (18.2)
Asia-Pacific	229 (35.2)	244 (37.3)
Rest of the world¶	297 (45.6)	291 (44.5)
Gleason score at initial diagnosis — no. (%)‖		
<8	122 (18.7)	118 (18.0)
≥8	505 (77.6)	516 (78.9)
Data missing	24 (3.7)	20 (3.1)
Metastasis stage at screening — no. (%)		
M1a, nonregional lymph-node metastases only	23 (3.5)	16 (2.4)
M1b, bone metastases with or without lymph-node metastases	517 (79.4)	520 (79.5)
M1c, visceral metastases with or without lymph-node or bone metastases	111 (17.1)	118 (18.0)
Median serum PSA level (range) — ng/ml**	30.3 (0.0–9219.0)	24.2 (0.0–11,947.0)
Median serum ALP level (range) — U/liter**	148 (40–4885)	140 (36–7680)
ALP category — no. (%)**		
<ULN	290 (44.5)	291 (44.5)
≥ULN	361 (55.5)	363 (55.5)

Smith et al. NEJM 2022

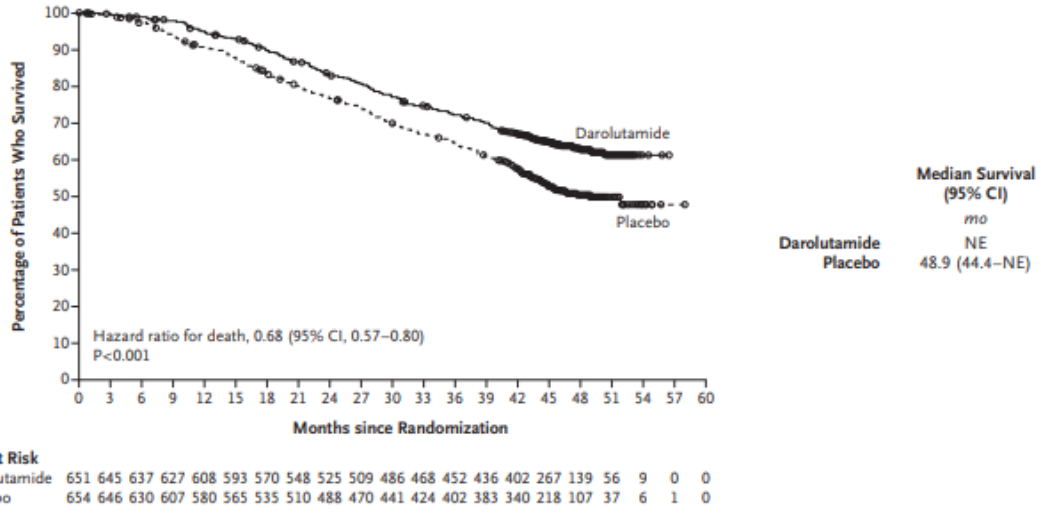


Figure 1. Overall Survival (Full Analysis Set).

Kaplan–Meier estimates of overall survival are shown. For the analysis of overall survival, data were censored as of the last known date the patients were alive. One patient who was randomly assigned to the placebo group but received darolutamide was included in the placebo group in the full analysis set. CI denotes confidence interval, and NE not estimable.

Darolutamide significantly prolonged **overall survival** compared to placebo (HR 0.68; 95% CI: 0.57 to 0.80; P<0.001)

Smith et al. NEJM 2022

Table 2. Secondary Efficacy End Points (Full Analysis Set).*

End Point	Darolutamide–ADT–Docetaxel (N=651)†		Placebo–ADT–Docetaxel (N=654)†		Hazard Ratio (95% CI)	P Value
	Median	Patients with Event	Median	Patients with Event		
	mo	*no. (%)*	*mo*	*no. (%)*		
Time to castration-resistant prostate cancer	NR	225 (35)	19.1	391 (60)	0.36 (0.30–0.42)	<0.001
Time to pain progression	NR	222 (34)	27.5	248 (38)	0.79 (0.66–0.95)	0.01
Symptomatic skeletal event–free survival	51.2	257 (40)	39.7	329 (50)	0.61 (0.52–0.72)	<0.001
Time to first symptomatic skeletal event	NR	95 (15)	NR	108 (17)	0.71 (0.54–0.94)	0.02
Time to initiation of subsequent systemic antineoplastic therapy	NR	219 (34)	25.3	395 (60)	0.39 (0.33–0.46)	<0.001
Time to worsening of disease-related physical symptoms	19.3	351 (54)	19.4	308 (47)	1.04 (0.89–1.22)	0.59
Time to initiation of opioid use for ≥7 consecutive days	NR	92 (14)	NR	117 (18)	0.69 (0.52–0.91)	NA

* NA denotes not applicable, and NR not reached.
† One patient who was randomly assigned to the placebo group but received darolutamide was included in the placebo group in the full analysis set.

Smith et al. NEJM 2022

Table 3. Adverse Events.*

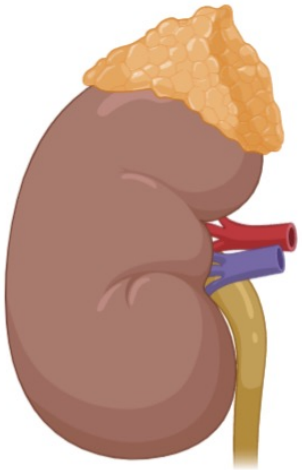
Event	Darolutamide–ADT–Docetaxel (N=652)†	Placebo–ADT–Docetaxel (N=650)†
	number of patients (percent)	
Any adverse event	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide or placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse events‡		
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 level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Three patients who underwent randomization never received the assigned trial treatment; all three patients were in the placebo group. One patient who was assigned to the placebo group but received darolutamide was included in the darolutamide group of the safety analysis set.
‡ In the column of data for patients who received darolutamide, ADT, and docetaxel, listed are all grade 3 or 4 events that occurred in at least 2% of the patients.
§ The neutropenia category includes the preferred terms of leukopenia, neutropenia, decreased neutrophil count, and decreased white-cell count.

Smith et al. NEJM 2022

Cholesterol

Abiraterone



17α-[illegible]oxylase

17-Hydroxypregenolone

3β-hydroxysteroid dehydrogenase

DHEA

3β-hydroxysteroid dehydrogenase

Androstenedione

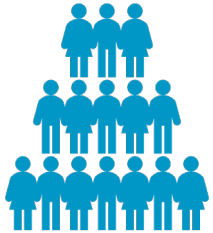
Aldo-keto reductase 1C3 (AKR1C3)

Testosterone

5α-reductase

DHT

*Patients also randomized to receive radiotherapy or no radiotherapy



1173 patients
De novo
Metastatic
Treatment Naive

ADT

Docetaxel 75mg/m2 x 6 cycles

Placebo

ADT

Docetaxel 75mg/m2 x 6 cycles

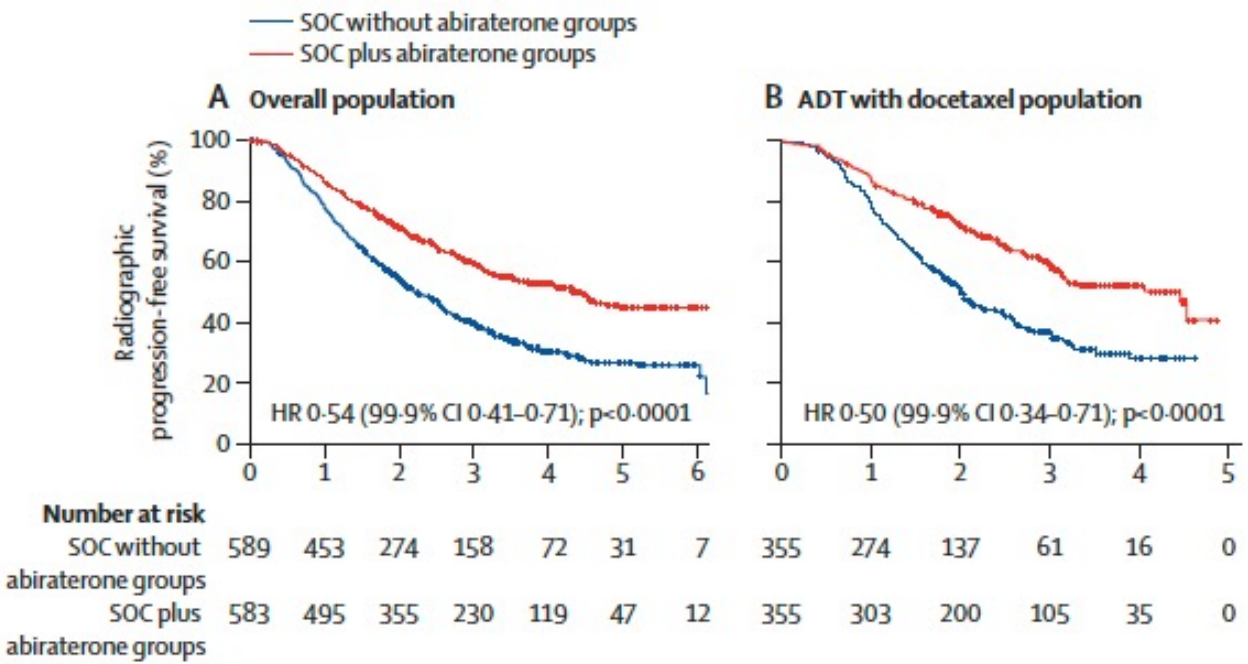
Abiraterone 1000mg daily
Prednisone 5mg PO BID

Fizazi et al. Lancet 2022

Baseline Characteristics

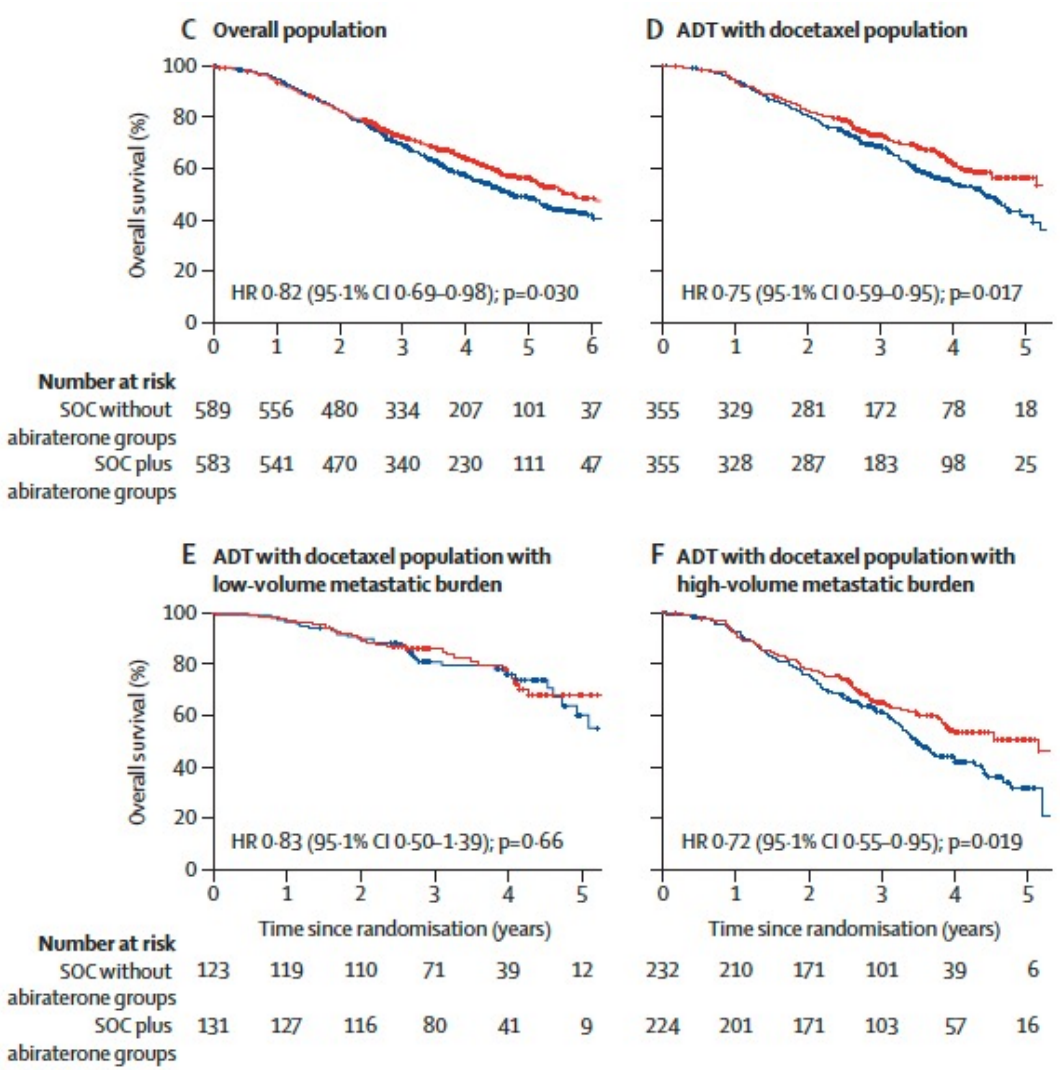
Time from diagnosis, months				
Median	2·3 (1·6–3·2)	2·3 (1·4–3·1)	2·2 (1·6–3·0)	2·2 (1·4–2·9)
Missing data	10 (2%)	10 (2%)	6 (2%)	7 (2%)
Metastatic localisation				
Bone†	472 (81%)	475 (81%)	287 (81%)	279 (79%)
Lymph node only	47 (8%)	52 (9%)	27 (8%)	29 (8%)
Visceral‡	64 (11%)	62 (11%)	41 (12%)	47 (13%)
Metastatic burden§				
High burden	331 (57%)	336 (57%)	224 (63%)	232 (65%)
Low burden	252 (43%)	253 (43%)	131 (37%)	123 (35%)

Fizazi et al. Lancet 2022



Abiraterone significantly prolonged **rPFS** compared to ADT/Docetaxel alone (HR 0.50; 99% CI: 0.34 to 0.71; P<0.0001)

Fizazi et al. Lancet 2022



Abiraterone significantly prolonged **overall survival** compared to ADT/Docetaxel alone (HR 0.75; 95% CI: 0.59 to 0.95; P=0.017)

Fizazi et al. Lancet 2022

	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy; n=347)	SOC without abiraterone groups (with or without radiotherapy; n=350)	SOC plus abiraterone groups (with or without radiotherapy; n=226)	SOC without abiraterone groups (with or without radiotherapy; n=237)
Any adverse events	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade ≥3) adverse events	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5) adverse events	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe adverse events				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Gamma-glutamyl transferase increase	17 (5%)	14 (4%)	6 (3%)	4 (2%)
Erectile dysfunction	7 (2%)	5 (1%)	12 (5%)	13 (5%)
Blood alkaline phosphatase increase	15 (4%)	12 (3%)	6 (3%)	13 (5%)
Other severe adverse events				
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

Data are n (%). As the patients were not randomly assigned according to docetaxel prescription, toxicities recorded in the ADT without docetaxel and ADT with docetaxel populations are not directly comparable. Percentages are rounded to the nearest integer. The safety population includes patients who actually received the assigned treatment. Severe adverse events (grade ≥3) were considered frequent if they occurred in at least 5% of patients in either group and are reported in decreasing order of occurrence according to the Medical Dictionary for Regulatory Affairs Preferred Term classification. ADT=androgen deprivation therapy. SOC=standard of care.

***Table 3*: Adverse events in the safety population**

Fizazi et al. Lancet 2022

ENZAMET

Subgroup	Enzalutamide	Standard Care	Hazard Ratio (95% CI)	P Value for Interaction	Adjusted P Value
	no. of events/total no.				
All patients	102/563	143/562	0.67 (0.52–0.86)		
Volume of disease				0.04	0.14
Low	22/272	46/265	0.43 (0.26–0.72)		
High	80/291	97/297	0.80 (0.59–1.07)		
Early docetaxel planned				0.04	0.14
Yes	52/254	55/249	0.90 (0.62–1.31)		
No	50/309	88/313	0.53 (0.37–0.75)		
ACE-27 score				0.73	0.81
2 or 3	31/141	42/143	0.73 (0.46–1.16)		
0 or 1	71/422	101/419	0.65 (0.48–0.88)		
Antiresorptive therapy				0.006	0.06
Yes	17/55	11/58	1.77 (0.83–3.77)		
No	85/508	132/504	0.59 (0.45–0.77)		
Region				0.25	0.42
Ireland and United Kingdom	22/102	22/93	1.04 (0.57–1.88)		
North America	21/117	31/129	0.72 (0.41–1.25)		
Australia and New Zealand	59/344	90/340	0.58 (0.42–0.81)		
Gleason score				0.66	0.81
≤7	13/152	23/163	0.59 (0.30–1.16)		
8 to 10	66/335	84/321	0.70 (0.50–0.96)		
ECOG performance status				0.96	0.96
1 or 2	44/158	59/157	0.66 (0.45–0.98)		
0	58/405	84/405	0.66 (0.47–0.92)		
Age				0.16	0.33
≥70 yr	47/257	79/257	0.56 (0.39–0.81)		
<70 yr	55/306	64/305	0.81 (0.56–1.15)		
Visceral metastases				0.16	0.33
Yes	18/62	18/67	1.05 (0.54–2.02)		
No	84/501	125/495	0.62 (0.47–0.82)		
Previous local treatment				0.72	0.81
Yes	39/238	49/235	0.72 (0.47–1.09)		
No	63/325	94/327	0.65 (0.47–0.89)		

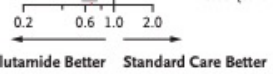


Figure 2. Subgroup Analysis of Overall Survival.

Shown are the results of subgroup analysis of overall survival in 10 key subgroups of patients in the enzalutamide group and the standard-care group. Hazard ratios and 95% confidence intervals are provided. The size of the gray shaded boxes is proportional to the number of events in the subgroup. The dashed vertical line indicates the overall hazard ratio in all the patients. Scores on the Eastern Cooperative Oncology Group (ECOG) performance-status scale range from 0 (no disability) to 5 (death). Scores on the Adult Comorbidity Evaluation 27 (ACE-27) are 0 (none) or 1 (mild) vs. 2 (moderate) or 3 (severe).

Davis et al. NEJM 2019

Triplet Therapy Takeaways

Triplet therapy with ADT/Docetaxel **and** Darolutamide **or** Abiraterone prolongs **overall survival**

Darolutamide studied in men with de novo or recurrent disease

Abiraterone studied in men with de novo metastatic disease

No OS benefit for Abiraterone in low-volume disease, but improvement in rPFS (and OS data immature)

Enzalutamide did not improve OS, did improve clinical and PSA PFS- updated results expected

Unanswered Questions

Is docetaxel necessary?

Should we treat high vs. low metastatic disease burden differently?

Should we treat patients with metachronous vs. synchronous metastatic disease differently?

Are there patients we should be *de-escalating* therapy?

PARPi Combination Therapy in CRPC

~11% of men with metastatic prostate cancer have germline HRR mutations

~20-30% of men with metastatic prostate cancer have somatic HRR mutations

Tumors with HRR mutations may respond to PARP inhibitors and other DNA damaging therapeutics (i.e. platinum chemotherapy)

Rucaparib approved for men with mCRPC and *BRCA1/2* mutations

Olaparib approved for men with mCRPC and mutations in one of 14 HRR genes

Preclinical evidence for synergy between AR targeting agents and PARP inhibitors

PARP inhibitors block repair of single strand DNA breaks and cause double strand DNA breaks

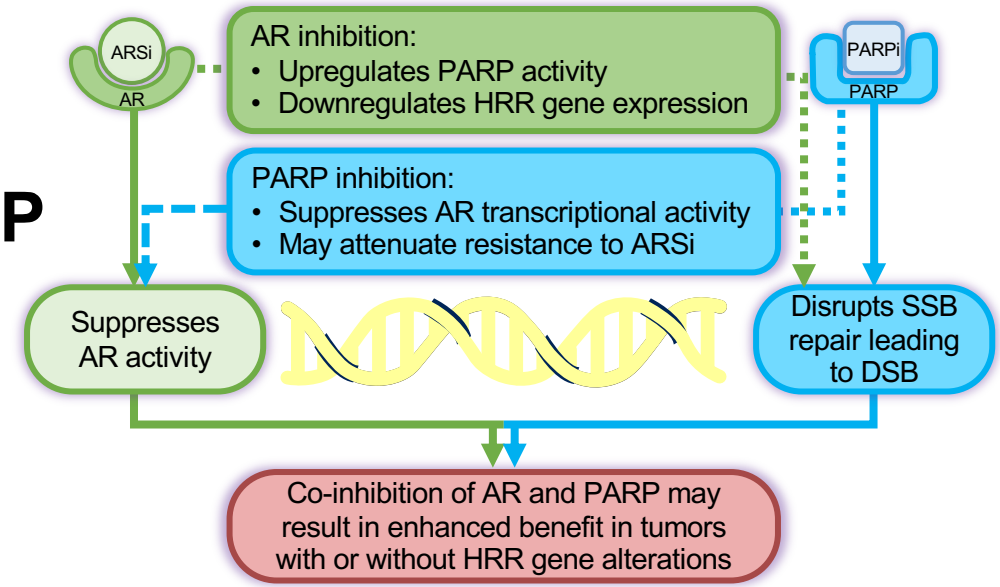


Figure presented at ASCO GU 2023 (Agarwal N, et al. *J Clin Oncol*. 2023;41(suppl 6):LBA17)

3 recent trials of NHT/PARPi combinations

PROpel

NEJM Evidence

Published June 3, 2022
NEJM Evid 2022; 1 (9)
DOI: 10.1056/EVIDoa2200043

ORIGINAL ARTICLE

Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer

Noel W. Clarke, M.B.B.S., Ch.M., F.R.C.S.,[1] Andrew J. Armstrong, Sc.M., M.D.,[2] Antoine Thiery-Vuillemin, M.D., Ph.D.,[3] Mototsugu Oya, M.D.,[4] Neal Shore, M.D.,[5] Eugenia Loredo, M.D.,[6] Giuseppe Procopio, M.D.,[7] Juliana de Menezes, M.D.,[8] Gustavo Girotto, M.D.,[9] Cagatay Arslan, M.D.,[10] Niven Mehra, M.D., Ph.D.,[11] Francis Parnis, F.R.A.C.P.,[12] Emma Brown, M.D.,[13] Friederike Schlürmann, M.D.,[14] Jae Y. Joung, M.D., Ph.D.,[15] Mikio Sugimoto, M.D., Ph.D.,[16] Juan A. Virizuela, M.D., Ph.D.,[17] Urban Emmenegger, M.D.,[18] Jiri Navratil, M.D.,[19] Gary L. Buchschacher, Jr., M.D., Ph.D.,[20] Christian Poehlein, M.D.,[21] Elizabeth A. Harrington, Ph.D.,[22] Chintu Desai, Ph.D.,[23] Jinyu Kang, M.D.,[24] Fred Saad, M.D., F.R.C.S.,[25] for the PROpel Investigators*

THE LANCET Oncology

Submit Article

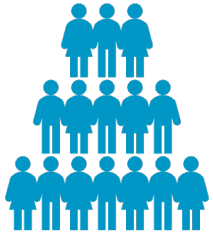
ARTICLES | VOLUME 24, ISSUE 10, P1094-1108, OCTOBER 2023 Download Full Issue

Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial

Prof Fred Saad, MD • Prof Noel W Clarke, ChM • Prof Mototsugu Oya, MD • Neal Shore, MD • Giuseppe Procopio, MD • João Daniel Guedes, MD • et al. Show all authors

Published: September 12, 2023 • DOI: https://doi.org/10.1016/S1470-2045(23)00382-0 • Check for updates

*Patients could have received docetaxel for mHSPC



1103 patients
Metastatic
First Line CRPC

ADT

Abiraterone

Placebo

ADT

Abiraterone

Olaparib
300mg BID

Clarke et al. NEJM Evidence 2022

Table 1. Characteristics of Patients at Baseline.*

Characteristic	Abiraterone and Olaparib (n=399)	Abiraterone and Placebo (n=397)
Age at random assignment — median (range), yr	69.0 (43–91)	70.0 (46–88)
Gleason score		
≥8	265 (66.4)	258 (65.0)
Missing	13 (3.3)	5 (1.3)
ECOG performance status		
0 (normal activity)	286 (71.7)	272 (68.5)
1 (restricted activity)	112 (28.1)	124 (31.2)
Missing	1 (0.3)	1 (0.3)
Prior docetaxel treatment		
Yes	97 (24.3)	98 (24.7)
At mHSPC stage	90 (22.6)	89 (22.4)
Prior treatment with NHA†		
Yes	1 (0.3)	0
Disease site‡		
Bone	349 (87.5)	339 (85.4)
Distant lymph nodes	133 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Prostate and adjacent structures	47 (11.8)	46 (11.6)
Respiratory (including lung)	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
HRRm status (aggregate)§		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)
BRCAm prevalence (aggregate)		
BRCA1	9 (2.3)	3 (0.8)
BRCA2	38 (9.5)	35 (8.8)
Baseline serum PSA — median (IQR), µg per liter	17.90 (6.09–67.00)	16.81 (6.26–53.30)

Clarke et al. NEJM Evidence 2022

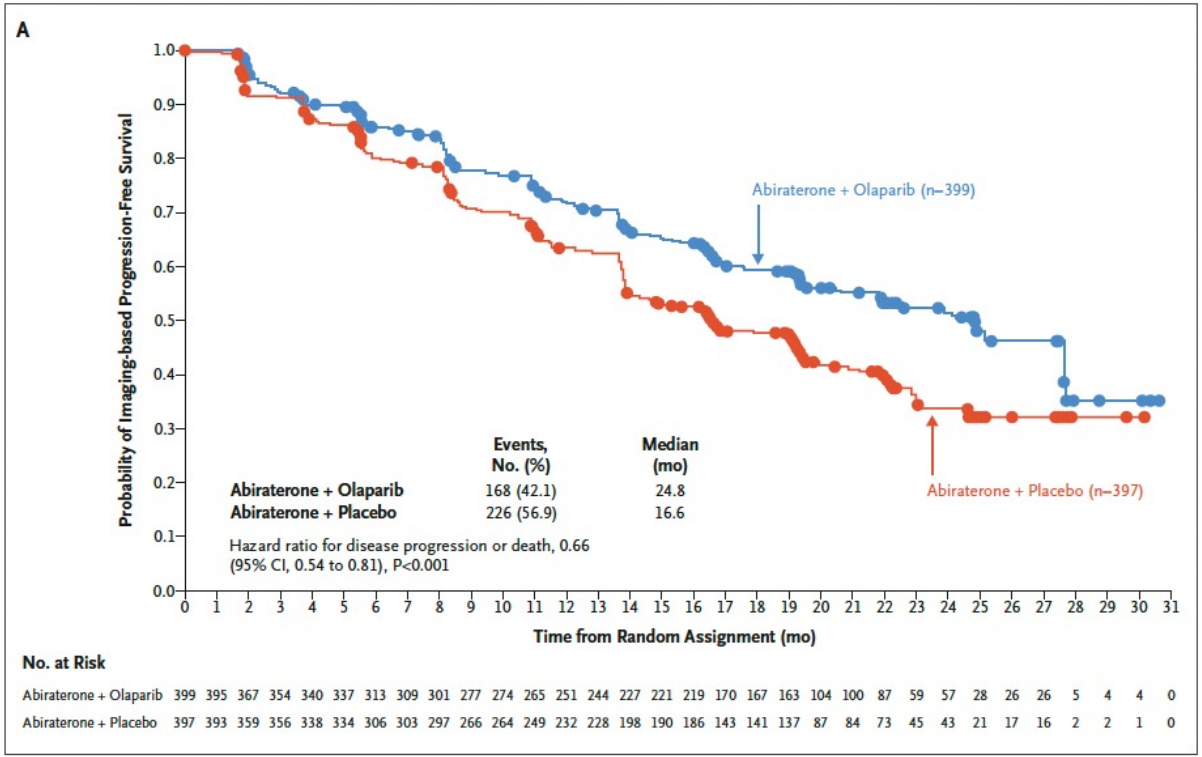
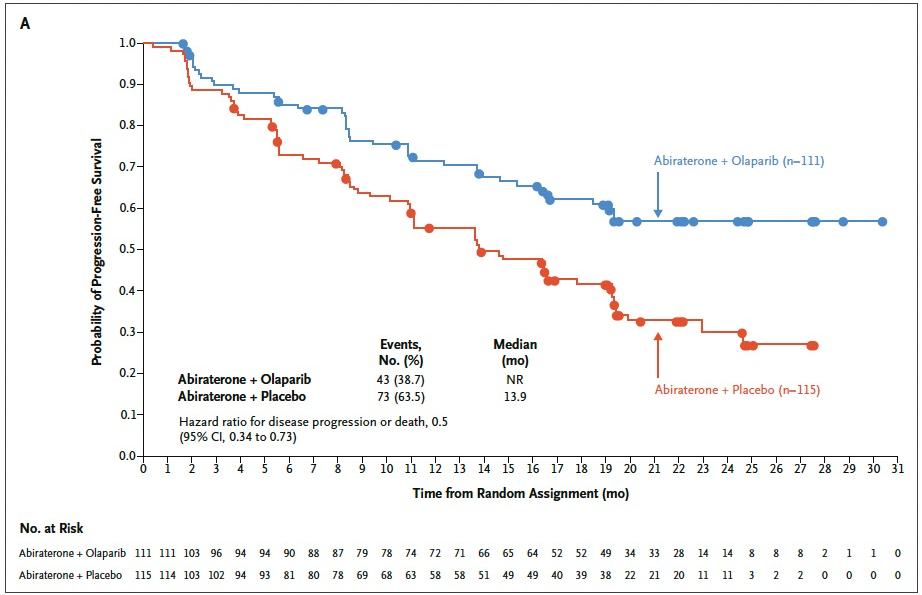


Figure 1. Kaplan–Meier Estimates of Imaging-Based Progression-Free Survival.

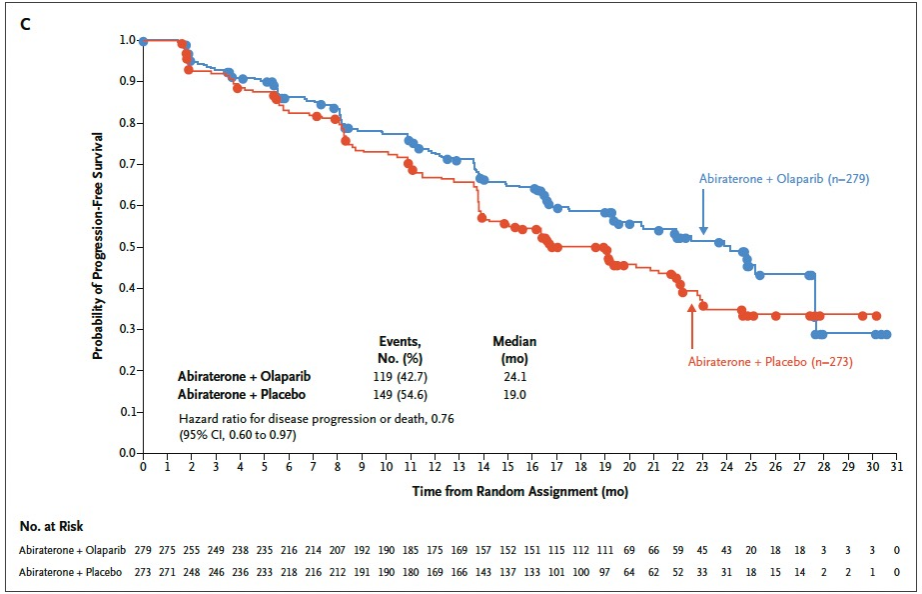
Olaparib significantly prolonged **rPFS** compared to abiraterone alone in the overall population (HR 0.66; 95% CI: 0.54 to 0.81; P<0.001)

Clarke et al. NEJM Evidence 2022

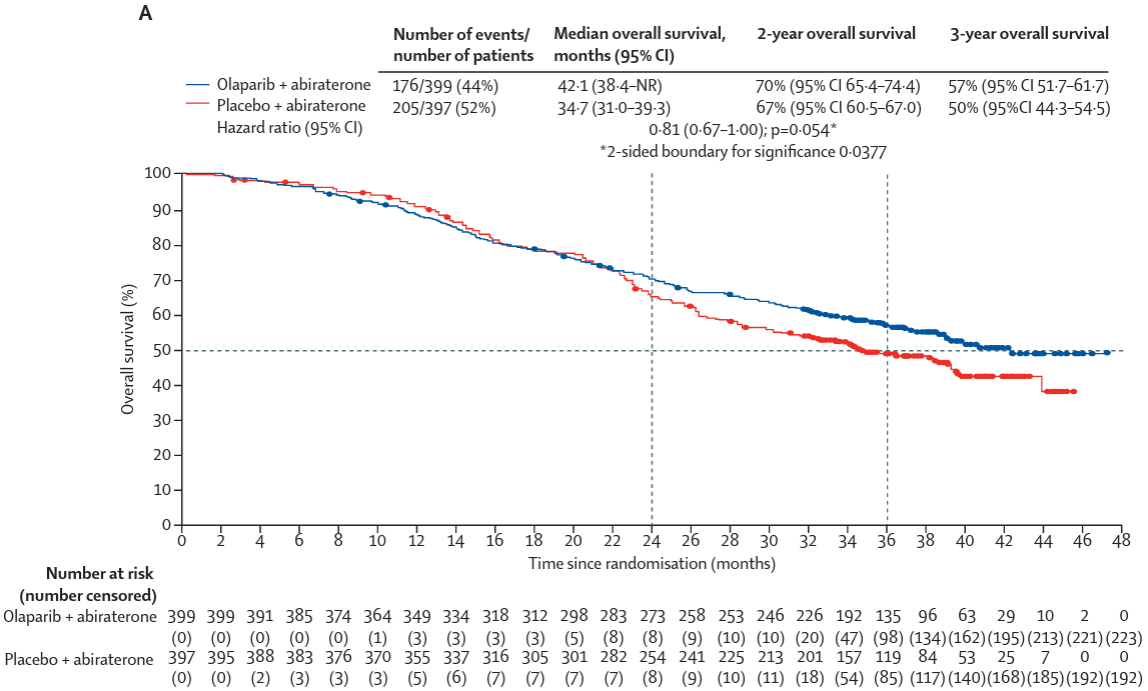
HRR mutated



Non-HRR mutated



Clarke et al. NEJM Evidence 2022

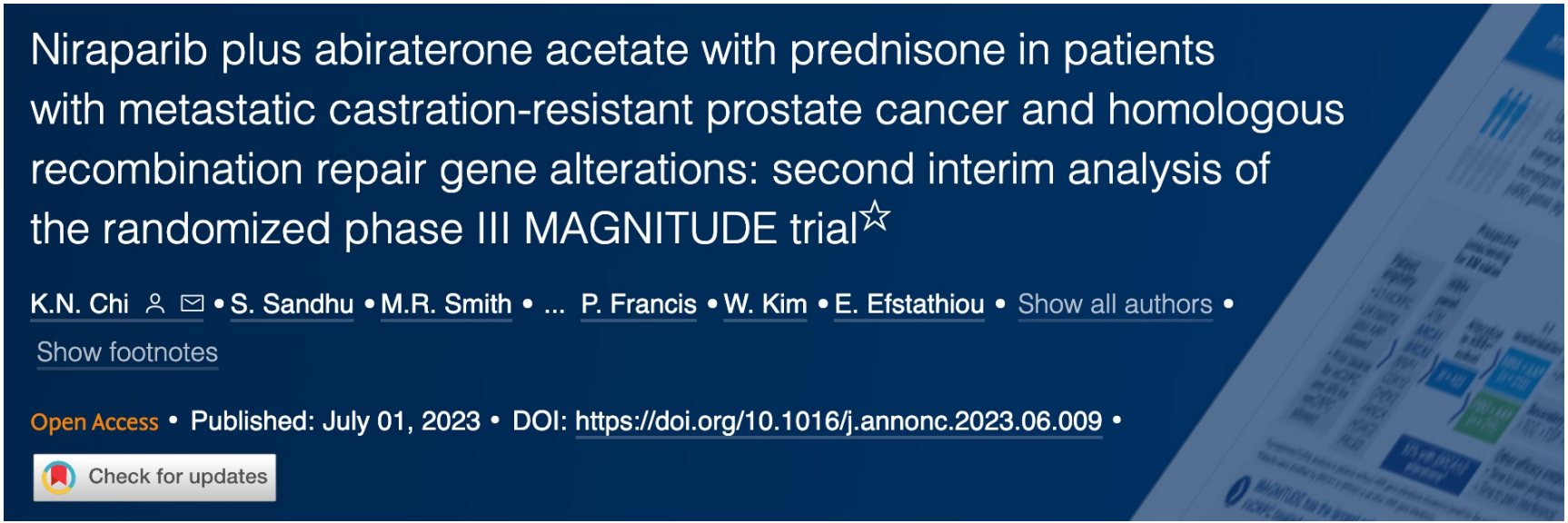


No difference in overall survival at final analysis

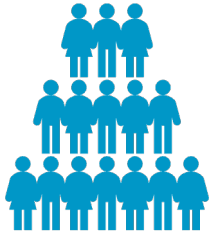
Benefit in OS in *BRCA* mutated subgroup, but only 5 patients in pbo group received subsequent PARPi

Saad et al. Lancet Oncology 2023

MAGNITUDE


Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial☆
K.N. Chi • S. Sandhu • M.R. Smith • ... P. Francis • W. Kim • E. Efstathiou • Show all authors • Show footnotes
Open Access • Published: July 01, 2023 • DOI: https://doi.org/10.1016/j.annonc.2023.06.009 •
Check for updates

*Patients could have received docetaxel and/or AR inhibitors for mHSPC



796 patients
Metastatic
First Line CRPC

212 HRRm patients

ADT

Abiraterone

Placebo

ADT

Abiraterone

Niraparib 200mg PO daily

Prospectively identified HRR- and HRR+ patients

Chi et al. Annals of Oncology. 2023

Prespecified Early Futility Analysis: NO benefit in HRR- patients

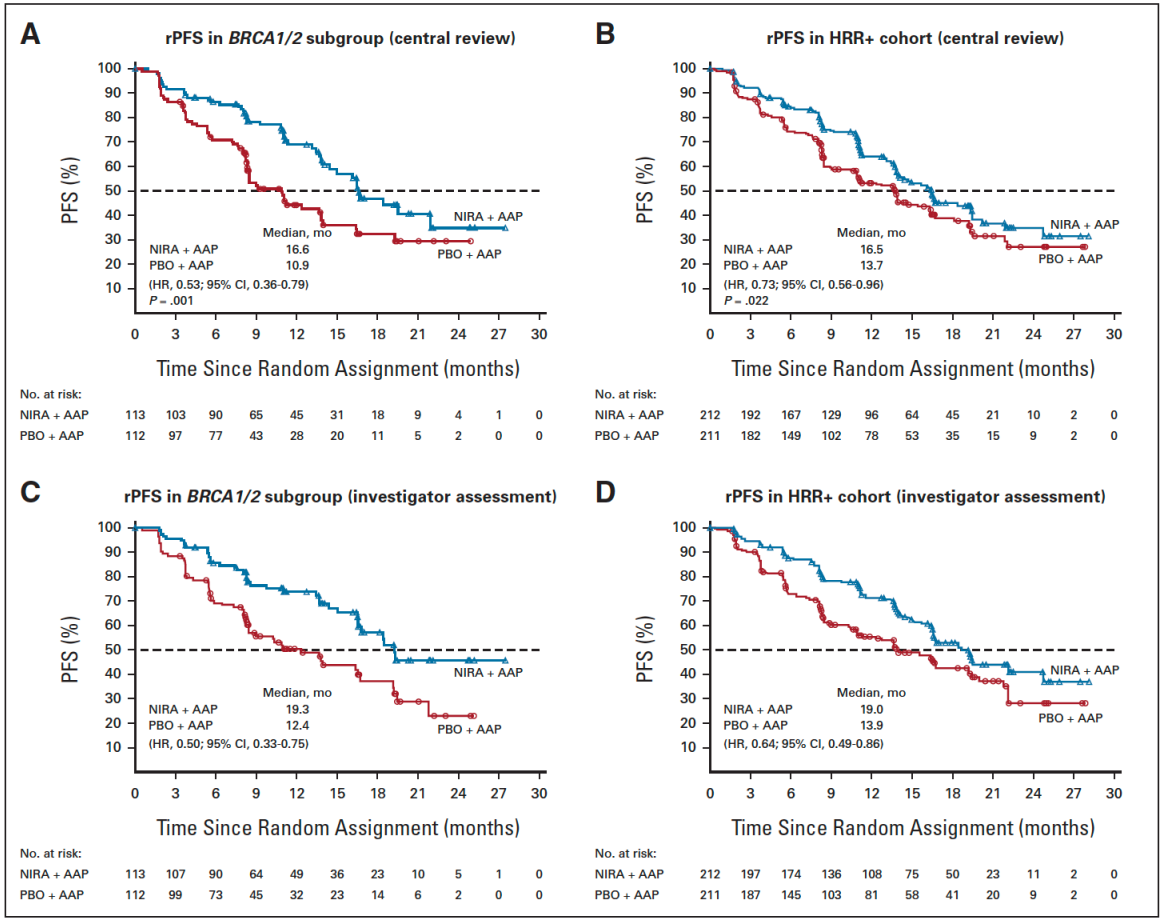
HRR mutated subset

Table 1. Baseline characteristics

	BRCA1/2 subgroup		HRR+ population[28]	
	NIRA + AAP (n = 113)	PBO + AAP (n = 112)	NIRA + AAP (n = 212)	PBO + AAP (n = 211)
Median age (range), years	67 (45-100)	68 (43-88)	69 (45-100)	69 (43-88)
ECOG PS, n (%), 0/1	69 (61.1)/44 (38.9)	80 (71.4)/32 (28.6)	130 (61.3)/82 (38.7)	146 (69.2)/65 (30.8)
Bone metastases, n (%)	99 (87.6)	93 (83.0)	183 (86.3)	170 (80.6)
Visceral metastases, n (%)	26 (23.0)	22 (19.6)	51 (24.1)	39 (18.5)
Liver	10 (8.8)	7 (6.3)	18 (8.5)	13 (6.2)
Lung	12 (10.6)	11 (9.8)	27 (12.7)	18 (8.5)
PSA at study entry (µg/l), median (range)	18.7 (0.1-2225.8)	14.1 (0.1-4400.0)	21.4 (0-4826.5)	17.4 (0.1-4400.0)
Prior taxane-based chemotherapy for nmCRPC/mCSPC, n (%)	26 (23.0)	29 (25.9)	41 (19.3)	44 (20.9)
Prior AR-targeted therapy for nmCRPC/mCSPC, n (%)	6 (5.3)	5 (4.5)	8 (3.8)	5 (2.4)
Prior AAP therapy for L1 mCRPC,[a] n (%)	30 (26.5)	29 (25.9)	50 (23.6)	48 (22.7)
Key laboratory values, median (range)				
Alkaline phosphatase enzyme, U/l	111.0 (36.0-5234.0)	97.0 (47.0-1892.0)	106.0 (36.0-5234.0)	100.0 (47.0-2651.0)
Hemoglobin, g/l	128.0 (64.0-160.0)	131.0 (75.0-161.0)	129.0 (64.0-172.0)	131.0 (75.0-161.0)
Lactate dehydrogenase enzyme, U/l	204.0 (98.0-2959.0)	197.0 (98.0-1530.0)	194.0 (84.0-645.0)	202.0 (131.0-758.0)

Chi et al. Annals of Oncology. 2023

rPFS significantly prolonged with NIRA + AAP



No OS benefit in HRR+ cohort

OS benefit in *BRCA* mutated cohort only by IPCW analysis

OS analysis immature

Chi et al. JCO 2023

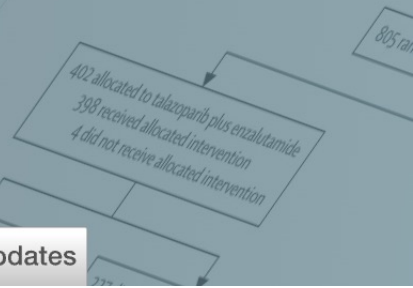
TALAPRO-2 (All-Comers)

THE LANCET

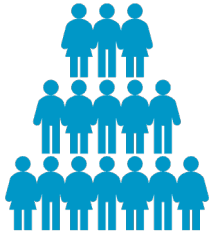
Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial

Prof Neeraj Agarwal, MD † • Arun A Azad, MBBS • Joan Carles, MD • Prof Andre P Fay, MD • Prof Nobuaki Matsubara, MD • Daniel Heinrich, MD • et al. Show all authors • Show footnotes

Published: June 04, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)01055-3 •



*Patients could have received docetaxel and/or abiraterone for mHSPC



805 patients
Metastatic
First Line CRPC

169 HRRm
636 HRR
unmutated/unknown

ADT

Enzalutamide Placebo

ADT

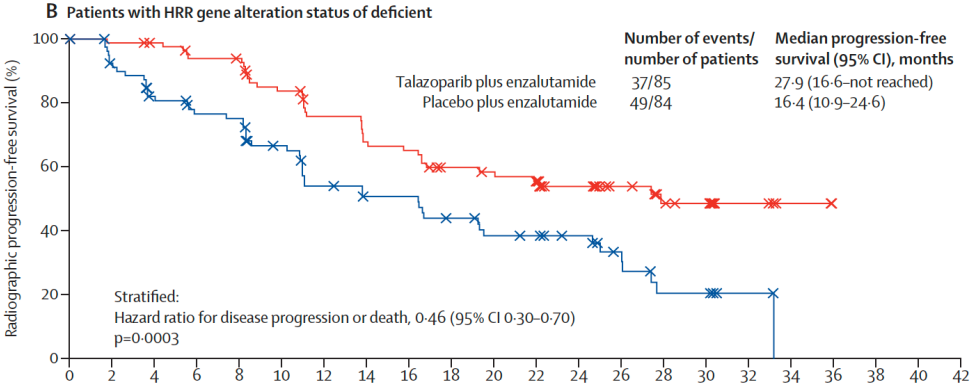
Enzalutamide Talazoparib 0.5 mg PO daily

Prospectively identified HRR- and HRR+ patients

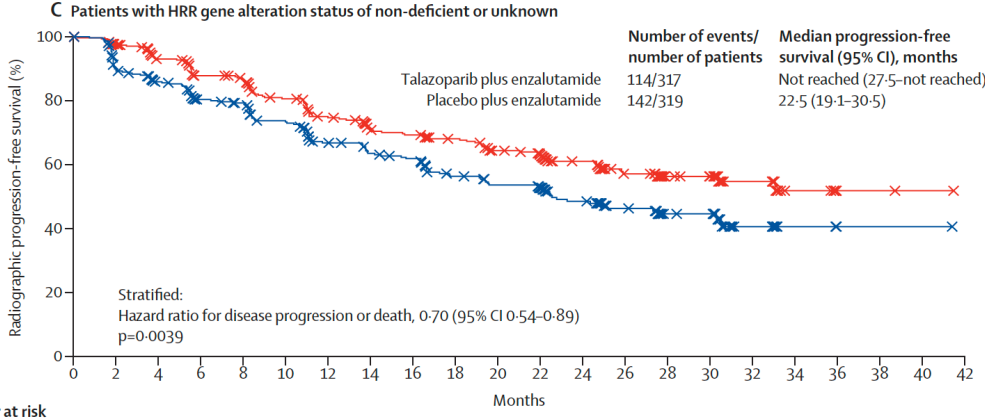
Agarwal et al. Lancet 2023

	Talazoparib plus enzalutamide (n=402)	Placebo plus enzalutamide (n=403)
Age, years	71 (66–76)	71 (65–76)
Race		
White	243 (60%)	255 (63%)
Black or African American	11 (3%)	5 (1%)
Asian	127 (32%)	120 (30%)
Multiracial	0	1 (<1%)
Other*	2 (<1%)	1 (<1%)
Not reported	19 (5%)	21 (5%)
Renal impairment†‡		
None or mild	344 (86%)	347 (86%)
Moderate	42 (10%)	41 (10%)
Baseline serum PSA, µg/L	18·2 (6·9–59·4)	16·2 (6·4–53·4)
Baseline circulating tumour cell count, cells per 7·5 mL of blood	1 (0–7)	1 (0–6)
Gleason score†		
<8	117 (29%)	113 (28%)
≥8	281 (70%)	283 (70%)
Disease site		
Bone (including with soft tissue component)	349 (87%)	342 (85%)
Lymph node	147 (37%)	167 (41%)
Visceral (lung)	45 (11%)	61 (15%)
Visceral (liver)	12 (3%)	16 (4%)
Other soft tissue	37 (9%)	33 (8%)
ECOG performance status		
0	259 (64%)	271 (67%)
1	143 (36%)	132 (33%)
Previous taxane-based chemotherapy§	86 (21%)	93 (23%)
Previous treatment with novel hormonal therapy	23 (6%)	27 (7%)
Abiraterone	21 (5%)	25 (6%)
Orteronel	2 (<1%)	2 (<1%)
HRR gene alteration status by randomisation stratification		
Deficient	85 (21%)	84 (21%)
Non-deficient or unknown	317 (79%)	319 (79%)
HRR gene alteration status by prospective tumour tissue testing¶		
Deficient	85 (21%)	82 (20%)
Non-deficient	207 (51%)	219 (54%)
Unknown	110 (27%)	102 (25%)
BRCA1/2 alteration	27 (7%)	32 (8%)

Agarwal et al. Lancet 2023



Number at risk (number censored)																						
Talazoparib plus enzalutamide	85	83	81	76	75	65	57	51	49	42	40	37	30	23	17	15	6	3	0	..	..	..
	(0)	(1)	(3)	(4)	(5)	(7)	(9)	(9)	(9)	(12)	(13)	(14)	(20)	(27)	(31)	(33)	(42)	(45)	(48)			
Placebo plus enzalutamide	84	72	61	55	54	43	34	30	30	25	21	20	17	11	6	6	2	0	0	..	..	..
	(0)	(6)	(9)	(11)	(11)	(16)	(17)	(19)	(19)	(20)	(21)	(22)	(25)	(29)	(30)	(30)	(34)	(35)	(35)			



Number at risk (number censored)																						
Talazoparib plus enzalutamide	317	296	272	250	243	220	199	183	177	167	153	138	106	74	50	46	23	10	2	2	1	0
	(0)	(13)	(24)	(31)	(34)	(41)	(46)	(53)	(54)	(61)	(66)	(78)	(106)	(132)	(155)	(159)	(181)	(193)	(201)	(201)	(202)	(203)
Placebo plus enzalutamide	319	274	250	224	218	194	166	155	149	129	119	104	79	57	37	36	12	3	1	1	1	0
	(0)	(14)	(26)	(36)	(39)	(47)	(58)	(61)	(63)	(70)	(74)	(87)	(105)	(124)	(142)	(143)	(165)	(174)	(176)	(176)	(176)	(177)

Agarwal et al. Lancet 2023

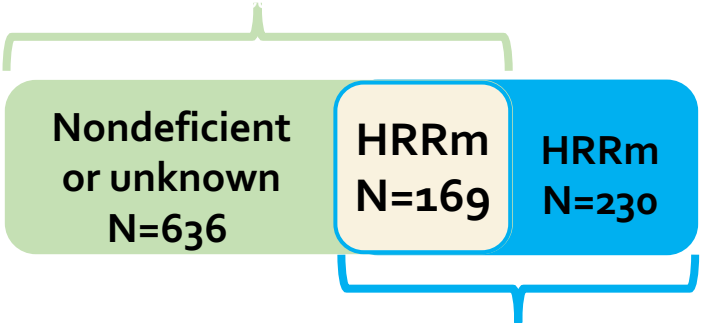
	Talazoparib plus enzalutamide (n=398)		Placebo plus enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any adverse event	392 (98%)	299 (75%)	379 (95%)	181 (45%)
Treatment-related adverse event	357 (90%)	234 (59%)	279 (70%)	71 (18%)
Serious adverse event	157 (39%)	145 (36%)	107 (27%)	94 (23%)
Serious and treatment-related adverse event	78 (20%)	68 (17%)	12 (3%)	11 (3%)
Adverse event resulting in dose interruption of:				
Talazoparib or placebo*	247 (62%)	..	84 (21%)	..
Enzalutamide†	156 (39%)	..	78 (19%)	..
Adverse event resulting in dose reduction of:				
Talazoparib or placebo*	210 (53%)	..	27 (7%)	..
Enzalutamide†	58 (15%)	..	32 (8%)	..
Adverse event resulting in permanent drug discontinuation of:				
Talazoparib or placebo*	75 (19%)	..	49 (12%)	..
Enzalutamide†	43 (11%)	..	44 (11%)	..
Grade 5 adverse event	13 (3%)‡	..	18 (4%)§	..
Most common adverse events (all grades in ≥10% of patients)¶				
Anaemia	262 (66%)	185 (46%)	70 (17%)	17 (4%)
Neutropenia	142 (36%)	73 (18%)	28 (7%)	6 (1%)
Fatigue	134 (34%)	16 (4%)	118 (29%)	8 (2%)
Thrombocytopenia	98 (25%)	29 (7%)	14 (3%)	4 (1%)
Back pain	88 (22%)	10 (3%)	72 (18%)	4 (1%)
Leukopenia	88 (22%)	25 (6%)	18 (4%)	0
Decreased appetite	86 (22%)	5 (1%)	63 (16%)	4 (1%)
Nausea	82 (21%)	2 (<1%)	50 (12%)	3 (<1%)
Constipation	72 (18%)	1 (<1%)	68 (17%)	2 (<1%)
Fall	71 (18%)	9 (2%)	59 (15%)	8 (2%)
Arthralgia	58 (15%)	2 (<1%)	79 (20%)	2 (<1%)
Asthenia	57 (14%)	11 (3%)	38 (9%)	3 (<1%)
Diarrhoea	57 (14%)	1 (<1%)	55 (14%)	0
Hypertension	55 (14%)	21 (5%)	62 (15%)	30 (7%)
Dizziness	48 (12%)	4 (1%)	23 (6%)‖	2 (<1%)
Hot flush	47 (12%)	0	53 (13%)‖	0
Lymphopenia	45 (11%)	20 (5%)	20 (5%)	4 (1%)
Oedema peripheral	42 (11%)	0	23 (6%)‖	0
Dyspnoea	41 (10%)	2 (<1%)	25 (6%)	1 (<1%)
Decreased weight	40 (10%)	2 (<1%)	33 (8%)	3 (<1%)

Agarwal et al. Lancet 2023

TALAPRO-2 (HRR-Mutated)

Presented at ASCO 2023 by Dr Karim Fizazi

All-comers (Cohort 1), N=805



HRRm only (Cohort 2), N=399

Recruitment continued after completion of enrollment in cohort 1, data cutoff: October 3, 2022

Overall Survival (24% immaturity)

Talazoparib + Enzalutamide: NR (36.4mos-NR)

Talazoparib + Placebo: 33.7mos (27.6-NR)

HR 0.69 (95% CI, 0.46-1.03), P=0.068

Subset analysis: benefit primarily seen in BRCA and CDK12 cluster (not ATM)

TALAPRO-2: Conclusions

In patients with mCRPC with HRR gene alterations, talazoparib plus enzalutamide resulted in a statistically significant and clinically meaningful improvement in the primary endpoint, rPFS by BICR, over placebo plus enzalutamide

Benefits seem to be greatest in ***BRCA2*** mutated population

Unanswered questions- synergy vs. sequential?, efficacy in non-HRR mutated prostate cancer, applicability in setting of NHT in first-line therapy

FDA approves talazoparib with enzalutamide for HRR gene-mutated metastatic castration-resistant prostate cancer

FDA D.I.S.C.O. Burst Edition: FDA approval of (olaparib), with abiraterone and prednisone, for BRCA-mutated metastatic castration-resistant prostate cancer

FDA approves niraparib and abiraterone acetate plus prednisone for BRCA-mutated metastatic castration-resistant prostate cancer

PARPi Combination Takeaways

rPFS Benefit of combination therapy seems clear in *BRCA+* patients, but sequence question not answered

Uncertain role in patients who received Abi/Enza in HSPC

Uncertain role in patients without HRR mutations

Phase II trial of veliparib/abiraterone without benefit in unselected mCRPC. Niraprib/abiraterone negative.

Differences in PARP trapping?

PARPi dosing?