How Do I Treat Metastatic Prostate Cancer after ASCO 2023
July 29, 2023

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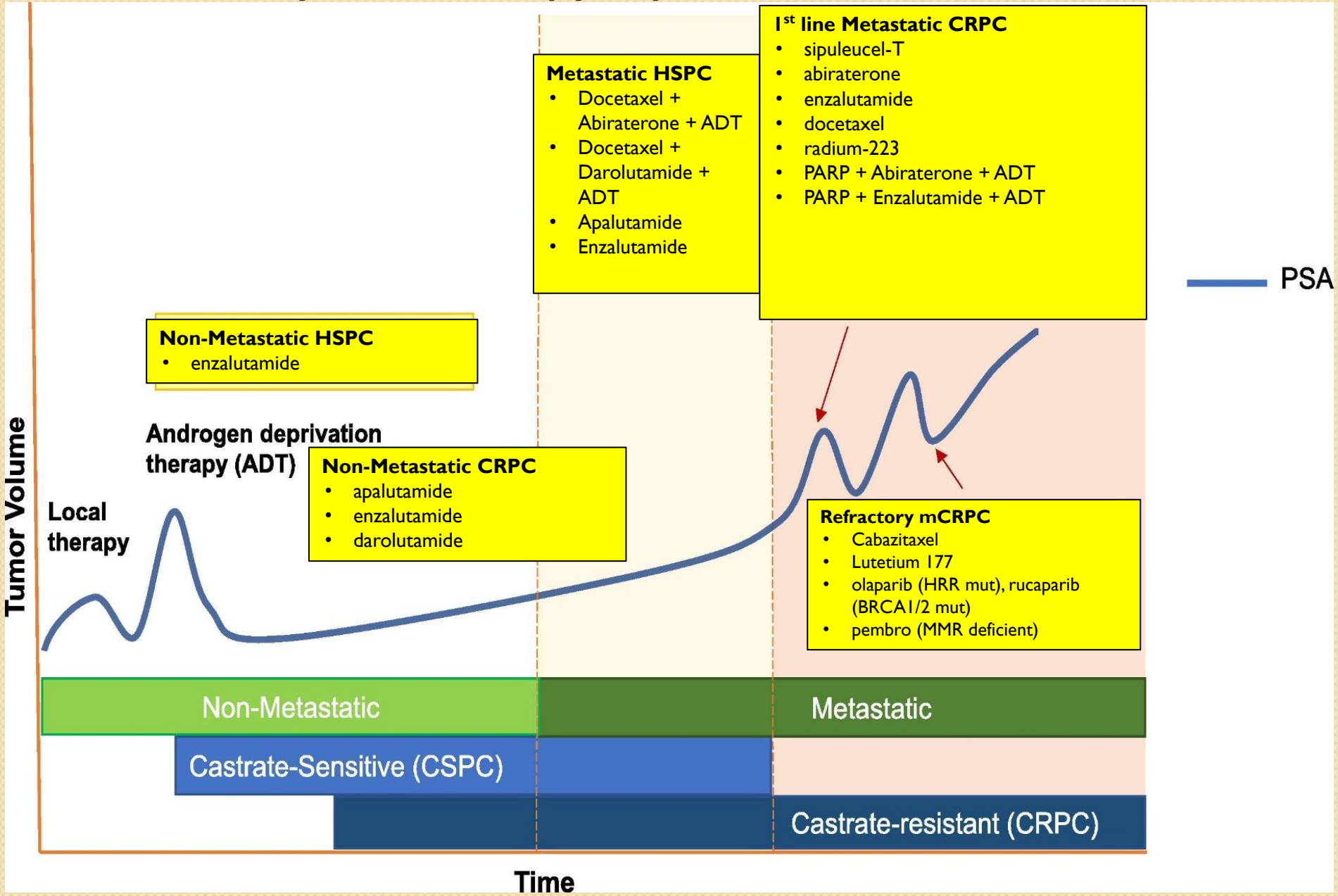
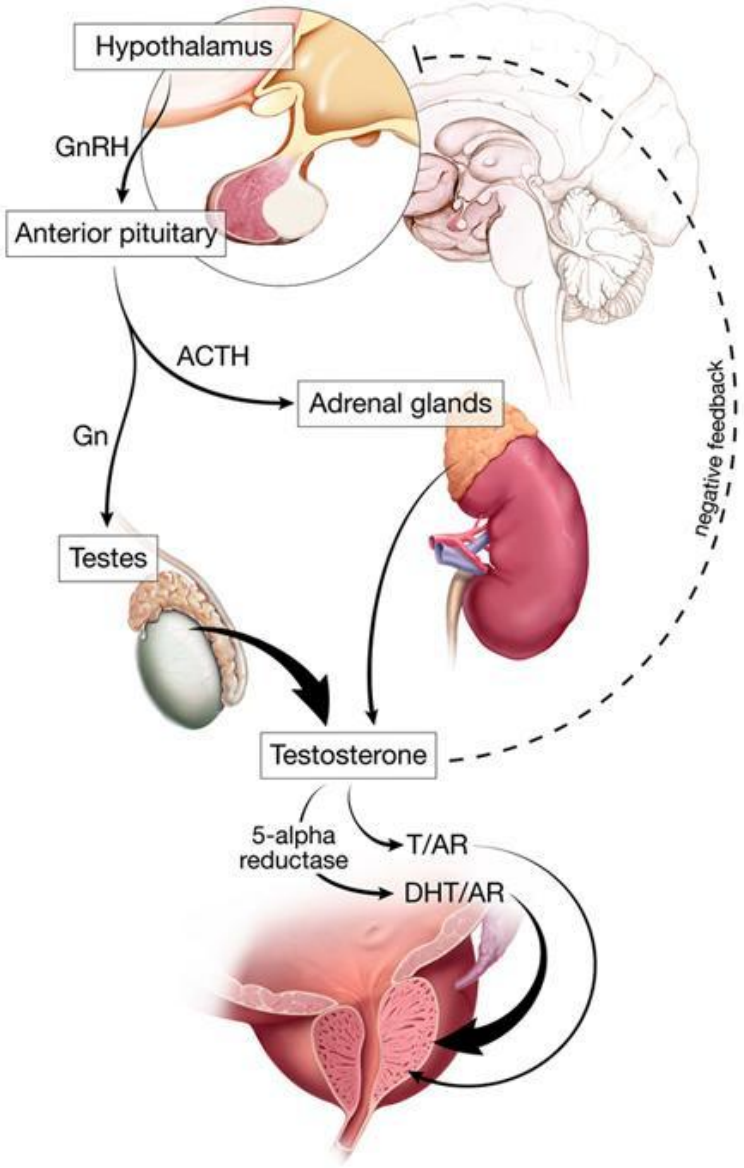
NORTON CANCER INSTITUTE

Systemic therapy of prostate cancer 2023



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

Prostate Cancer Axis

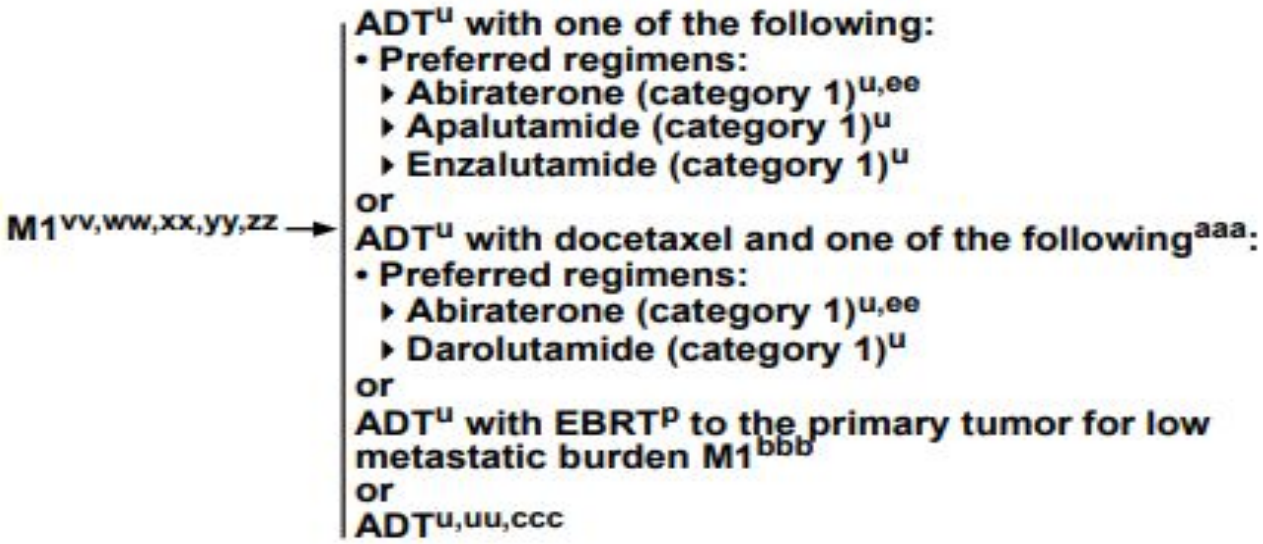


- **Testosterone**

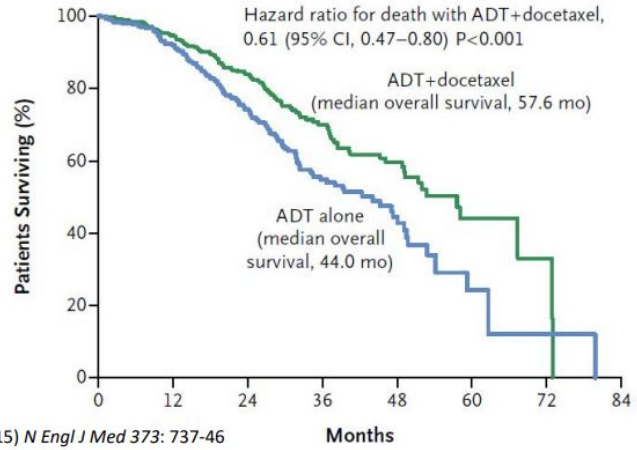
1. **GnRH pathway**
2. **Adrenal Gland**
3. **Testis**
4. **Prostate Cancer**

Metastatic Hormone Sensitive Prostate Cancer

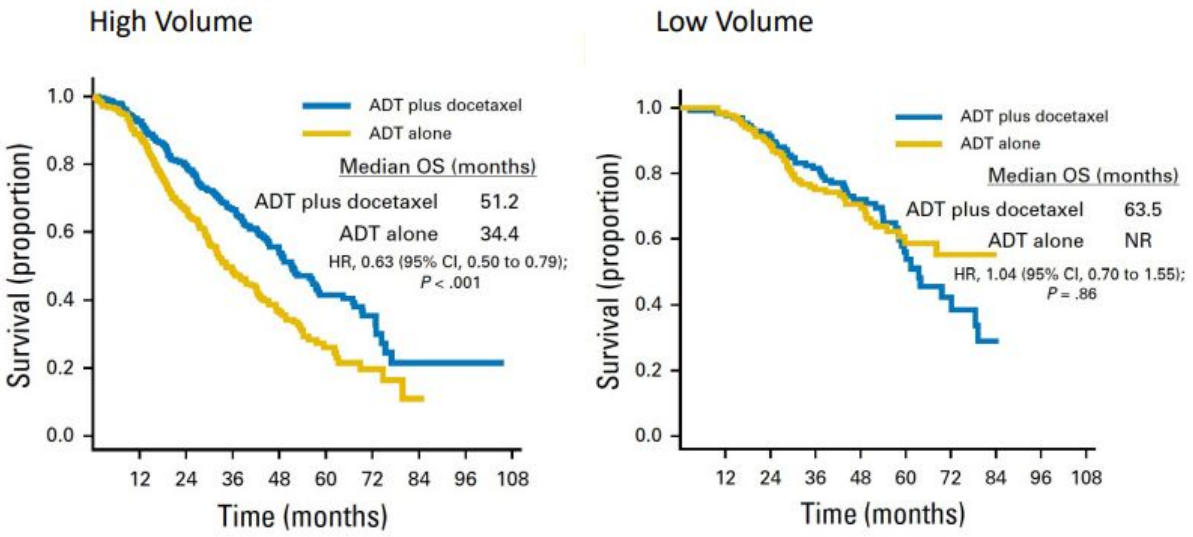
- Clinical Problem
- Triplet vs Doublet Treatment
- NCCN Guidelines 1.2023



Historical Data: CHAARTED Study



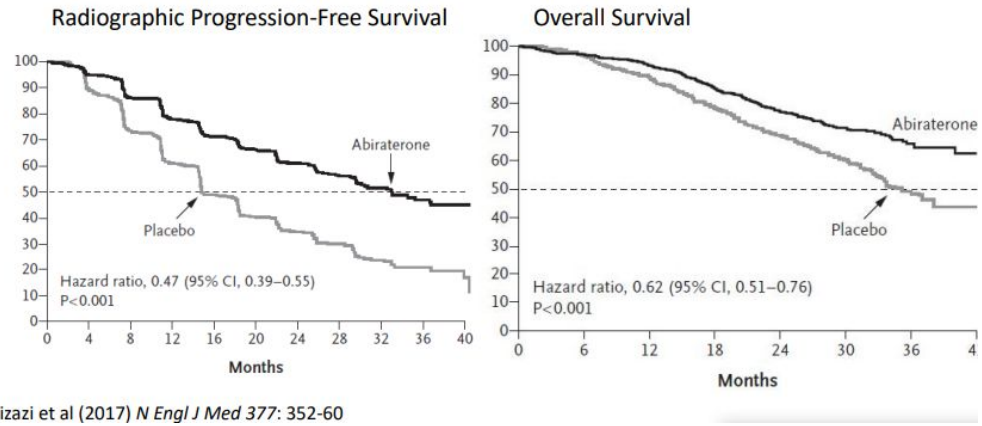
Sweeney et al (2015) *N Engl J Med 373*: 737-46



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

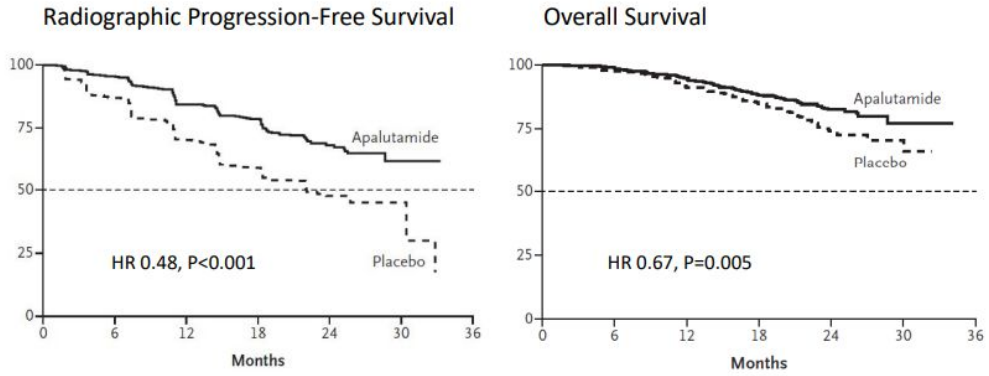
Androgen Pathway Inhibitors

LATITUDE: Abiraterone Acetate for mHSPC



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

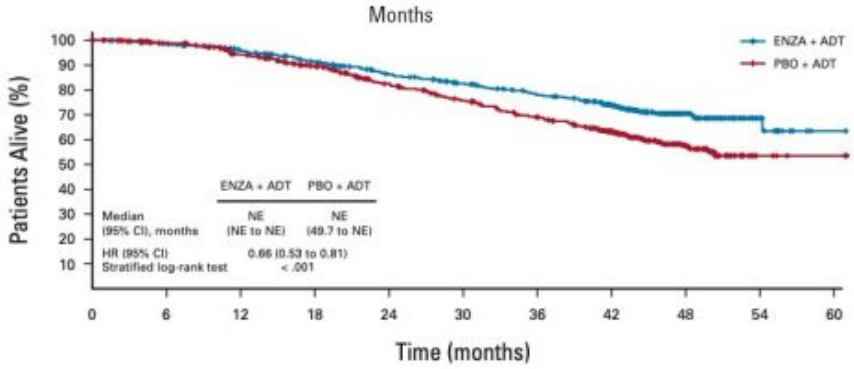
TITAN: Apalutamide for mHSPC



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

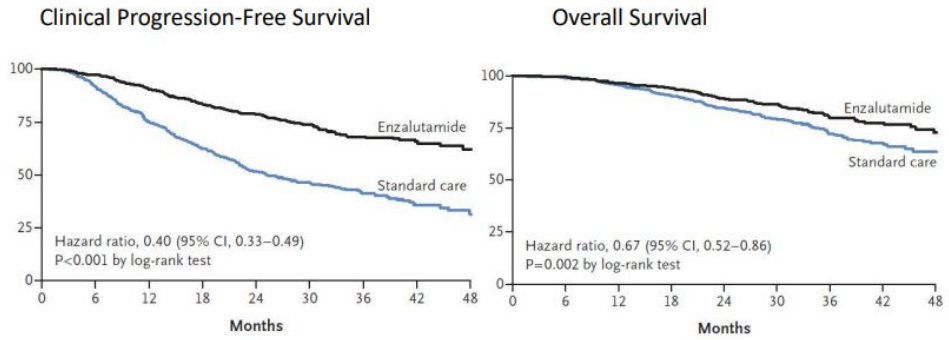
ARCHES and ENZAMET

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

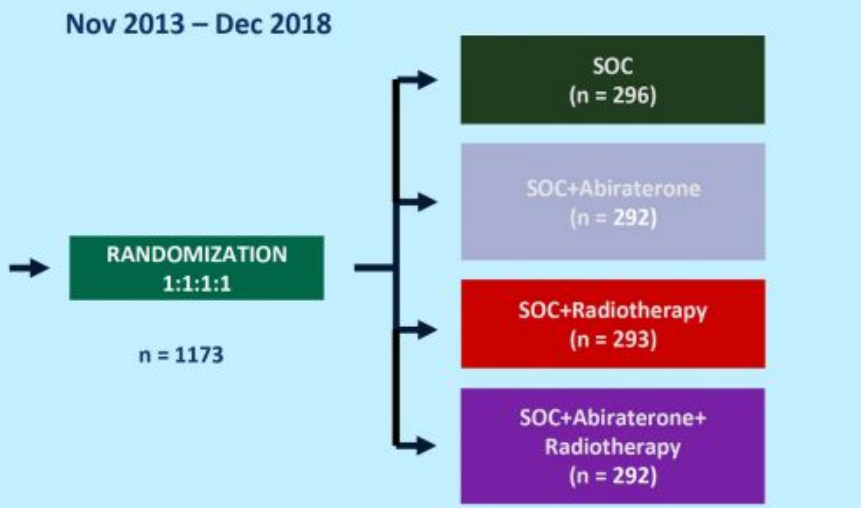
PEACE -1

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

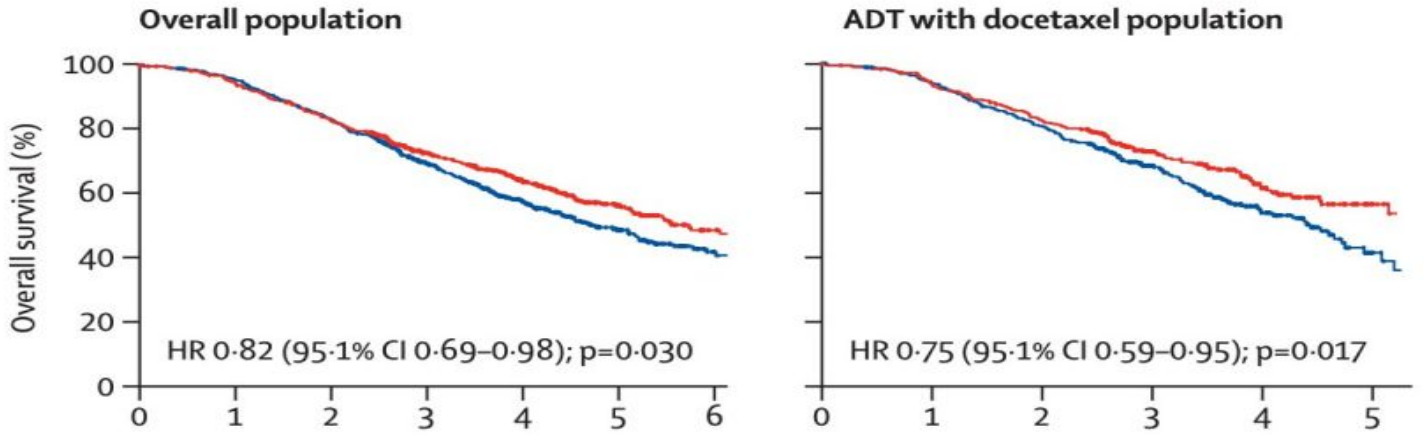
On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status



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

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2023 ASCO ANNUAL MEETING
PEACE
Prostate Cancer Consortium Europe
Prostate irradiation in men with *de novo*, low-volume, metastatic castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design
Alberto BOSSI,
Institut Gustave Roussy, Amethyst RT Group, France
Stéphanie Foulon, Xavier Maldonado, Paul Sargos, Ray McDermott, Paul Kelly, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Naji Salem, Fabio Calabro', Jean-François Berdah, Ali Hasbini, Marlon Silva, Jihane Boustani, Hélène Ribault, Karim Fizazi
2023 ASCO ANNUAL MEETING
#ASCO23
PRESENTED BY: Alberto Bossi
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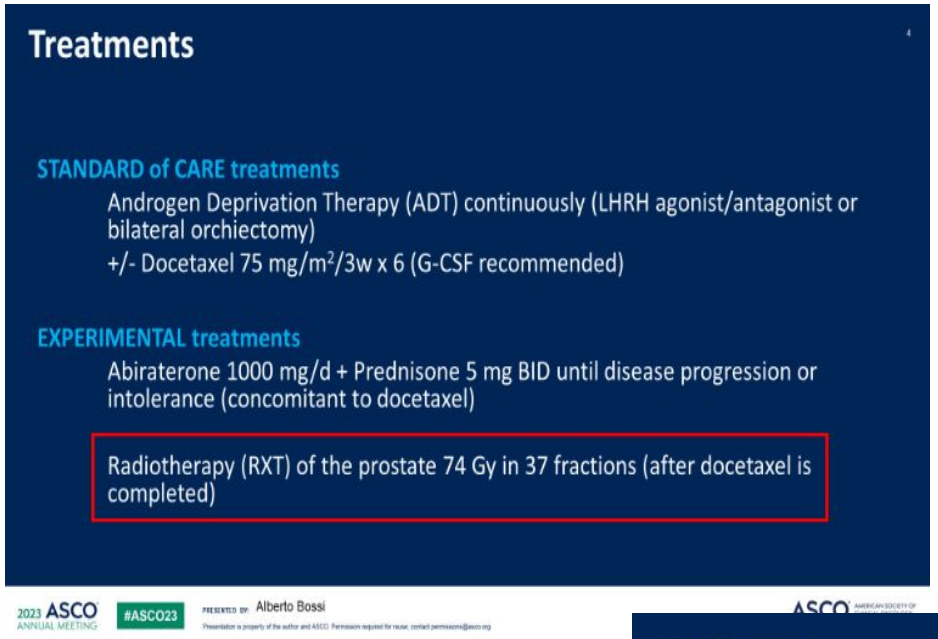
Treatments
STANDARD of CARE treatments
Androgen Deprivation Therapy (ADT) continuously (LHRH agonist/antagonist or bilateral orchiectomy)
+/- Docetaxel 75 mg/m²/3w x 6 (G-CSF recommended)
EXPERIMENTAL treatments
Abiraterone 1000 mg/d + Prednisone 5 mg BID until disease progression or intolerance (concomitant to docetaxel)
Radiotherapy (RXT) of the prostate 74 Gy in 37 fractions (after docetaxel is completed)
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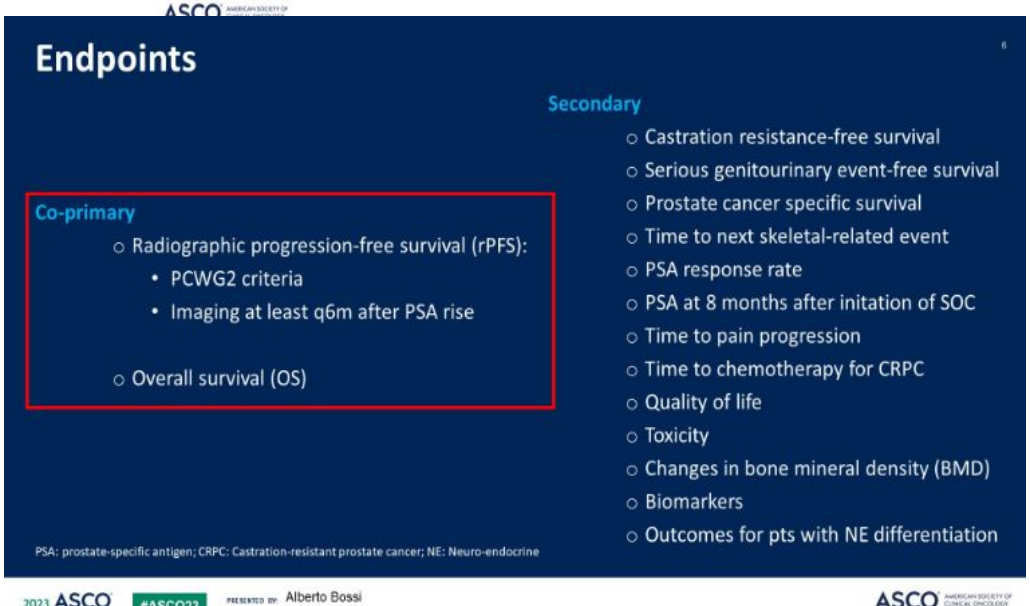
Endpoints
Co-primary
Radiographic progression-free survival (rPFS):
PCWG2 criteria
Imaging at least q6m after PSA rise
Overall survival (OS)
Secondary
Castration resistance-free survival
Serious genitourinary event-free survival
Prostate cancer specific survival
Time to next skeletal-related event
PSA response rate
PSA at 8 months after initation of SOC
Time to pain progression
Time to chemotherapy for CRPC
Quality of life
Toxicity
Changes in bone mineral density (BMD)
Biomarkers
Outcomes for pts with NE differentiation
PSA: prostate-specific antigen; CRPC: Castration-resistant prostate cancer; NE: Neuro-endocrine
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Patients' characteristics (overall population)

		SOC (+/- Abi) (n = 588)	SOC (+/- Abi) + Radiotherapy (n = 584)
Median age, year (Min-Max)		67 (43–88)	66 (37–94)
ECOG PS score, n (%)	0 1-2	411 (70) 177 (30)	413 (71) 171 (29)
Gleason score at diagnosis, n (%)	≤ 7 ≥ 8 Missing	142 (23) 429 (74) 17 (3)	136 (24) 441 (75) 7 (1)
Median time from diagnosis, month (IQR)		2.2 (1.5-3.1)	2.3 (1.5-3.2)
Metastatic sites, n (%)	Lymph nodes only Bone only Visceral	51 (9) 474 (81) 63 (11)	48 (8) 473 (81) 63 (11)
Disease volume, n (%)	Low High	253 (43) 335 (57)	252 (43) 332 (57)
Median baseline PSA, ng/mL (IQR)		13.1 (3.5-57.1)	12.6 (3-62.4)
Docetaxel, n (%)	Yes No	355 (60) 233 (40)	355 (61) 229 (39)

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Patients' characteristics (low volume population)

		SOC (+/- Abi) (n = 253)	SOC (+/- Abi) + Radiotherapy (n = 252)
Median age, year (Min-Max)		67 (43–86)	66 (46–84)
ECOG PS score, n (%)	0 1-2	180 (71) 73 (29)	194 (77) 58 (23)
Gleason score at diagnosis, n (%)	≤ 7 ≥ 8 Missing	71 (27) 173 (70) 9 (3)	66 (26) 184 (73) 2 (1)
Median time from diagnosis, month (IQR)		2.5 (1.8-3.4)	2.6 (1.7-3.5)
Metastatic sites, n (%)	Lymph nodes only Bone only	47 (19) 206 (81)	41 (16) 211 (84)
Median baseline PSA, ng/mL (IQR)		10.3 (3.3-31)	9 (2.3-39.1)
Docetaxel, n (%)	Yes No	127 (50) 126 (50)	127 (50) 125 (50)

median follow-up : 73 months

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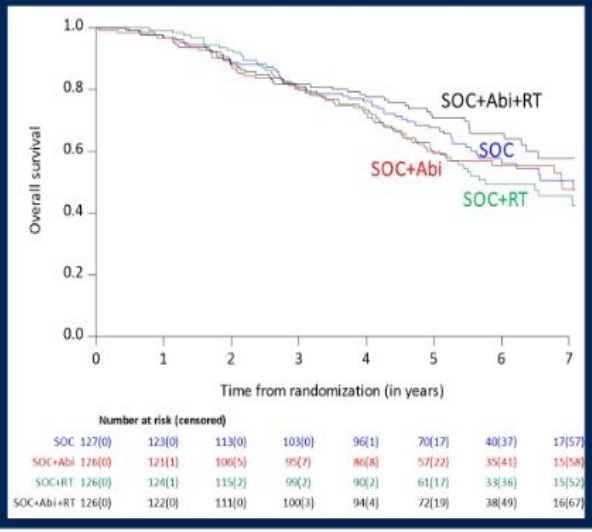
OS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (95.1% CI)	7.1 (5.6-NE)	5.8 (5.1-NE)	6.9 (5.0-NE)	NE (6.4-NE)
Events, n.	57	60	54	44
HR (95.1% CI)*	Ref	1.19 (0.82-1.72)	1.05 (0.72-1.54)	0.81 (0.55-1.21
Global p-value	0.29			
HR (95.1% CI)*	Ref	1.18 (0.81-1.71)	Ref	0.77 (0.51-1.16)
P-values arms w/wo Abi	0.39		0.21	

*Adjusted on Abiraterone and stratification factors (PS, type of castration, docetaxel)

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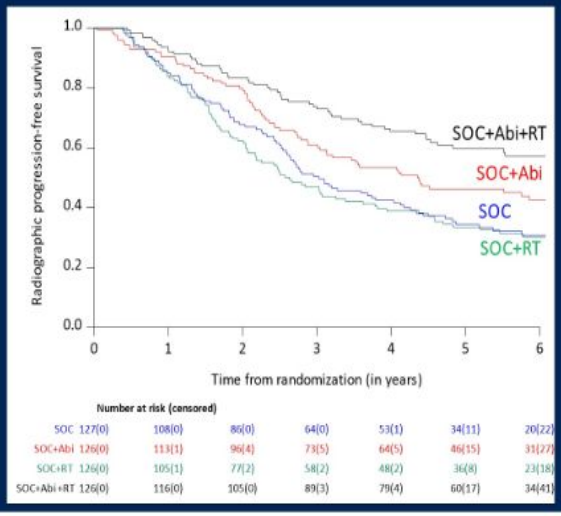
rPFS (low volume population)



	SOC (n=127)	SOC+RT (n=126)	SOC+Abi (n=126)	SOC+Abi+RT (n=126)
Median, ys. (99.9% CI)	3.0 (2.3-4.8)	2.6 (1.7-4.6)	4.4 (2.5-7.3)	7.5 (4,0-NE)
Events, n.	87	89	74	55
HR (99.9%CI)*	Ref	1.11 (0.67-1.84)	0.76 (0.45-1,28)	0.50 (0.28-0.88)
Global p-value	<0.0001			
HR (99.9% CI)*	Ref	1.08 (0.65-1.80)	Ref	0.65 (0.36-1.19)
P-values arms w/wo Abi	0.61		0.02	

*Adjusted on stratification factors (PS, type of castration, docetaxel)

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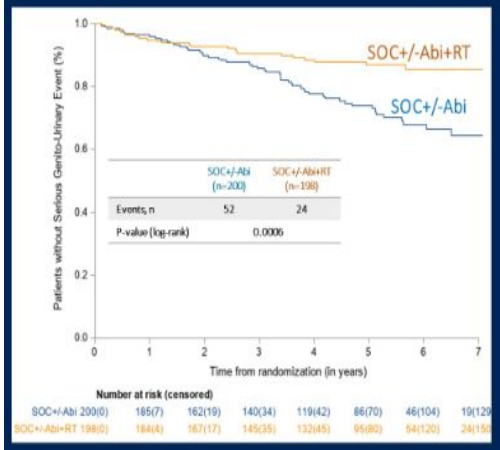
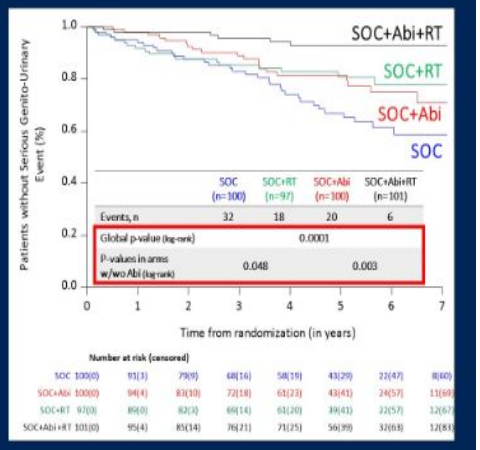
Time to Serious Genito-Urinary events (low volume pop.)





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Serious Genito-Urinary events (low volume population*)

	No RT (n=200)	RT (n=198)
Urinary Catheter	9	6
Double J Stent	13	12
Nephrostomy	2	1
Prostate RT or TURP	27	4 TURP (all RT)
Radical Prostatectomy	1	1

*with available data regarding Serious Genito-Urinary events

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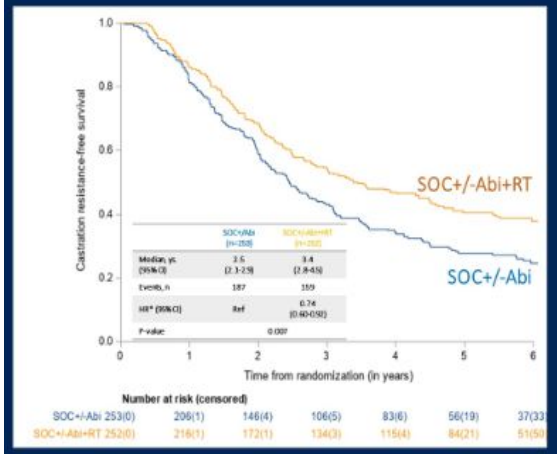
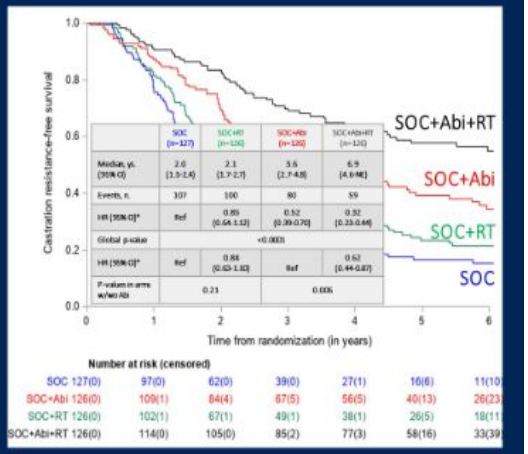
Castration Resistance Free-Survival (low volume pop.)





interaction p-value = 0.15

*Adjusted on abiraterone and stratification factors (PS, type of castration, docetaxel)

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Toxicity, Grade 3-5 (overall safety population*)

	SOC+/-Abi (n=604)	SOC+/-Abi+RT* (n=560)
	n (%)	n (%)
Hypertension	110 (18)	127 (23)
Neutropenia	40 (7)	29 (5)
Febrile neutropenia	20 (3)	19 (3)
Hepatotoxicity	22 (4)	18 (3)
Fatigue	17 (3)	12 (2)
Gastro-Intestinal disorders	29 (5)	17 (3)
Rectal Haemorrhage	0 (0)	5 (1)

*Safety population: patients who received any part of study treatment, according to study treatments actually received

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Conclusions

- Combining prostate RT with intensified systemic treatment (Abiraterone w/wt docetaxel) improves rPFS and CRPC free-survival in men with low burden, *de-novo* mCSPC.
- No detectable impact of prostate RT on OS, minimal added toxicity.
- For the first time, PEACE-1 also establishes a role of RT in the prevention of serious GU events, irrespective of the metastatic burden.
- A triplet of ADT+Abiraterone+prostate RT should be considered a standard in men with *de-novo* low burden mCSPC (additive effect). RT may also be considered in selected men with *de-novo* high burden mCSPC ("quadruplet").

Practice Confirming

- My practice based on PEACE-1 study
- Metastatic hormone sensitive prostate cancer based on STAMPEDE trial. Radiation to primary prostate cancer showed overall survival.
- Peace-1 may not have shown overall survival however decreased GU events such as hydronephrosis, TURBT etc

ARASENS Study (Triplet)

ASCO Genitourinary Cancers Symposium

Overall survival with darolutamide versus placebo in combination with androgen-deprivation therapy and docetaxel for metastatic hormone-sensitive prostate cancer in the phase 3 ARASENS trial

Matthew R. Smith, MD, PhD,[1] Maha Hussain, MD,[2] Fred Saad, MD,[3] Karim Fizazi, MD, PhD,[4] Cora N. Sternberg, MD,[5] E. David Crawford, MD,[6] Evgeny Kopyltsov, MD,[7] Chandler H. Park, MD,[8] Boris Alekseev, MD,[9] Álvaro Montesa Pino, MD,[10] Dingwei Ye, MD,[11] Francis Parnis, MB, BS,[12] Felipe Melo Cruz, MD,[13] Teuvo L.J. Tammela, MD, PhD,[14] Hiroyoshi Suzuki, MD, PhD,[15] Heikki Joensuu, MD,[16] Silke Thiele, MD,[17] Rui Li, MS,[18] Iris Kuss, MD,[17] Bertrand Tombal, MD, PhD[19]

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL; [3]University of Montreal Hospital Center, Montreal, Quebec, Canada; [4]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [5]Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY; [6]UC San Diego School of Medicine, San Diego, CA; [7]Clinical Oncological Dispensary of Omsk Region, Omsk, Russian Federation; [8]Norton Cancer Institute, Louisville, KY; [9]P. Hertsen Moscow Oncology Research Institute, Moscow, Russian Federation; [10]UGC Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen Victoria, IBIMA, Málaga, Spain; [11]Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China; [12]Ashford Cancer Centre Research, Kurralta Park, SA, Australia; [13]Núcleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; [14]Tampere University Hospital, Tampere, Finland; [15]Toho University Sakura Medical Center, Chiba, Japan; [16]Orion Corporation Orion Pharma, Espoo, Finland; [17]Bayer AG, Berlin, Germany; [18]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA; [19]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

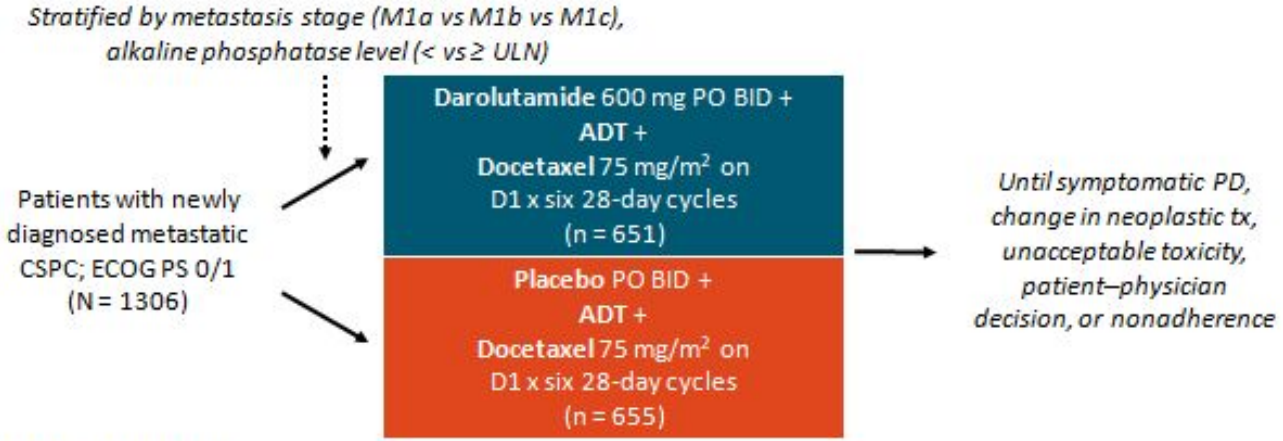
Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, 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

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

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

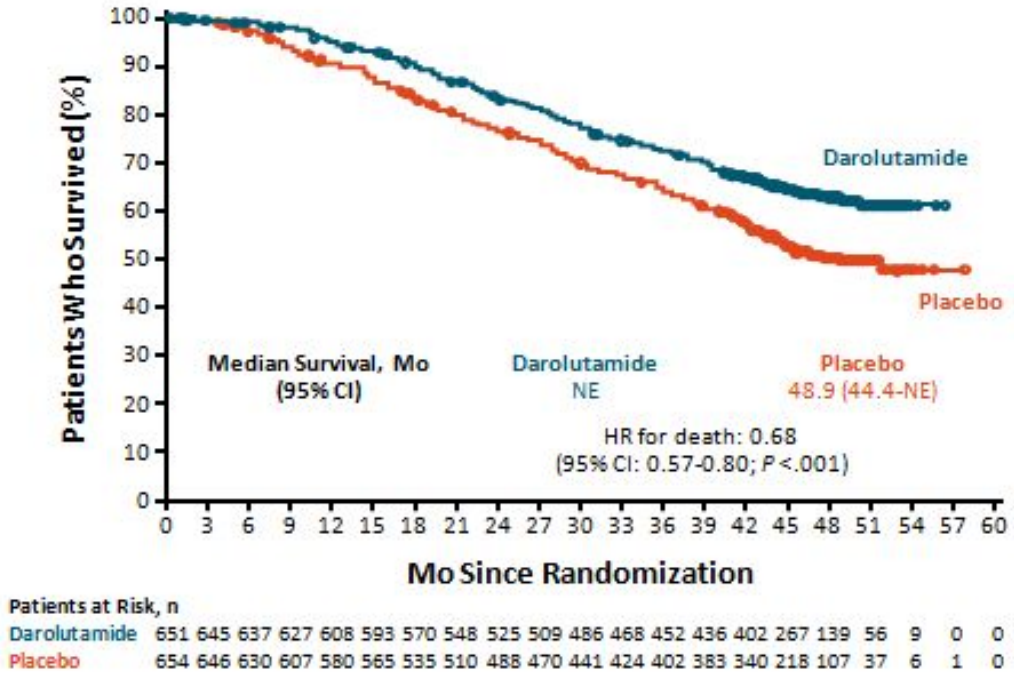


- **Primary endpoint:** OS
- **Secondary endpoints tested hierarchically in this order:** time to CRPC, time to pain progression, SSE-free survival, time to first SSE, time to initiation of subsequent anticancer therapy, time to worsening of physical symptoms, time to first opioid use, safety

Smith. NEJM. 2022;[Epub]. Smith. ASCO GU 2022. Abstr 13. NCT02799602.

Overall Survival

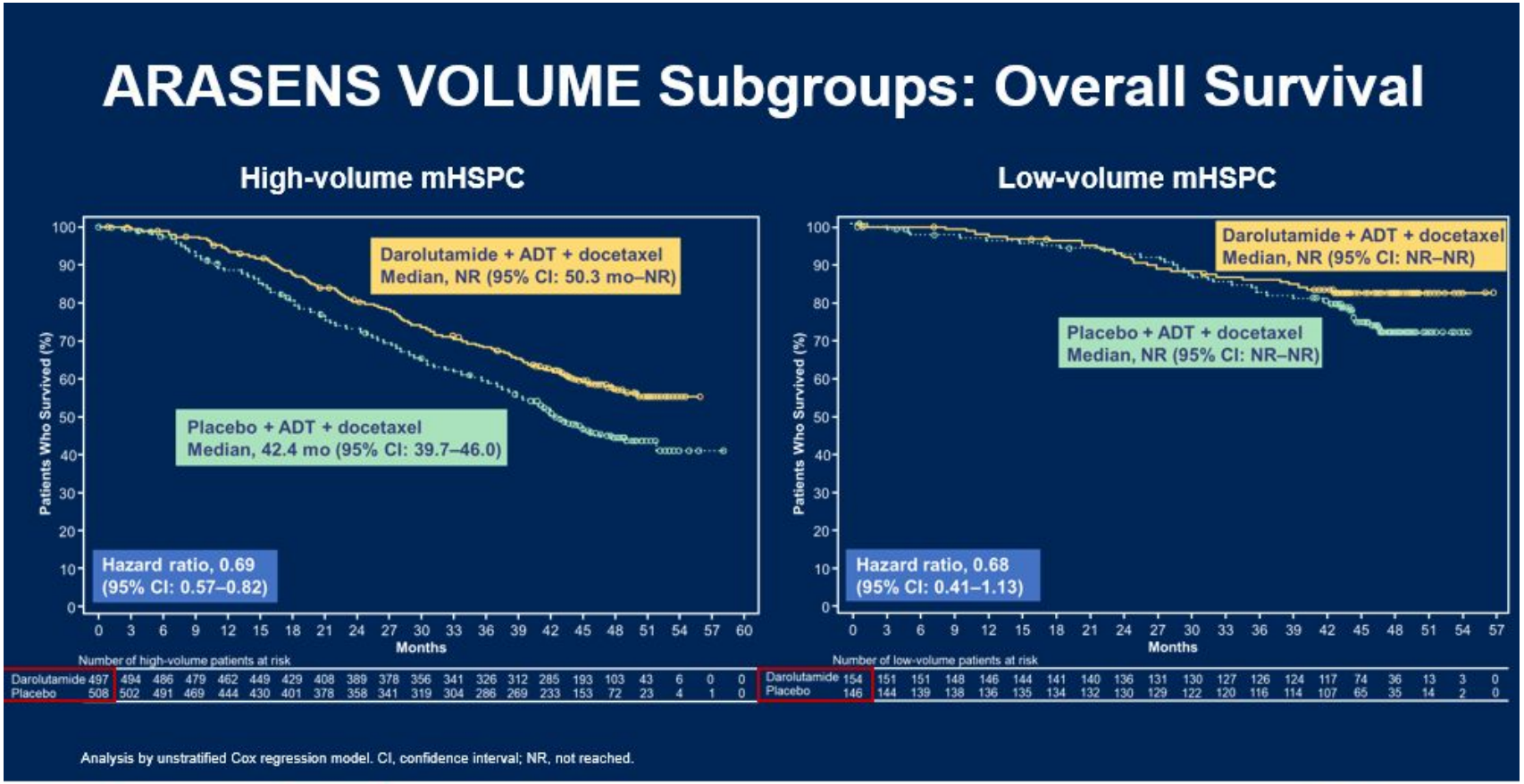
ARASENS: OS (Primary Endpoint)



- 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)

Smith. NEJM. March 2023

ASCO GU 2023 Update



ASCO Genitourinary Cancers Symposium #GU23 PRESENTED BY: Maha Hussain, MD, FACP, FASCO

Courtesy of Maha Hussain, MD, FACP, FASCO

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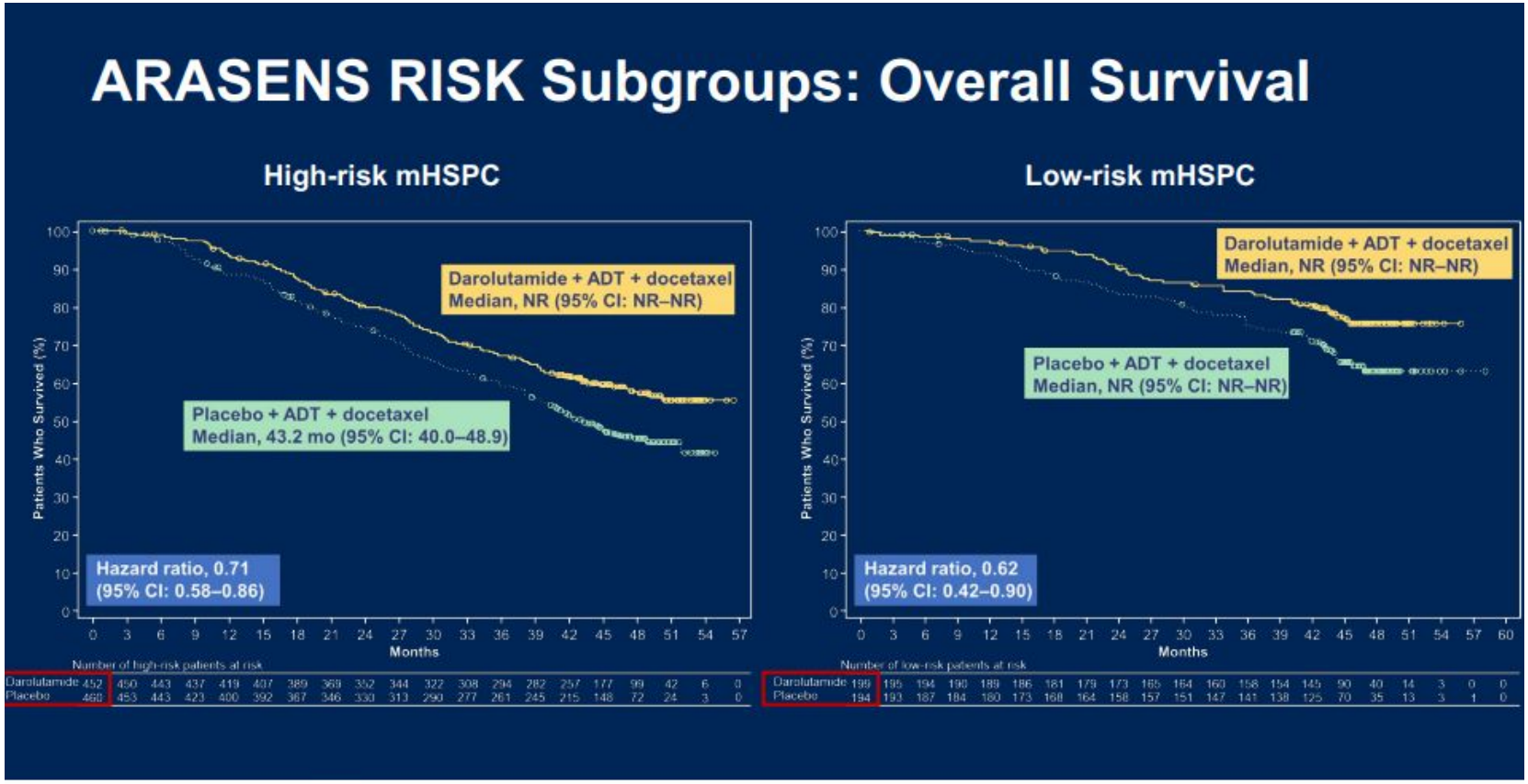
ASCO GU 2023 Update



ASCO Genitourinary Cancers Symposium #GU23

PRESENTED BY: Maha Hussain, MD

How do you decide?
Triplet vs Doublet

Prostate Cancer Classification

High Volume

- Visceral
- Greater than 3 bone lesions with 1 extra-axial

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

Relapsing after previous RP or RT with ≥1 of:

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

High Risk

Gleason 8-10

At least 3 bone lesion

Measurable visceral lesions

All patients

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Full criteria

www.stampedetrial.org

Synchronous vs Metachronous Prostate Cancer

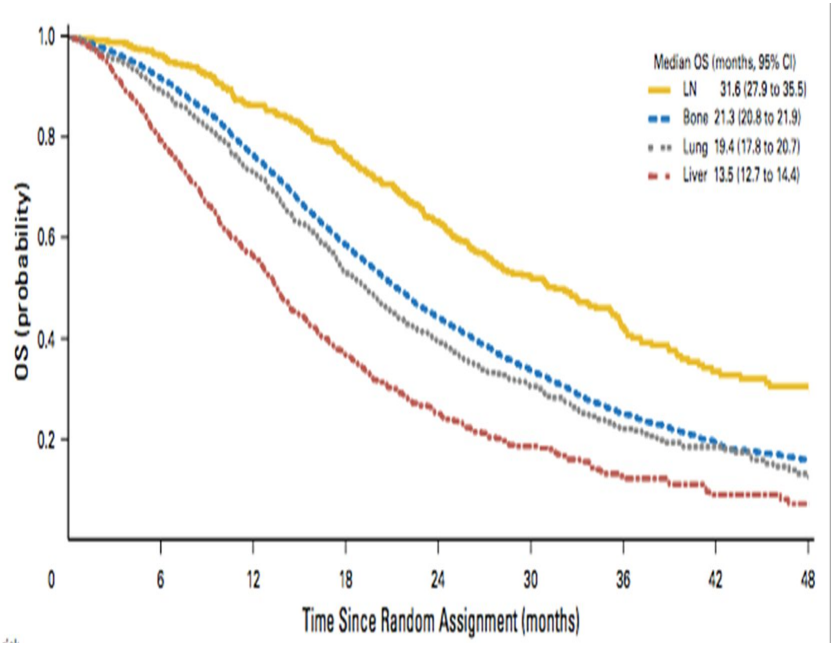
Synchronous

- Patients diagnosed with a primary prostate cancer and metastases simultaneously

Metachronous

- Patients diagnosed with nonmetastatic disease at initial diagnosis and develop metastases during follow up

Staging prognostication



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

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

My Practice

Synchronous High Volume **AR Pathway inhibitor, Docetaxel, and ADT**	**Metachronous High Volume** **Darolutamide, Docetaxel, and ADT**
Synchronous Low Volume (exceptions) **Darolutamdie, Docetaxel, and ADT (p53, RB1, PTEN, BRCA Liver Mets)**	**Metachronous Low Volume** **AR Pathway Inhibitor and ADT**

NCCN guidelines mCRPC 1.2023

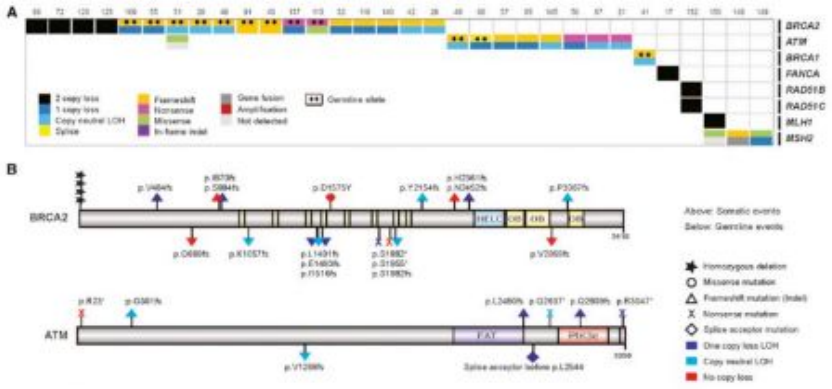
SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm] • Preferred regimens ▸ Abiraterone[u,nnn] (category 1[ooo]) ▸ Docetaxel[fff,ppp] (category 1) ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,qqq] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[u]	**Prior novel hormone therapy/no prior docetaxel[mmm,sss]** • Preferred regimens ▸ Docetaxel (category 1)[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Olaparib for HRRm (category 1)[ttt] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCA mutation[uuu] ▸ Sipuleucel-T[fff,qqq] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Abiraterone + dexamethasone[nnn,vvv] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]
Prior docetaxel/no prior novel hormone therapy[mmm] • Preferred regimens ▸ Abiraterone[u,nnn] (category 1) ▸ Cabazitaxel[fff] ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,qqq] • Other recommended regimens ▸ Other secondary hormone therapy[u]	**Prior docetaxel and prior novel hormone therapy[mmm,sss]** • Useful in certain circumstances ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[www] (The following systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▸ Cabazitaxel[fff] (category 1[ooo]) ▸ Docetaxel rechallenge[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Olaparib for HRRm (category 1[ooo])[ttt] ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1[ooo]) ▸ Rucaparib for BRCA mutation[uuu] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]

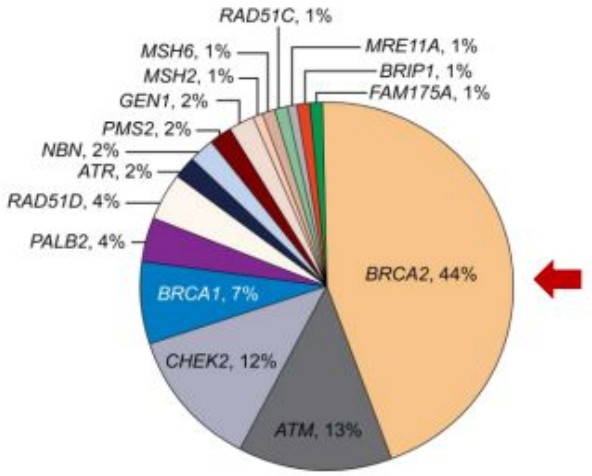
Prostate cancer genetics

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**



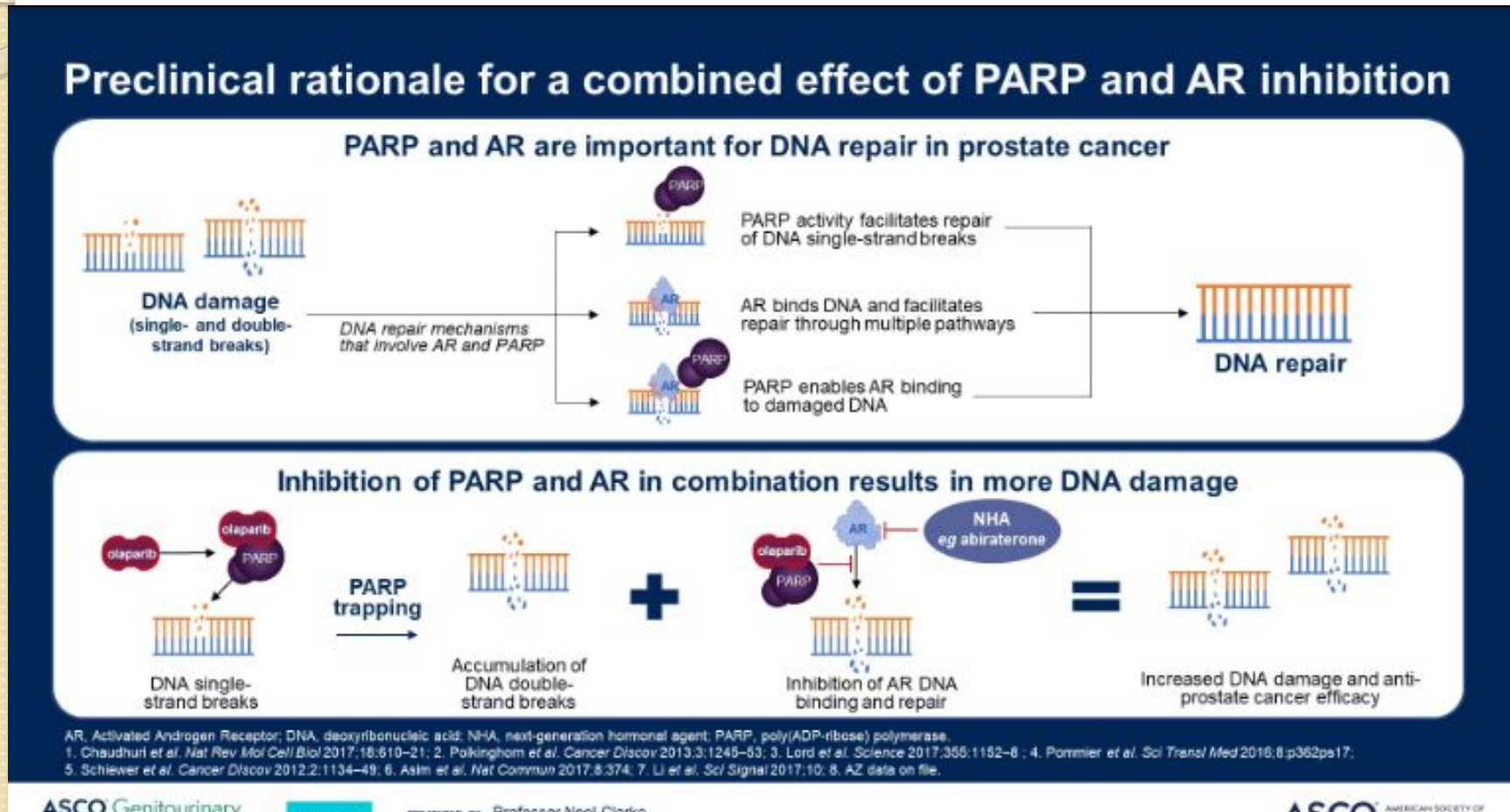
Germline



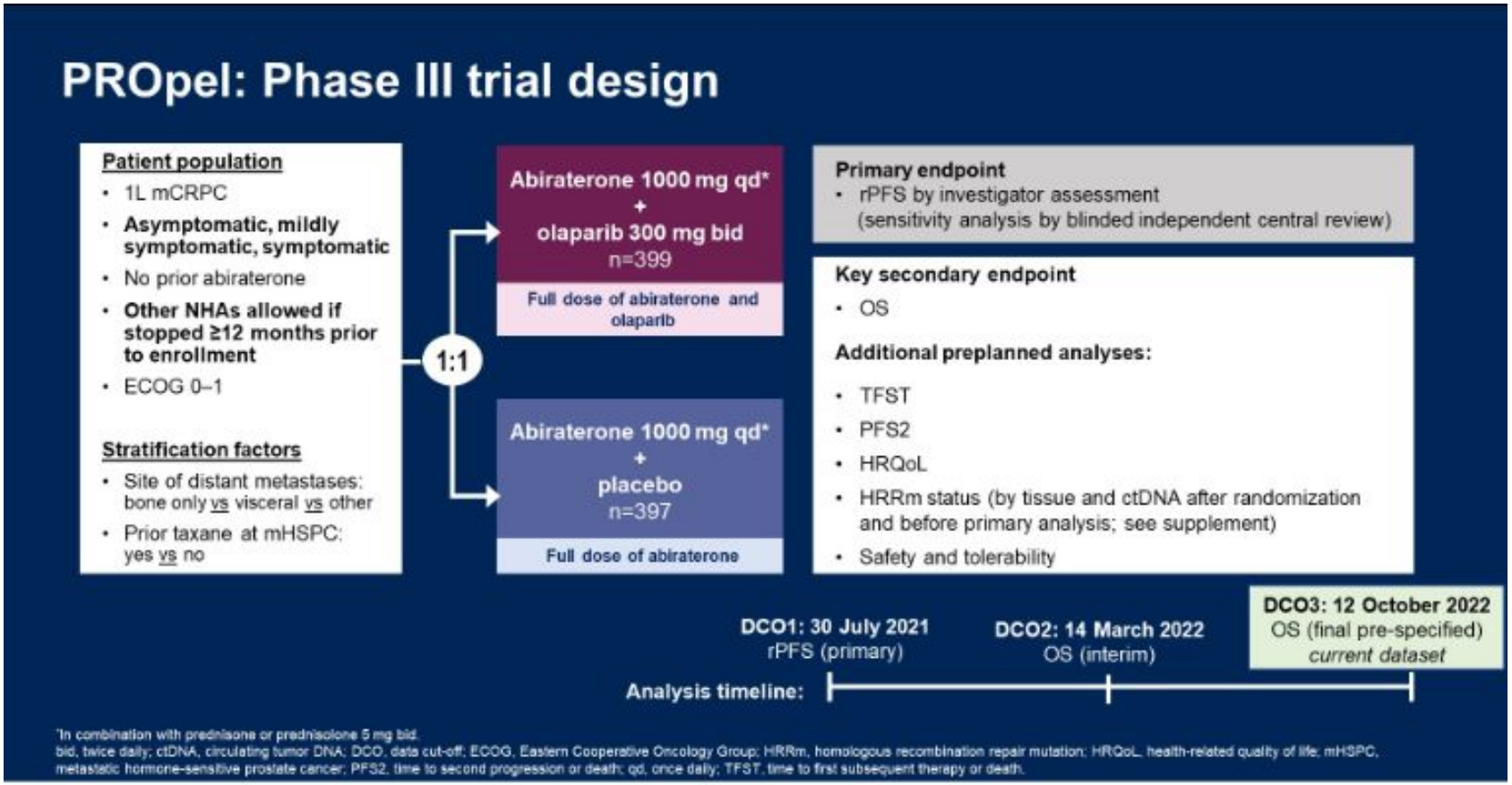
- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

1. Robinson D, et al. Cell. 2015;161:1215-28. **2.** Pritchard CC, et al. N Engl J Med. 2016;375:443-53.

ASCO 2023 PROpel



ASCO 2023 PROpel



ASCO 2023 PROpel

PROpel: baseline characteristics[1]

Balanced between trial arms

	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Median (range) age, years	69.0 (43–91)	70.0 (46–88)
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
Symptomatic (BPI-SF item #3 score ≥4 and/or opiate use), n (%)	103 (25.8)	80 (20.2)
Site of metastases, n (%)		
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)
Lung	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
Docetaxel treatment at mHSPC stage, n (%)	90 (22.6)	89 (22.4)
Median PSA, ug/L (IQR)	17.90 (6.09–67.00)	16.81 (6.26–53.30)
HRRm status, n (%)*		
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, n (%)*		
BRCAm	47 (11.8)	38 (9.6)
Non-BRCAm	343 (86.0)	350 (88.2)

*The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). BRCAm, *BRCA1* and/or *BRCA2* mutation; BPI-SF, Brief Pain Inventory – Short Form; IQR, interquartile range; PSA, prostate-specific antigen.

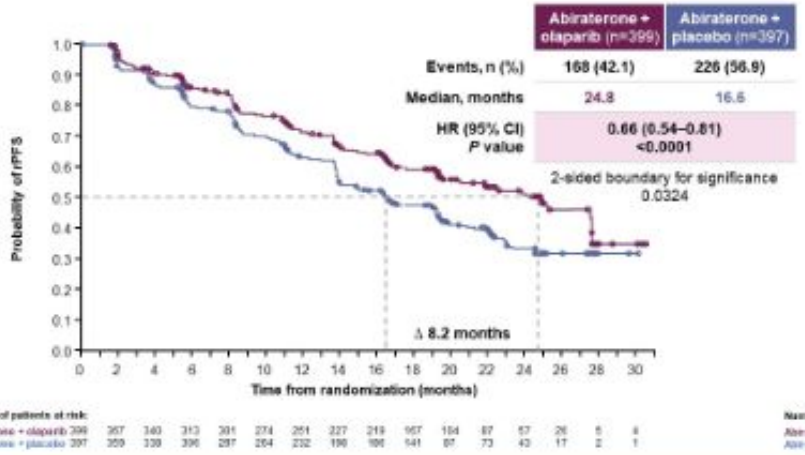
1. Clarke N *et al. NEJM Evidence* 2022;1(9).

ASCO 2023 PROpel

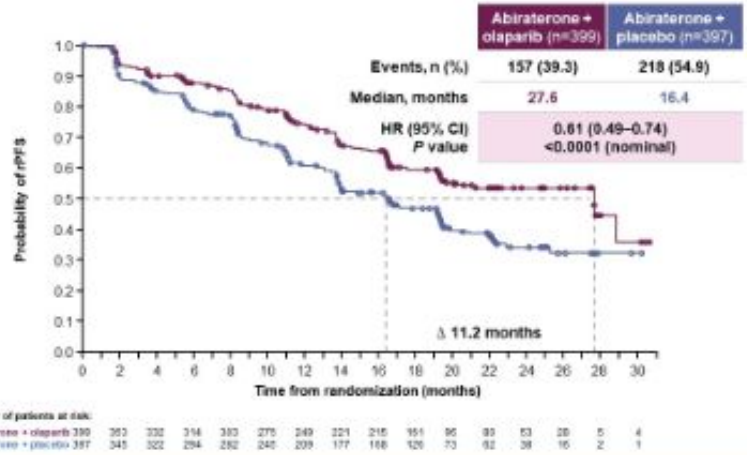
PROpel: primary rPFS results (DCO1)[1]

Abiraterone + olaparib significantly prolonged rPFS versus abiraterone + placebo in the ITT population

rPFS by investigator assessment (INV)



rPFS by blinded independent central review (BICR)



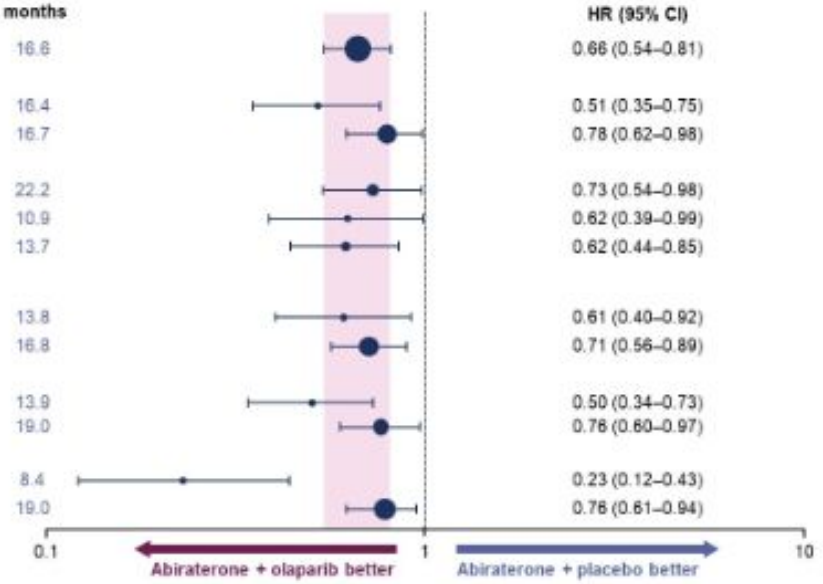
DCO1: 30 July 2021.
Median duration of follow-up for investigator-assessed rPFS for censored patients was 19.3 months in the abiraterone and olaparib arm, and 19.4 months in the abiraterone and placebo arm (19.3 and 19.2 months, respectively, for BICR).
ITT, intention-to-treat.
1. Clarke N *et al. NEJM Evidence* 2022;1(9). Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical society.

ASCO 2023 PROpel

PROpel: rPFS in subgroups (DCO1)[1]

rPFS benefit observed across all subgroups

	Number of events/ patients	Median rPFS, months		HR (95% CI)
All patients	394/796	24.8	16.6	0.66 (0.54–0.81)
Age at randomization, years				
<65	106/227	NR	16.4	0.51 (0.35–0.75)
≥65	288/569	22.0	16.7	0.78 (0.62–0.98)
Site of distant metastases				
Bone only	177/434	27.6	22.2	0.73 (0.54–0.98)
Visceral	71/105	13.7	10.9	0.62 (0.39–0.99)
Other	146/257	20.5	13.7	0.62 (0.44–0.85)
Docetaxel treatment at mHSPC stage				
Yes	95/189	27.6	13.8	0.61 (0.40–0.92)
No	299/607	24.8	16.8	0.71 (0.56–0.89)
HRRm status*				
HRRm	116/226	NR	13.9	0.50 (0.34–0.73)
Non-HRRm	268/552	24.1	19.0	0.76 (0.60–0.97)
BRCAm status*				
BRCAm	42/85	NR	8.4	0.23 (0.12–0.43)
Non-BRCAm	342/693	24.1	19.0	0.76 (0.61–0.94)



DCO1: 30 July 2021. Results are by investigator assessment. Results by blinded independent review are consistent and are available in the supplement. Global interaction test across stratification factor subgroups not significant at 10% level. *The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients' HRRm status (see supplement for more details). Results shown are by investigator assessment. NR, not reached. 1. Clarke N *et al. NEJM Evidence* 2022;1(9). Copyright © 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical society.

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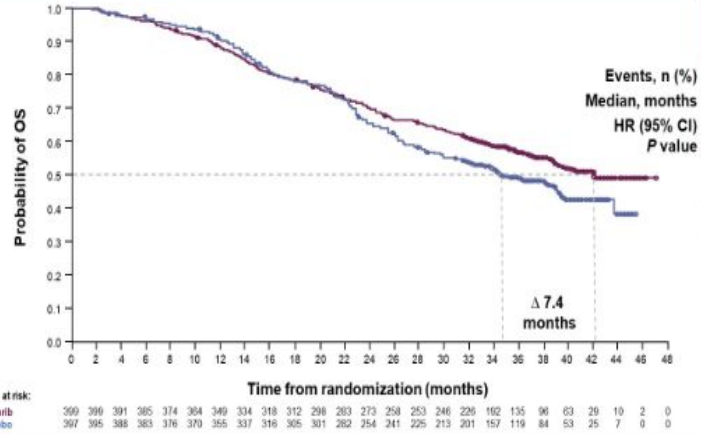
PROpel: OS at final pre-specified analysis (DCO3)

In the ITT population, median OS was >7 months longer in the abiraterone + olaparib arm



	Abiraterone + olaparib (n=399)	Abiraterone + placebo (n=397)
Events, n (%)	176 (44.1)	205 (51.6)
Median, months	42.1	34.7
HR (95% CI)	0.81 (0.67–1.00)	
P value	0.0544	
2-sided boundary for significance	0.0377	
	47.9% maturity	

DCO3: 12 October 2022.
Median (range) duration of follow-up for censored patients at DCO3

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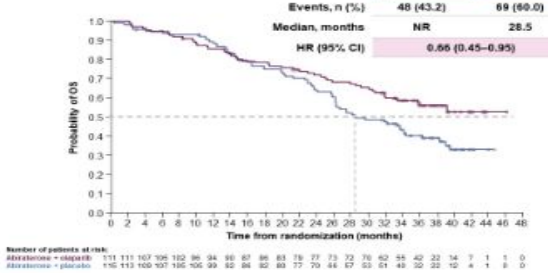
PROpel: OS in HRRm and non-HRRm subgroups (DCO3)

A trend towards OS benefit was observed across HRRm and non-HRRm subgroups

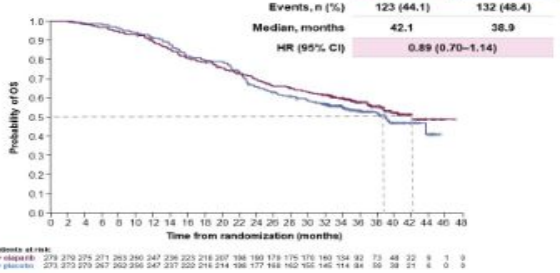
HRRm (28.4% of ITT population)

	Abiraterone + olaparib (n=111)	Abiraterone + placebo (n=116)
Events, n (%)	48 (43.2)	69 (60.0)
Median, months	NR	28.5
HR (95% CI)	0.66 (0.45–0.95)	



Non-HRRm (69.3% of ITT population)

	Abiraterone + olaparib (n=279)	Abiraterone + placebo (n=273)
Events, n (%)	123 (44.1)	132 (48.4)
Median, months	42.1	38.9
HR (95% CI)	0.89 (0.70–1.14)	



DCO3: 12 October 2022.
The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). 18 patients had unknown HRRm status.

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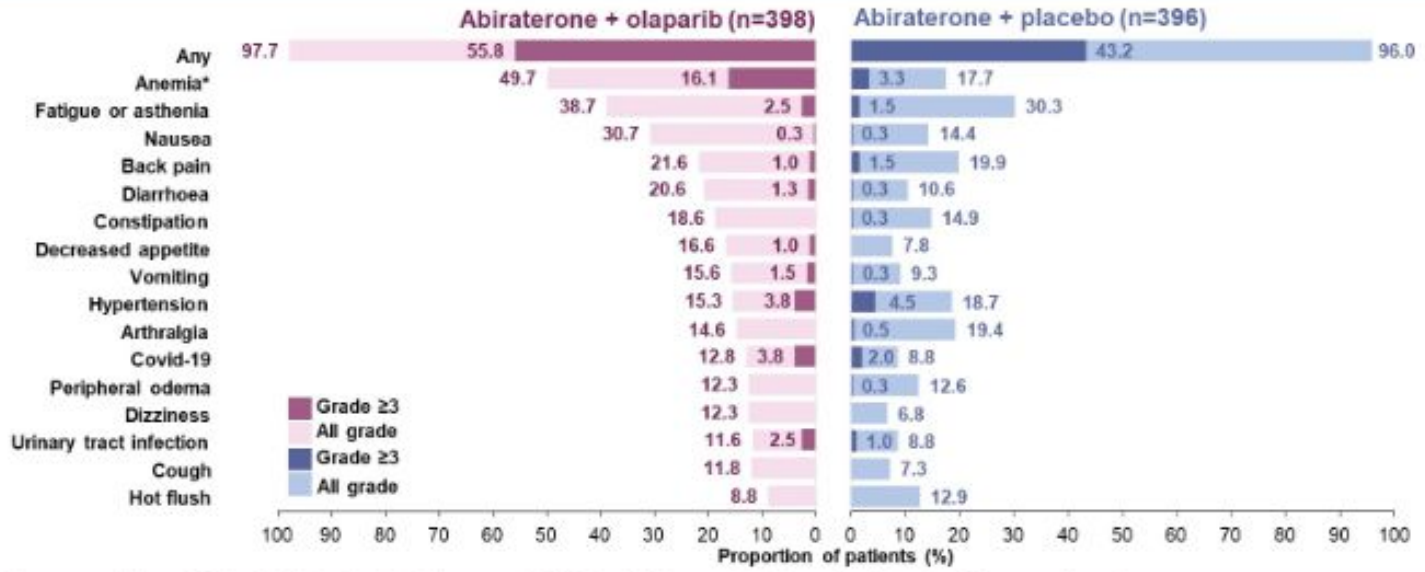
PROpel: most common AEs (>10% patients; DCO3)

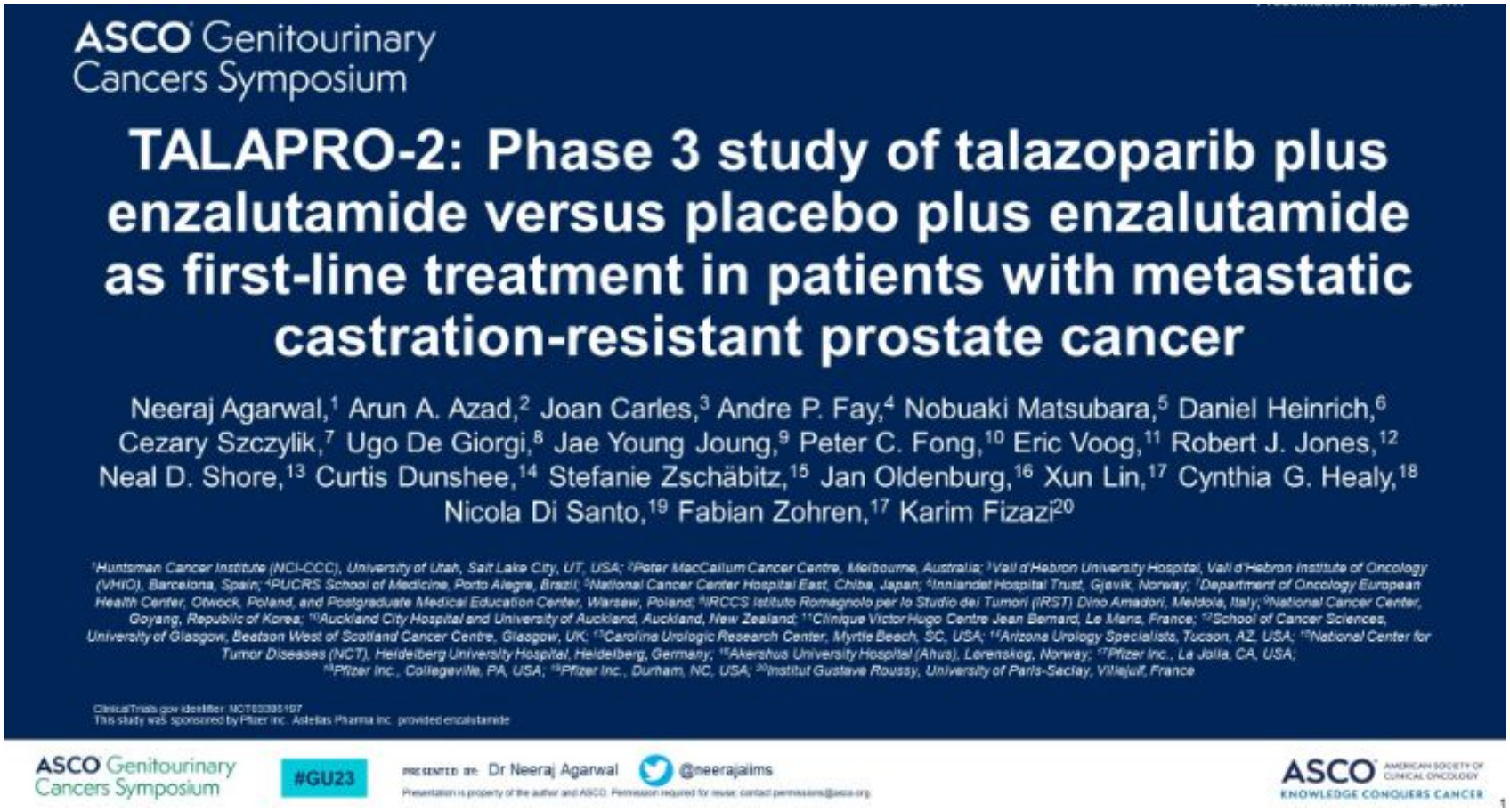
Consistent with the known safety profiles of abiraterone and olaparib



Pulmonary embolism (7.3% vs 2.3%) and cardiac failure events (1.8% vs 1.8%) were similar to earlier data cut-offs (see supplement)

DCO3: 12 October 2022. Safety was assessed through the reporting of AEs according to NCI CTCAE v4.03 and laboratory assessments. *Grouped term anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia and normocytic anemia.

ASCO 2023 TALAPRO-2



May 31, 2023

ASCO 2023 PROpel

FDA approves olaparib with abiraterone and prednisone (or prednisolone) for BRCA-mutated metastatic castration-resistant prostate cancer

PROpel: conclusions

- **PROpel met its primary endpoint demonstrating a statistically significant and clinically meaningful rPFS benefit in the ITT population of patients with mCRPC treated with abiraterone + olaparib versus abiraterone + placebo**
  - Median 24.8 months vs 16.6 months, HR 0.66 (95% CI 0.54–0.81); *P*<0.0001
- **OS trend observed with abiraterone + olaparib versus abiraterone was sustained at final pre-specified analysis**
  - Abiraterone + olaparib prolonged OS by >7 months versus standard-of-care abiraterone
  - Median OS of >42 months is the longest reported to date in a Phase III trial in 1L mCRPC
- **rPFS and OS benefit was observed across subgroups**
- **The safety profile remained consistent over time, with no new signals observed**
- **Overall results support combination treatment with abiraterone + olaparib as an important new 1L treatment option for patients with mCRPC**

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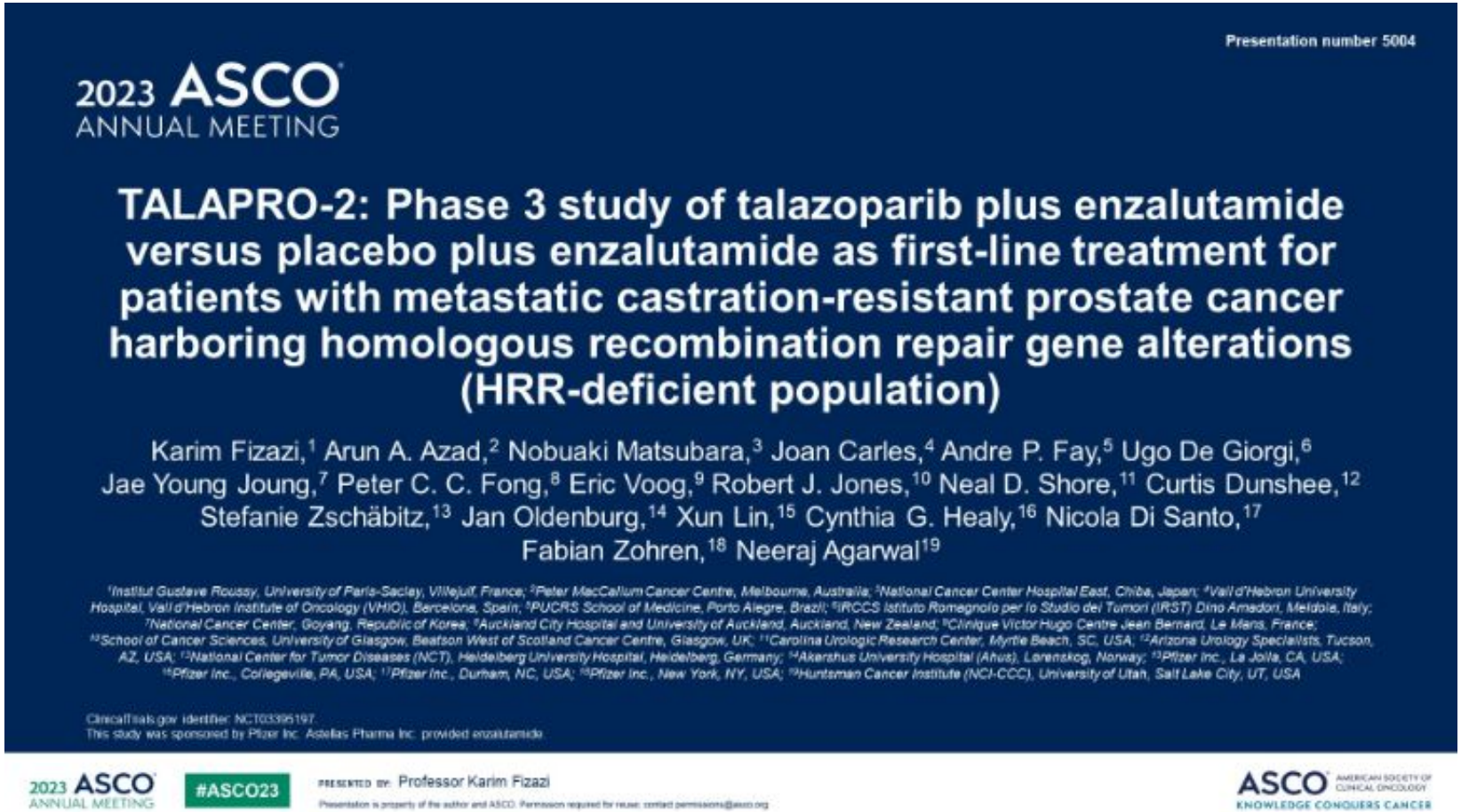
Presentation number 5004
2023 ASCO ANNUAL MEETING
TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment for patients with metastatic castration-resistant prostate cancer harboring homologous recombination repair gene alterations (HRR-deficient population)
Karim Fizazi,[1] Arun A. Azad,[2] Nobuaki Matsubara,[3] Joan Carles,[4] Andre P. Fay,[5] Ugo De Giorgi,[6] Jae Young Joung,[7] Peter C. C. Fong,[8] Eric Voog,[9] Robert J. Jones,[10] Neal D. Shore,[11] Curtis Dunshee,[12] Stefanie Zschäbitz,[13] Jan Oldenburg,[14] Xun Lin,[15] Cynthia G. Healy,[16] Nicola Di Santo,[17] Fabian Zohren,[18] Neeraj Agarwal[19]
[1]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]National Cancer Center Hospital East, Chiba, Japan; [4]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [5]PUCRS School of Medicine, Porto Alegre, Brazil; [6]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [7]National Cancer Center, Goyang, Republic of Korea; [8]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [9]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [10]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [11]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [12]Arizona Urology Specialists, Tucson, AZ, USA; [13]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [14]Akershus University Hospital (Ahus), Lørenskog, Norway; [15]Pfizer Inc., La Jolla, CA, USA; [16]Pfizer Inc., Collegeville, PA, USA; [17]Pfizer Inc., Durham, NC, USA; [18]Pfizer Inc., New York, NY, USA; [19]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA
ClinicalTrials.gov identifier: NCT03395197.
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.
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PRESENTED BY: Professor Karim Fizazi
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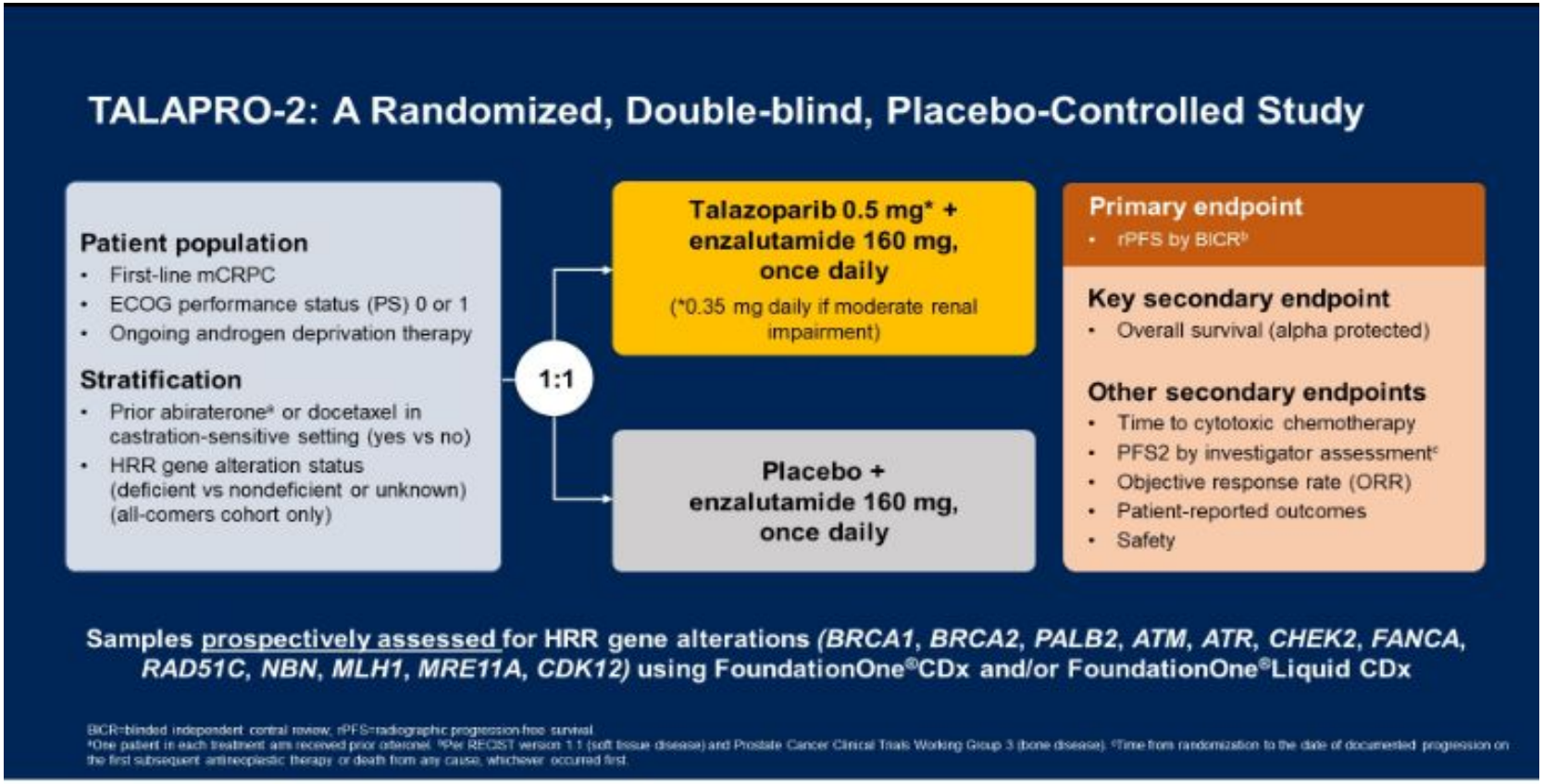

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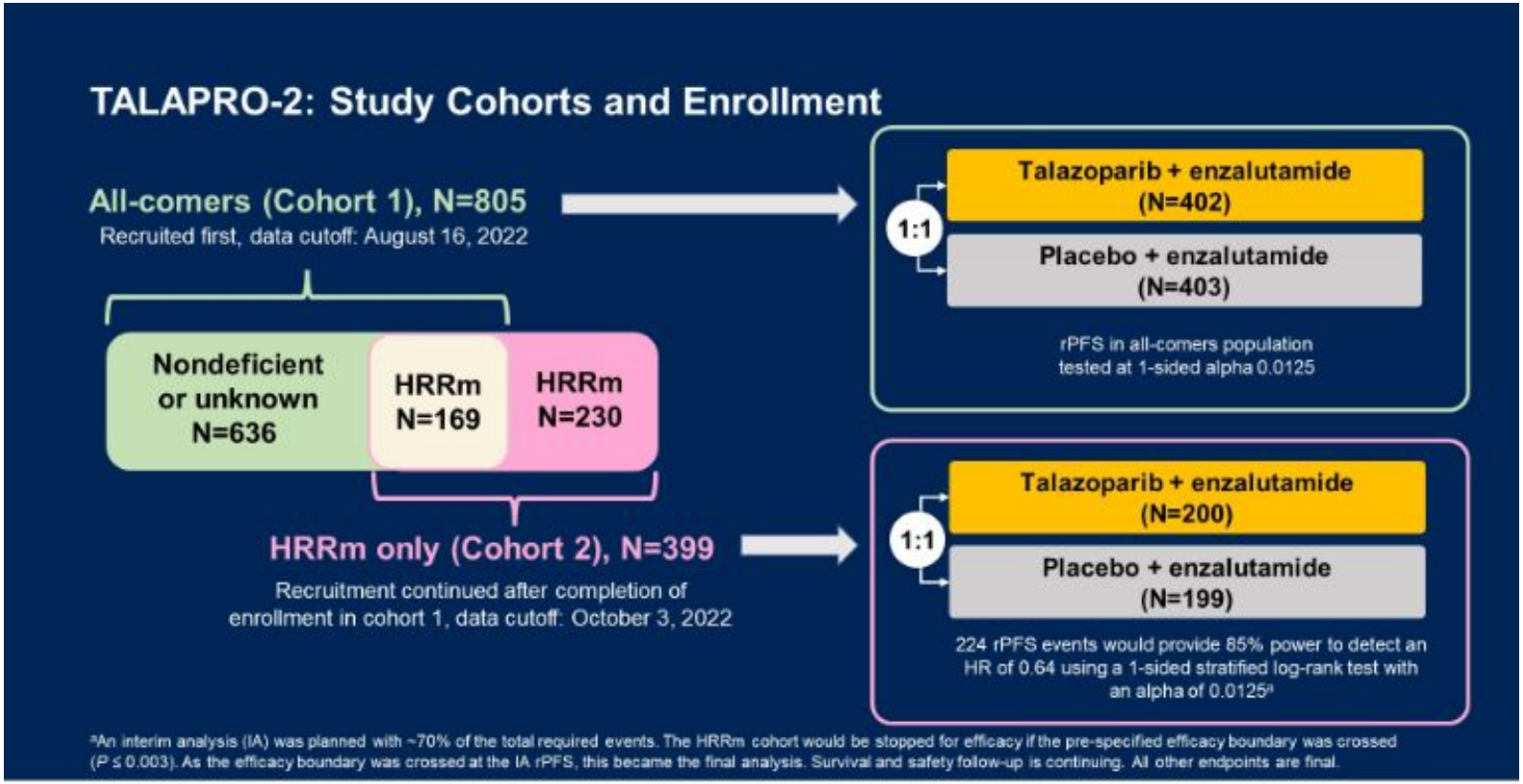
TALAPRO-2: Study Cohorts and Enrollment
All-comers (Cohort 1), N=805
Recruited first, data cutoff: August 16, 2022
Nondeficient or unknown N=636
HRRm N=169
HRRm N=230
HRRm only (Cohort 2), N=399
Recruitment continued after completion of enrollment in cohort 1, data cutoff: October 3, 2022
1:1
Talazoparib + enzalutamide (N=402)
Placebo + enzalutamide (N=403)
rPFS in all-comers population tested at 1-sided alpha 0.0125
1:1
Talazoparib + enzalutamide (N=200)
Placebo + enzalutamide (N=199)
224 rPFS events would provide 85% power to detect an HR of 0.64 using a 1-sided stratified log-rank test with an alpha of 0.0125[a]
[a]An interim analysis (IA) was planned with ~70% of the total required events. The HRRm cohort would be stopped for efficacy if the pre-specified efficacy boundary was crossed (P ≤ 0.003). As the efficacy boundary was crossed at the IA rPFS, this became the final analysis. Survival and safety follow-up is continuing. All other endpoints are final.

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TALAPRO-2 HRR-Deficient: Baseline Demographics and Disease Characteristics

These were well-balanced between treatment arms

	Talazoparib + Enzalutamide (N=200)	Placebo + Enzalutamide (N=199)
Age, median (range), years	70 (41–90)	71 (44–90)
Prostate-specific antigen (PSA), median (range), ng/mL	19.6 (0.2–3412.0)	18.0 (0.0–1055.0)
Disease site, n (%)		
Bone	175 (87.5)	158 (79.4)
Lymph node	82 (41.0)	94 (47.2)
Visceral (lung/liver)	23 (11.5)/9 (4.5)	26 (13.1)/6 (3.0)
ECOG PS 0/1, n (%)	128 (64.0)/72 (36.0)	118 (59.3)/81 (40.7)
Prior abiraterone[a] or docetaxel, n (%)	75 (37.5)	74 (37.2)
Abiraterone	16 (8.0)	16 (8.0)
Docetaxel	57 (28.5)	60 (30.2)
Tissue source for prospective HRR gene alteration testing, n (%)		
Tumor tissue only	76 (38.0)	80 (40.2)
Tumor tissue and blood (circulating tumor DNA)	121 (60.5)	115 (57.8)
Blood (circulating tumor DNA) only	3 (1.5)	4 (2.0)

[a]One patient in each treatment arm received prior orteronel

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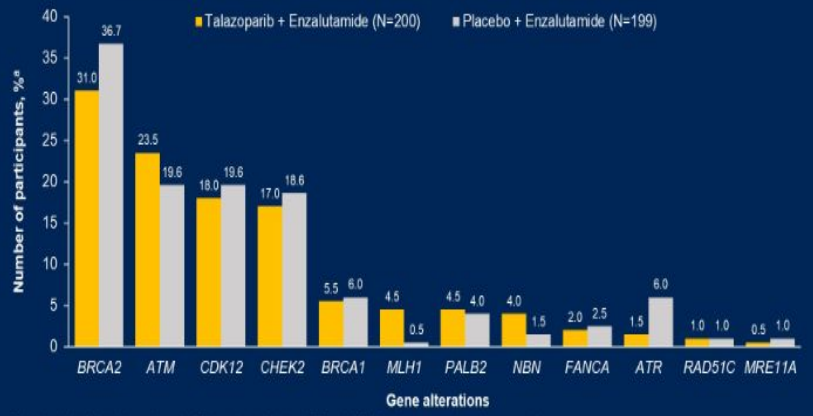
TALAPRO-2 HRR-Deficient: Baseline HRR Gene Alterations

Representation of HRR gene alterations was consistent with previously published studies



During the mid-point of the study (January-November 2021), recruitment of patients with ATM and/or CDK12 alterations was paused to avoid over representation.

[a]Number of participants with one or more alterations in corresponding gene. Three patients (1 in the talazoparib arm and 2 in the placebo arm) did not have HRR gene alterations, and 1 patient in the talazoparib arm was of unknown HRR gene alteration status.

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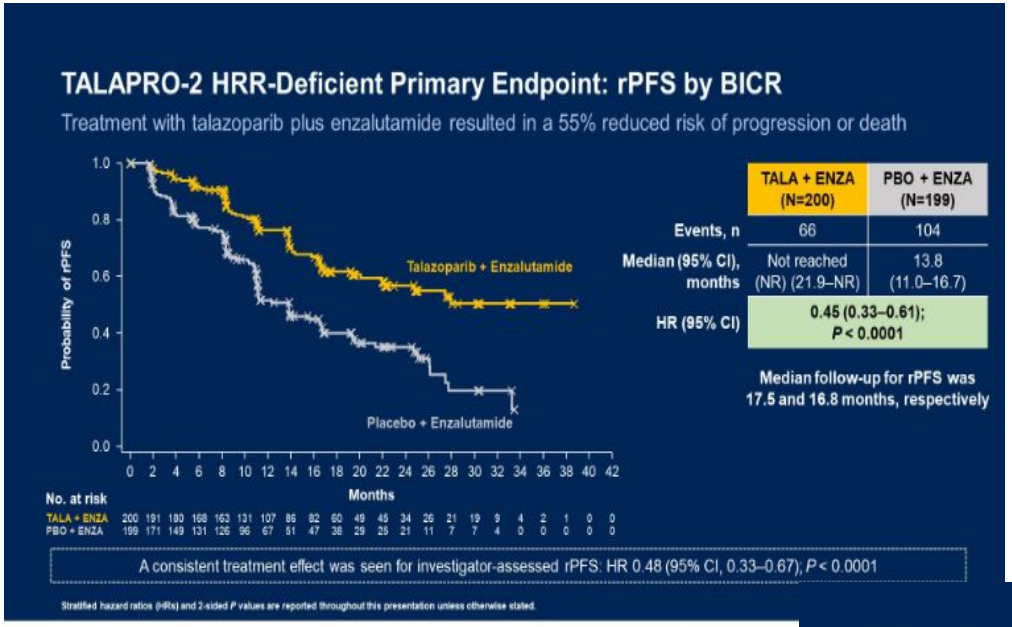
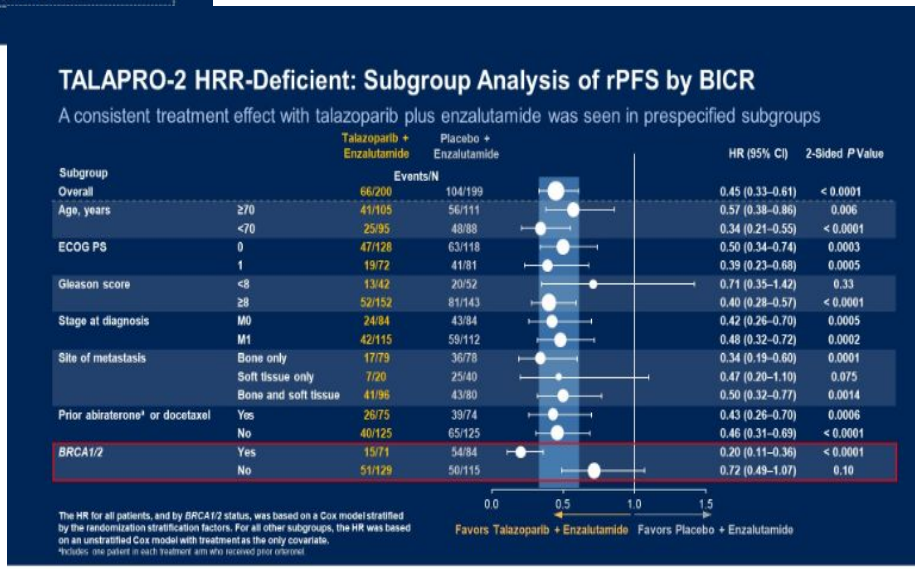
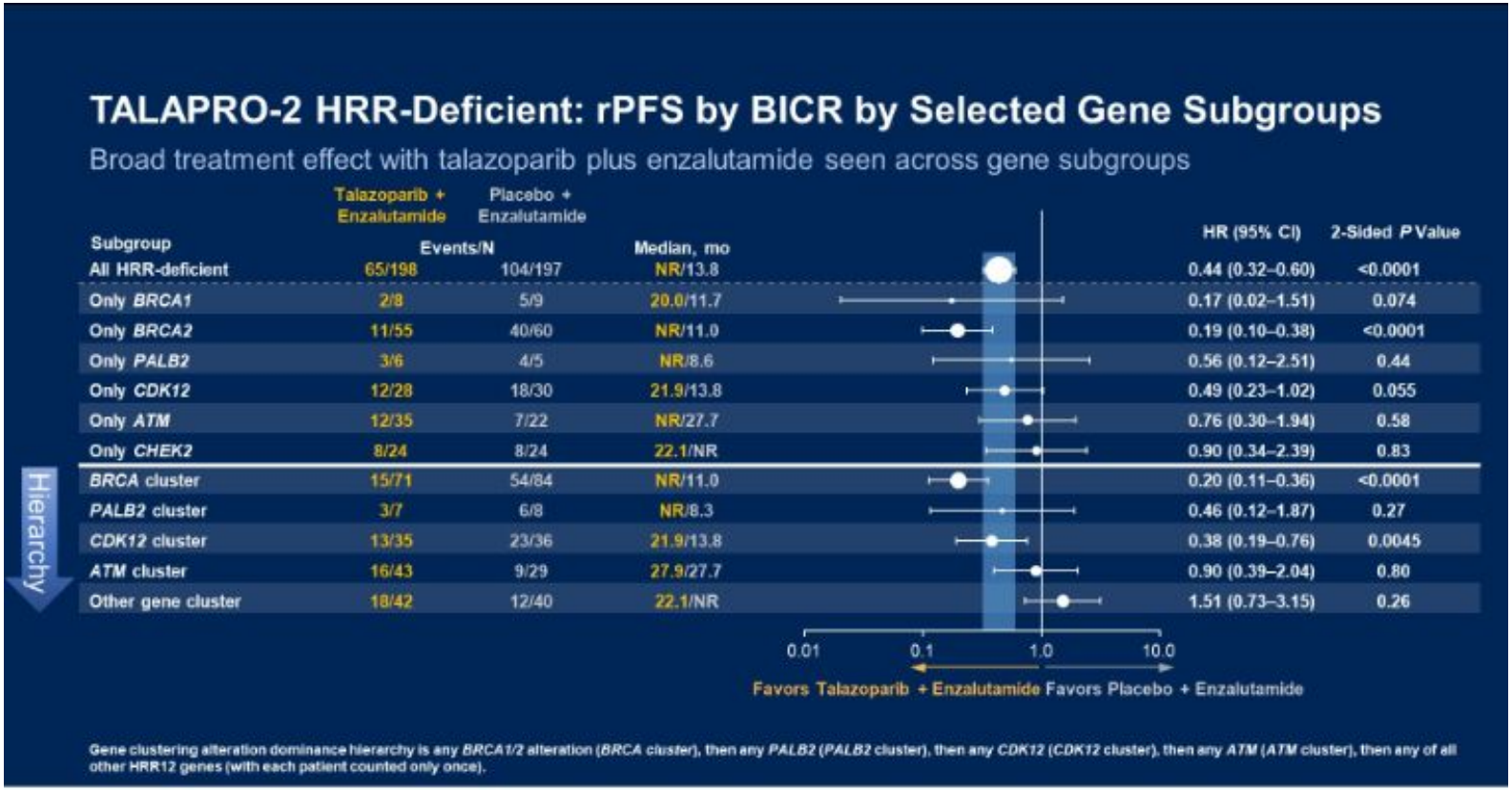




ASCO 2023


TALAPRO-2 HRR-Deficient: rPFS by BICR by Selected Gene Subgroups
Broad treatment effect with talazoparib plus enzalutamide seen across gene subgroups
Talazoparib + Enzalutamide
Placebo + Enzalutamide
Subgroup
Events/N
Median, mo
HR (95% CI)
2-Sided P Value
All HRR-deficient 65/198 104/197 NR/13.8 0.44 (0.32–0.60) <0.0001
Only BRCA1 2/8 5/9 20.0/11.7 0.17 (0.02–1.51) 0.074
Only BRCA2 11/55 40/60 NR/11.0 0.19 (0.10–0.38) <0.0001
Only PALB2 3/6 4/5 NR/8.6 0.56 (0.12–2.51) 0.44
Only CDK12 12/28 18/30 21.9/13.8 0.49 (0.23–1.02) 0.055
Only ATM 12/35 7/22 NR/27.7 0.76 (0.30–1.94) 0.58
Only CHEK2 8/24 8/24 22.1/NR 0.90 (0.34–2.39) 0.83
BRCA cluster 15/71 54/84 NR/11.0 0.20 (0.11–0.36) <0.0001
PALB2 cluster 3/7 6/8 NR/8.3 0.46 (0.12–1.87) 0.27
CDK12 cluster 13/35 23/36 21.9/13.8 0.38 (0.19–0.76) 0.0045
ATM cluster 16/43 9/29 27.9/27.7 0.90 (0.39–2.04) 0.80
Other gene cluster 18/42 12/40 22.1/NR 1.51 (0.73–3.15) 0.26
Hierarchy
0.01
0.1
1.0
10.0
Favors Talazoparib + Enzalutamide
Favors Placebo + Enzalutamide
Gene clustering alteration dominance hierarchy is any BRCA1/2 alteration (BRCA cluster), then any PALB2 (PALB2 cluster), then any CDK12 (CDK12 cluster), then any ATM (ATM cluster), then any of all other HRR12 genes (with each patient counted only once).
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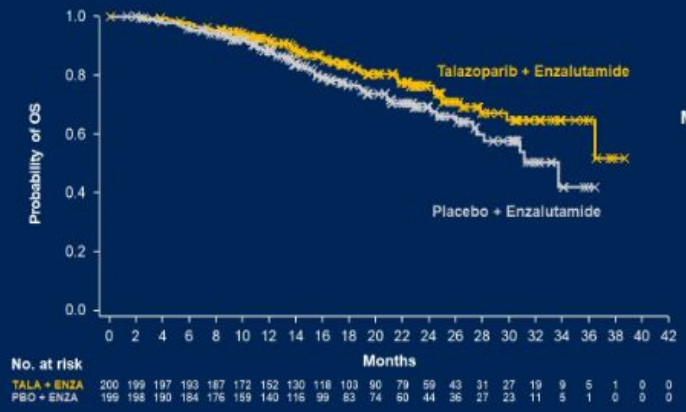
KNOWLEDGE CONQUERS CANCER

ASCO 2023

TALAPRO-2 HRR-Deficient: Overall Survival (Interim Analysis)

Overall survival data are immature (24% maturity overall)



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	43	53
Median (95% CI), months	NR (36.4–NR)	33.7 (27.6–NR)
HR (95% CI)	HR 0.69 (95% CI, 0.46–1.03) *P* = 0.068	

*BRCA*m HR 0.61 (95% CI, 0.31–1.23; *P* = 0.16)
non-*BRCA*m HR 0.71 (95% CI, 0.43–1.18; *P* = 0.18)

18 patients in the control arm and 3 patients in the talazoparib arm subsequently received olaparib

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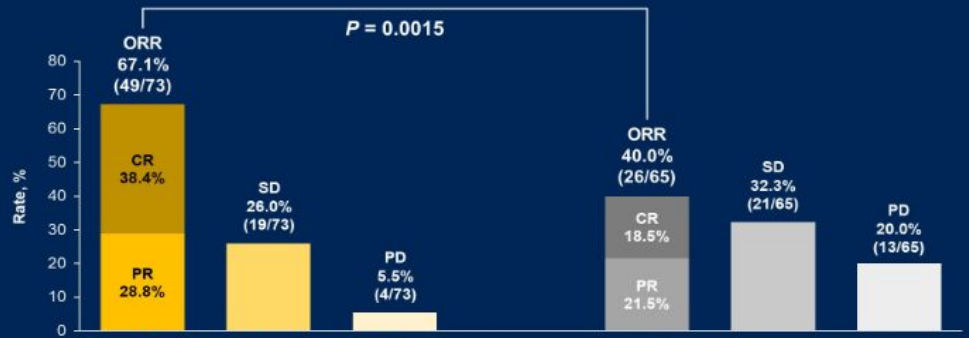
TALAPRO-2 HRR-Deficient: Objective Response by BICR

Higher rates of complete response (CR) suggest a cooperative effect of talazoparib plus enzalutamide treatment



PD=progressive disease; PR=partial response; SD=stable disease

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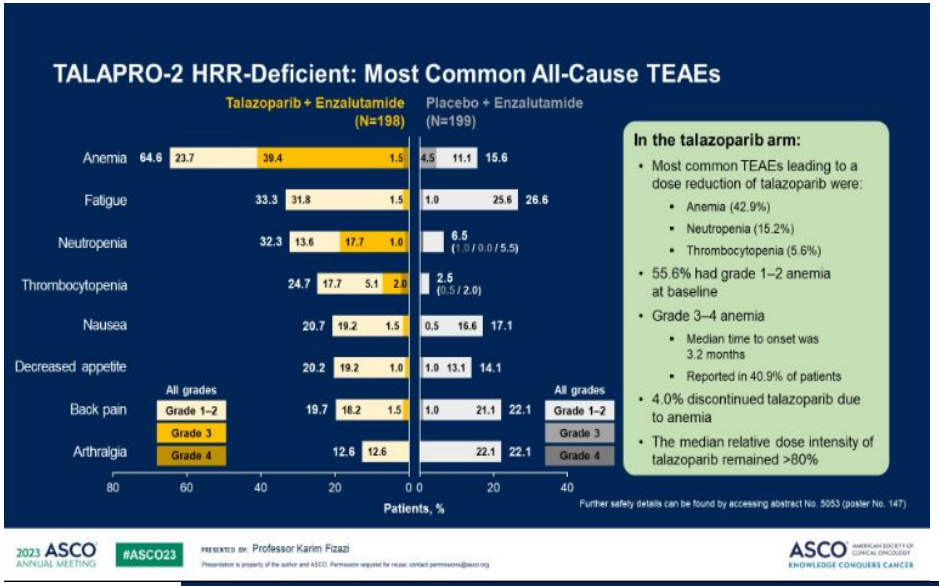
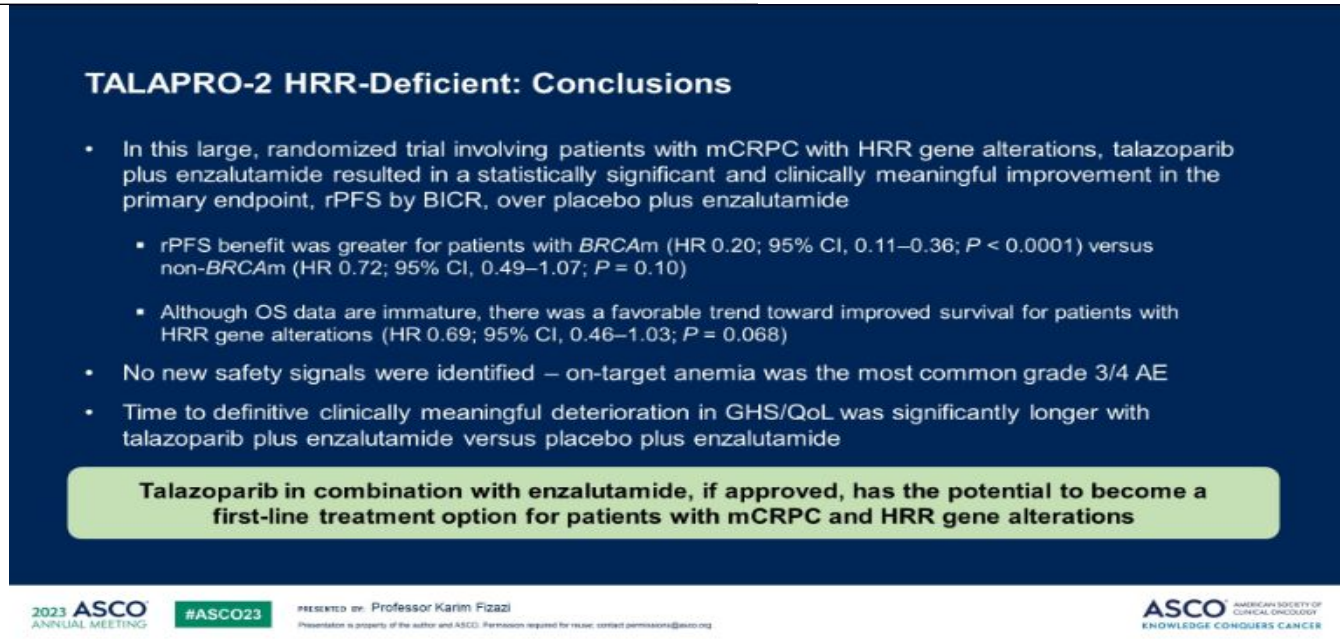


June 20, 2023

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

- **HRR genes (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C)**



Practice Changing

- Patients with metastatic castrate resistant prostate cancer (mCRPC) with BRCA1 and BRCA2 have a poor prognosis

- In my practice, patients with mCRPC with BRCA1 and BRCA2 mutation I will treat with PARP inhibitor, AR pathway inhibitor, and ADT.

Post Androgen receptor pathway inhibitor and Taxane

VISION Study

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

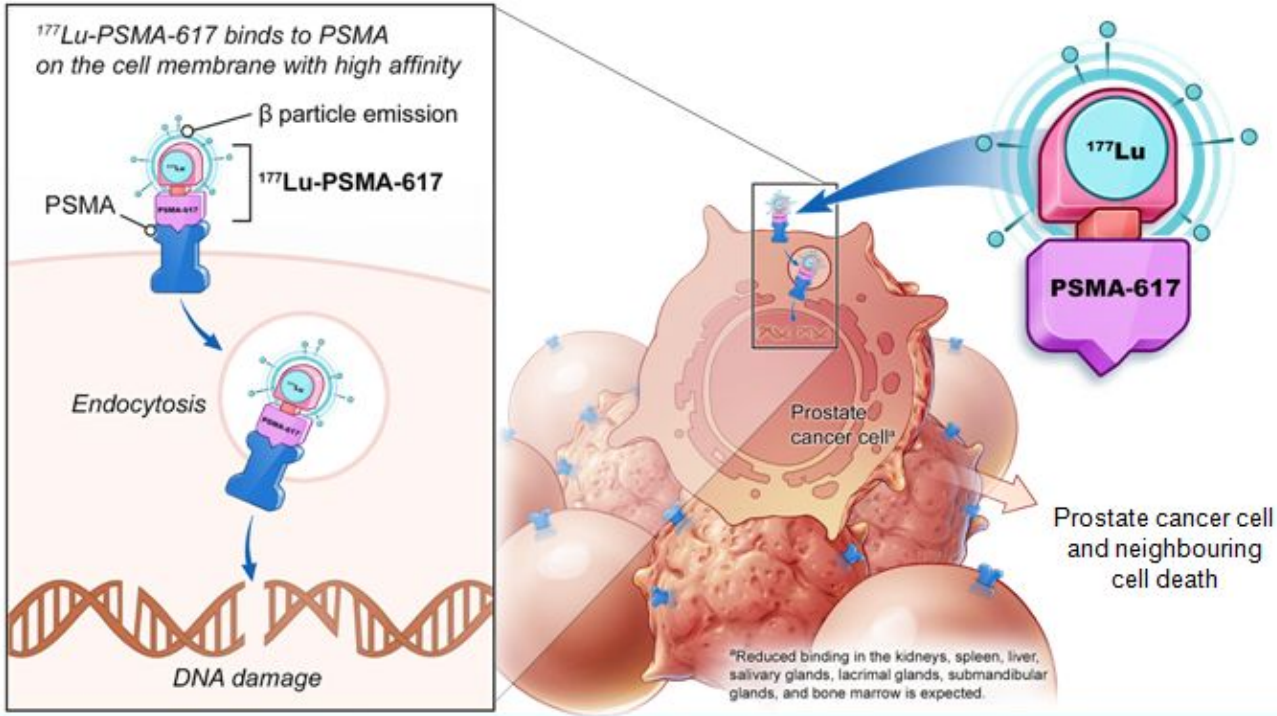
Oliver Sartor, M.D., Johann de Bono, M.B., Ch.B., Ph.D., Kim N. Chi, M.D., Karim Fizazi, M.D., Ph.D., Ken Herrmann, M.D., Kambiz Rahbar, M.D., Scott T. Tagawa, M.D., Luke T. Nordquist, M.D., Nitin Vaishampayan, M.D., Ghassan El-Haddad, M.D., Chandler H. Park, M.D., Tomasz M. Beer, M.D., et al., for the VISION Investigators*

September 16, 2021
N Engl J Med 2021; 385:1091-1103
DOI: 10.1056/NEJMoa2107322
Chinese Translation 中文翻译

Lutetium 177 FDA approval
March 23, 2022

Mechanism of Action

^{177}Lu-PSMA-617 targeted radioligand therapy



VISION Study

Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

- Previous treatment with both
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

2:1

Protocol-permitted SOC + ^{177}Lu-PSMA-617
7.4 GBq (200 mCi) every 6 weeks
4 cycles, increasable to 6

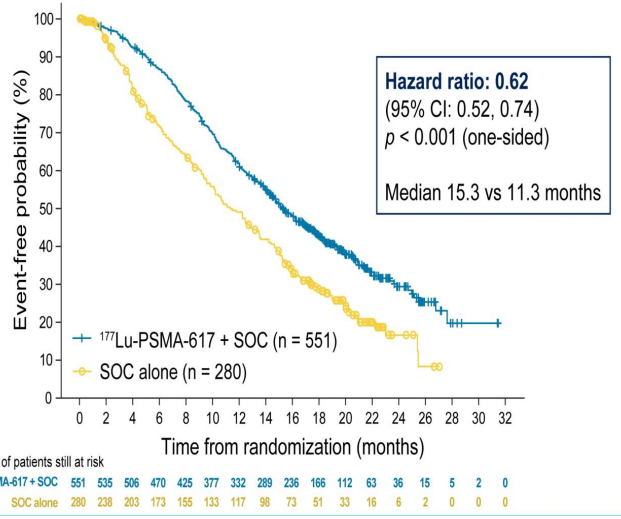
Protocol-permitted SOC alone

Treatment → Follow-up → Final analysis

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis
All randomized patients
(N = 831)



How do I treat post taxane and AR pathway inhibitor

1. Review somatic mutation, germline mutations.
2. If somatic mutation checked in metastatic hormone sensitive state, recheck now in metastatic castrate resistant state.
3. Lutetium 177 vs Cabzitaxel vs Cabizitaxel/Carboplatin vs PARP inhibitor
4. Oral cyclophosphamide (ESMO 2023) ?

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