Second Opinion: Urologic Oncology Investigators Discuss How They Apply Clinical Research in the Care of Patients with Prostate Cancer

A CME Satellite Symposium Held in Conjunction with the American Urological Association Annual Meeting 2024 (AUA2024)

Friday, May 3, 2024

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Rahul Aggarwal, MD
Adam S Kibel, MD
Laurence Klotz, CM, MD
Sandy Srinivas, MD

Moderator

Elisabeth I Heath, MD

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Dr Aggarwal — Disclosures
Faculty

No relevant conflicts of interest to disclose

Dr Kibel — Disclosures
Faculty

Advisory Committees	Janssen Biotech Inc, Pfizer Inc, ProFound Therapeutics, Roche Laboratories Inc
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Dr Klotz — Disclosures
Faculty

No relevant conflicts of interest to disclose

Dr Srinivas — Disclosures
Faculty

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Dr Heath — Disclosures
Moderator

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Dr Hafron — Disclosures
Consulting Faculty

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Dr Morris — Disclosures
Consulting Faculty

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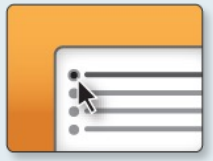

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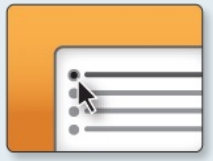

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Agenda

Module 1: Recent Data Defining the Optimal Use of Hormonal Therapy for Nonmetastatic Prostate Cancer — Dr Kibel

Module 2: Side Effects and Other Practical Considerations with Hormonal Therapy for Nonmetastatic Prostate Cancer — Dr Klotz

Module 3: Current and Future Approaches to Hormonal Therapy for Metastatic Prostate Cancer — Dr Aggarwal

Module 4: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Srinivas

Module 5: Other Novel Therapies for Patients with Metastatic Prostate Cancer — Dr Heath

Consulting Faculty

Jason Hafron, MD
Michigan Institute of Urology
West Bloomfield, Michigan

David S Morris, MD
Urology Associates
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MODULE 1: Recent Data Defining the Optimal Use of Hormonal Therapy for Nonmetastatic Prostate Cancer — Dr Kibel

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Consulting Faculty Comments

Optimal use of androgen deprivation therapy (ADT) for M0 disease

Neil Love, MD

Jason Hafron, MD

David S Morris, MD

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QUESTIONS FOR THE FACULTY

Jason Hafron, MD

Have you extrapolated the STAMPEDE data and applied that as a standard of care within your practice for patients with high-risk localized prostate cancer?

Would you substitute another AR pathway inhibitor (ie, apalutamide, darolutamide or enzalutamide) for abiraterone for these patients?

David S Morris, MD

For patients receiving ADT intensified therapy, what is the ideal duration of ADT that you recommend?

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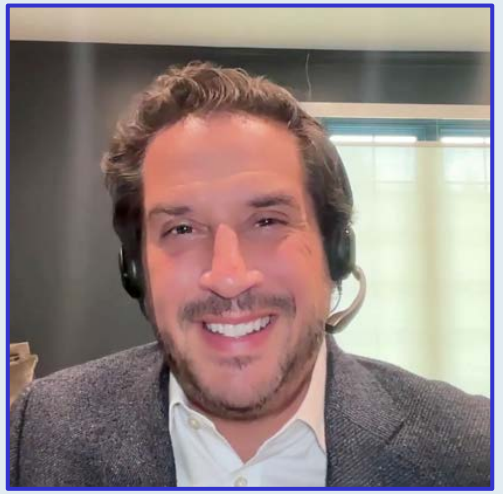
Consulting Faculty Comments

Incorporating ADT in the salvage and perioperative settings

Neil Love, MD

David S Morris, MD



Jason Hafron, MD

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QUESTIONS FOR THE FACULTY

David S Morris, MD

Are you combining ADT with salvage pelvic radiotherapy for patients with recurrence after surgery?

Are you recommending ADT combination therapy for those patients without evidence of metastasis or nodal involvement on imaging?

Jason Hafron, MD

Is there any role for ADT for patients with high-risk and very high-risk localized disease who are surgical candidates? Is there any role for ADT intensification or chemotherapy?

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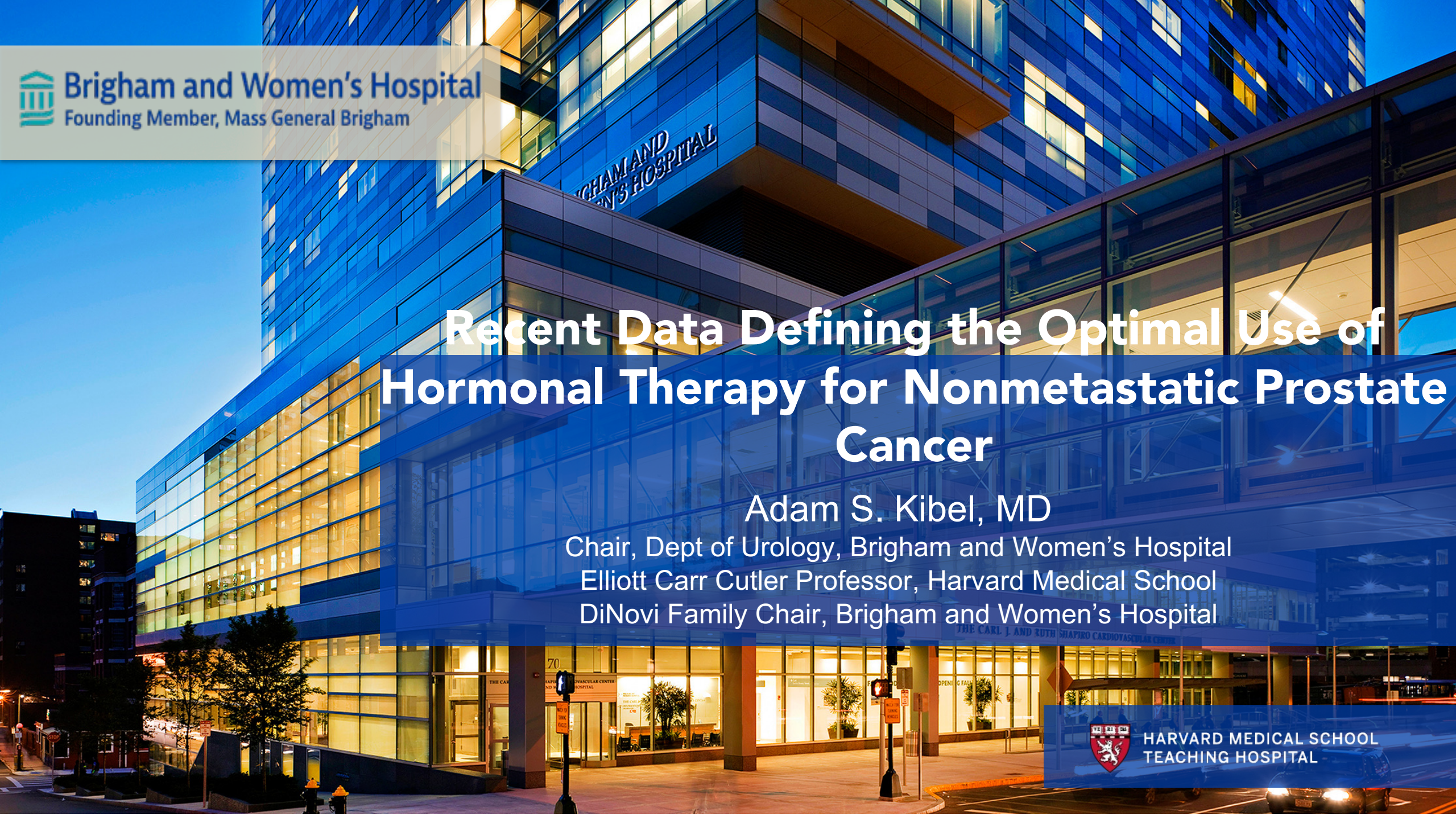


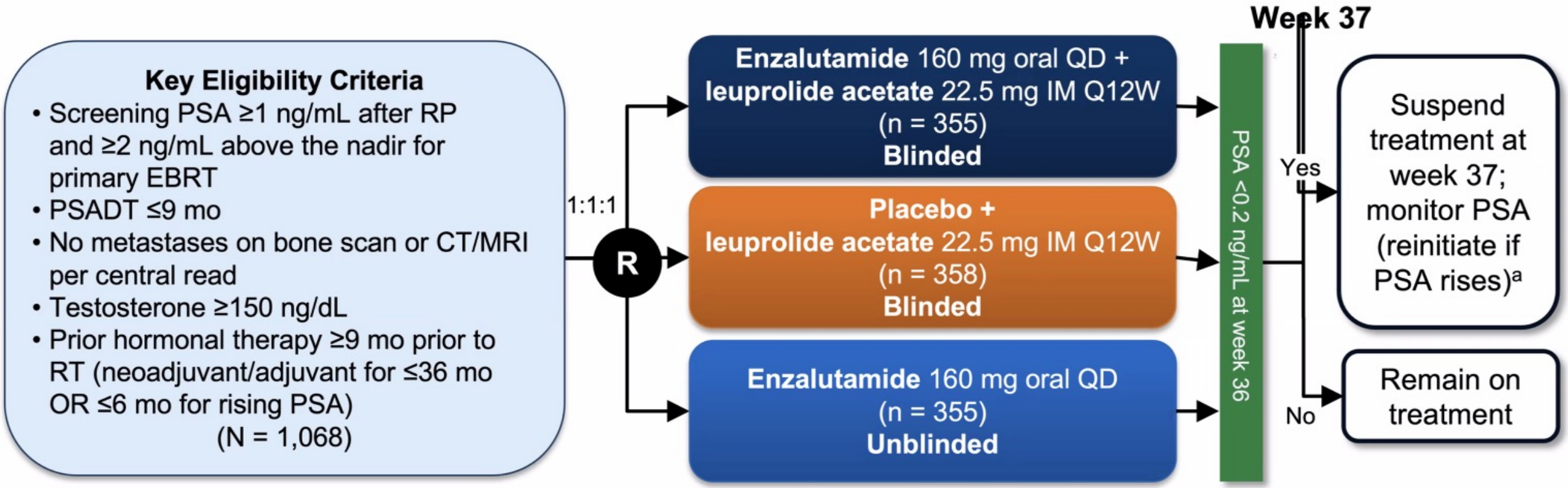
Recent Data Defining the Optimal Use of Hormonal Therapy for Nonmetastatic Prostate Cancer

Adam S. Kibel, MD
Chair, Dept of Urology, Brigham and Women's Hospital
Elliott Carr Cutler Professor, Harvard Medical School
DiNovi Family Chair, Brigham and Women's Hospital

Outline – Nonmetastatic Prostate Cancer Trials

- nmHSPC
  - EMBARK Trial (enzalutamide)
  - PRESTO Trial (apalutamide)
- nmCRPC
  - PROSPER (enzalutamide)
  - SPARTAN (apalutamide)
  - ARAMIS (darolutamide)
- Future Directions

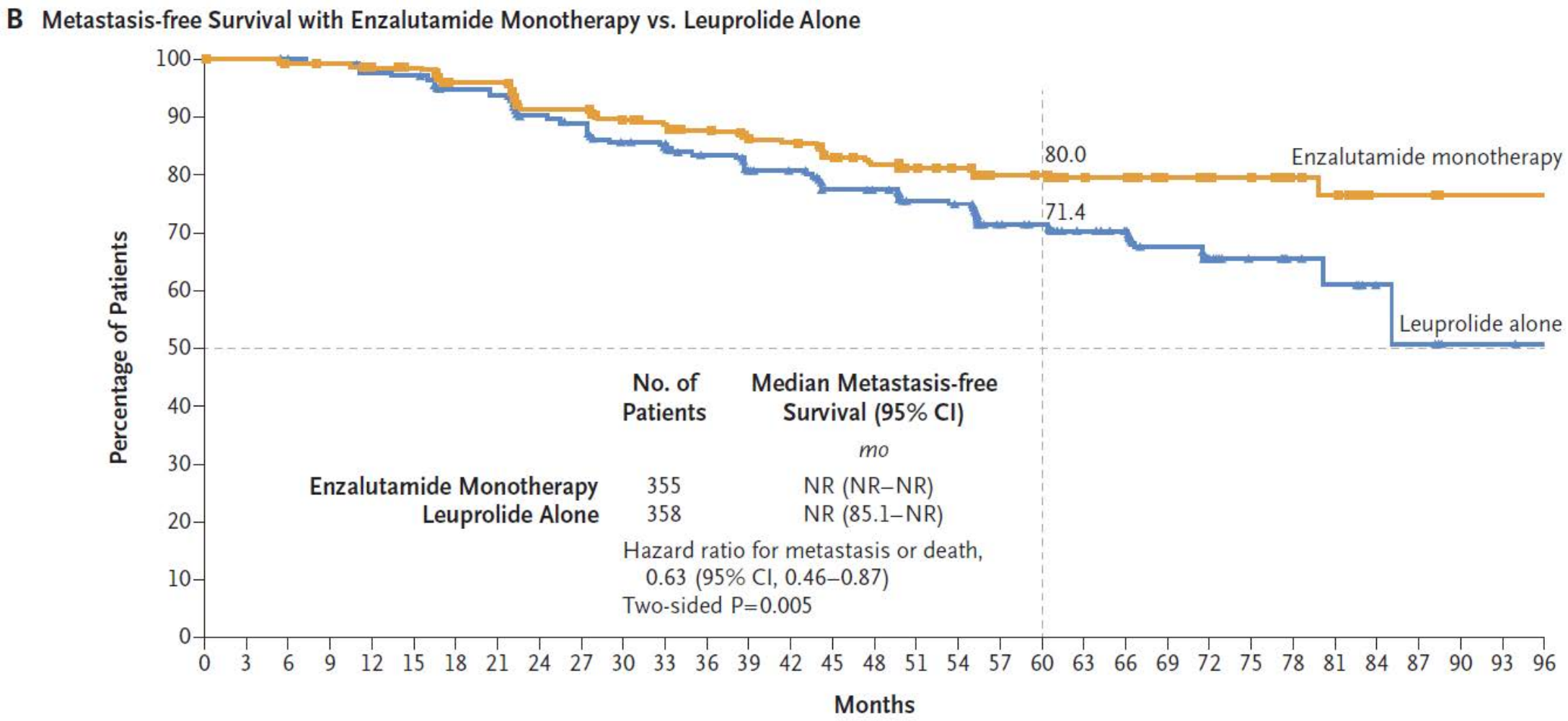
EMBARK: Enzalutamide Plus Leuprolide Acetate[1-6]



- **Stratification factors:** screening PSA (≤10 ng/mL vs >10 ng/mL), PSADT (≤3 mo vs >3 to ≤9 mo), prior hormonal therapy (yes vs no)
- **Primary endpoint[b]:** MFS by BICR (enzalutamide + leuprolide acetate vs leuprolide acetate)
- **Key secondary endpoints[b,c]:** MFS by BICR (enzalutamide vs leuprolide acetate), time to PSA progression, time to first use of new antineoplastic therapy, OS[c]
- **Other secondary endpoints:** safety,[d] PRO

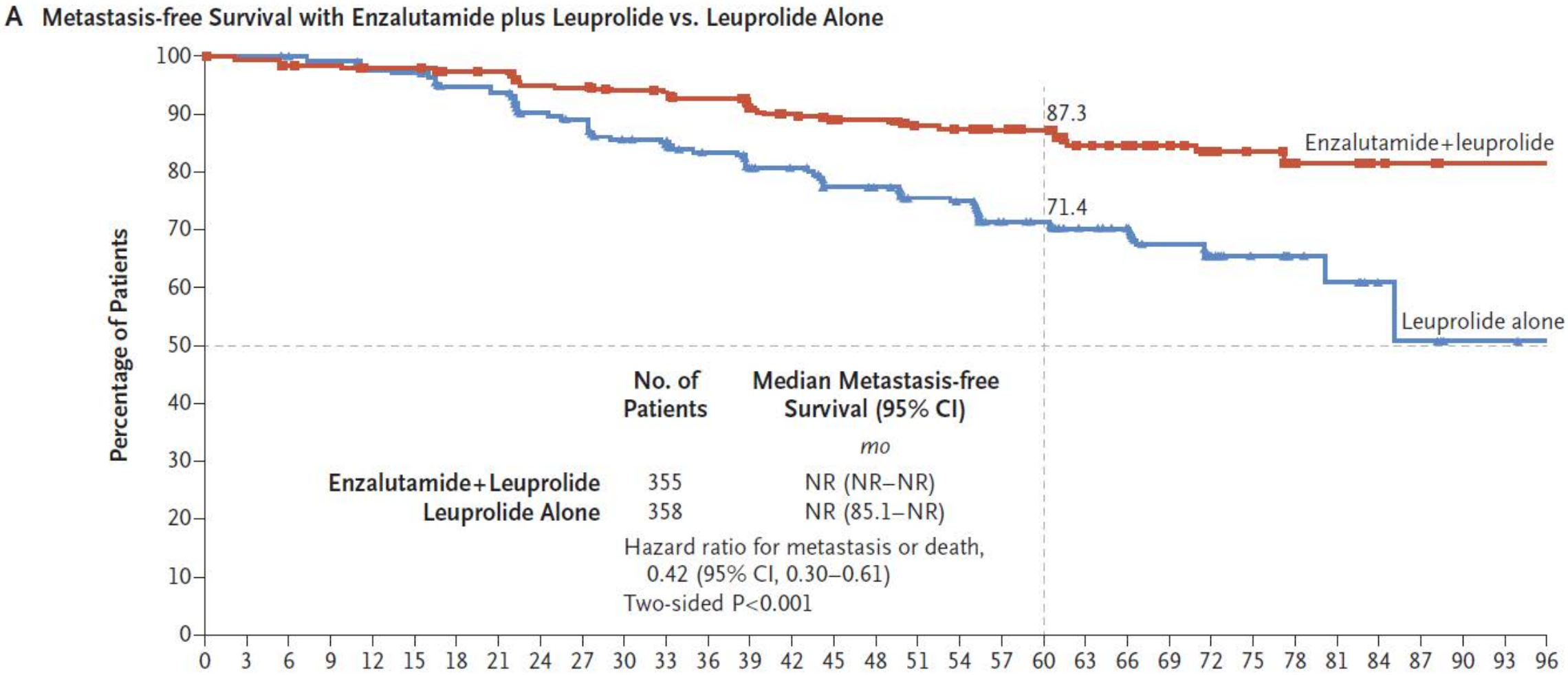
[a] Study treatment was suspended once at week 37 if PSA was <0.2 ng/mL and restarted when PSA was ≥5.0 ng/mL (without prior RP) and ≥2 ng/mL (prior RP). [b] ITT population. [c] Primary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. *P* value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. [d] Safety population.

EMBARK



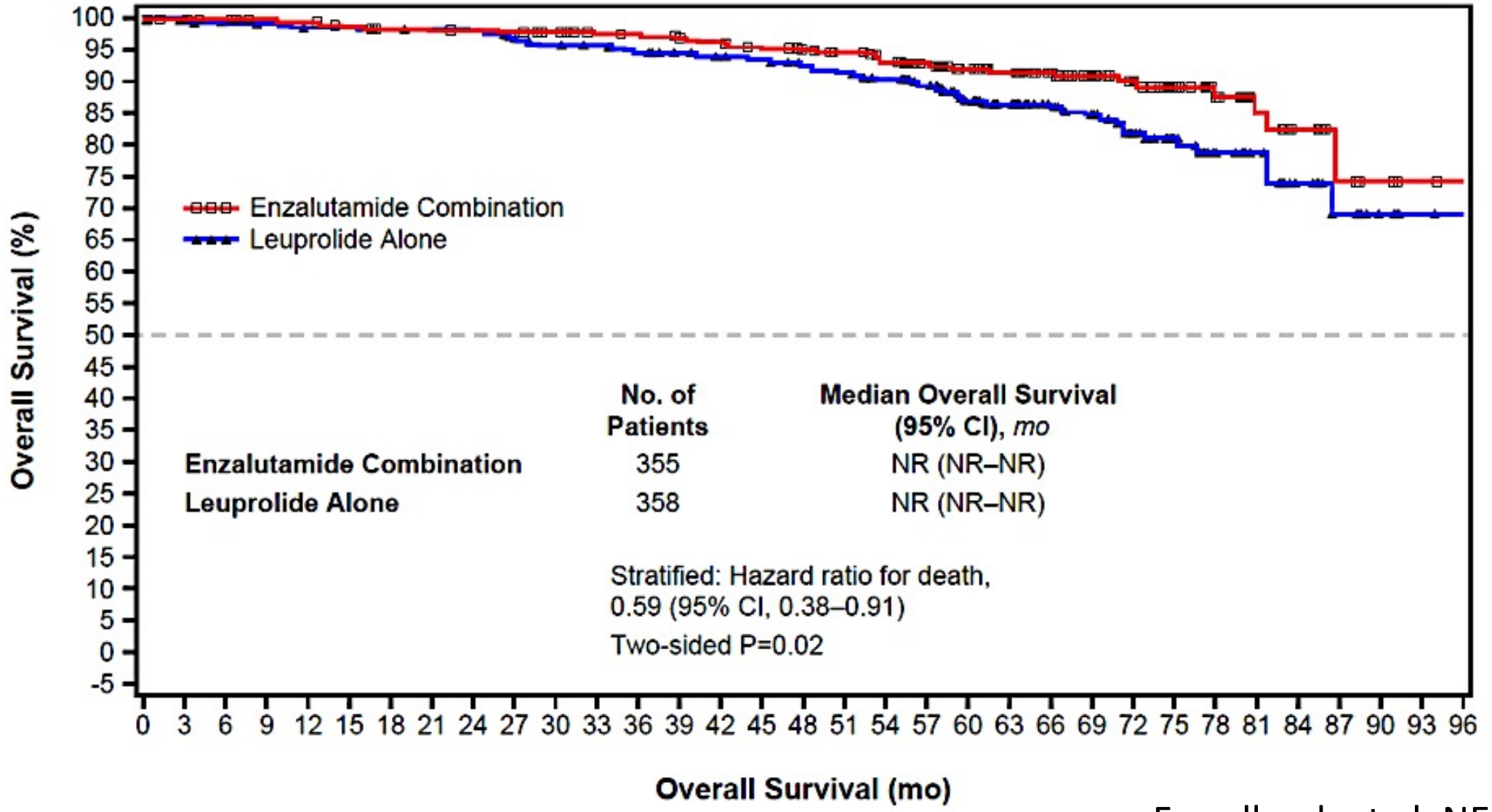
Freedland, et al. NEJM, 2023.

EMBARK



Freedland, et al. NEJM, 2023.

EMBARK

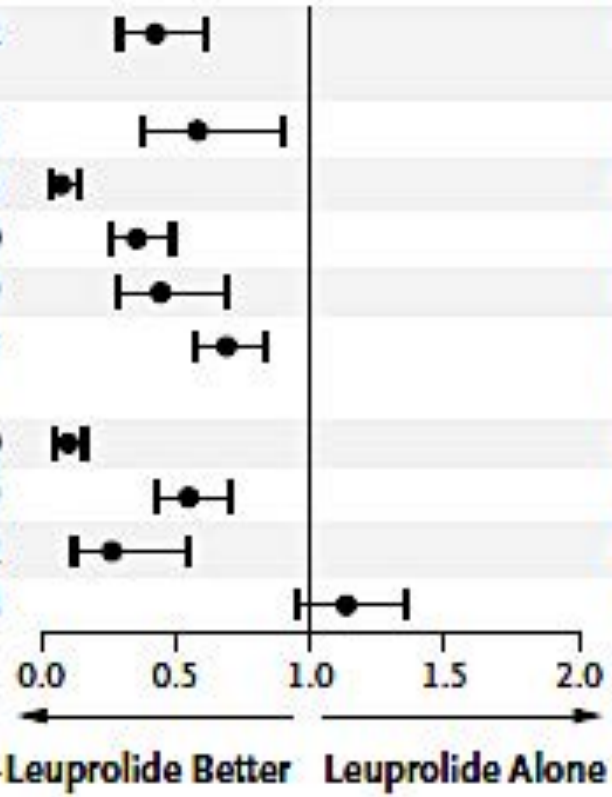


Freedland, et al. NEJM, 2023.

EMBARK

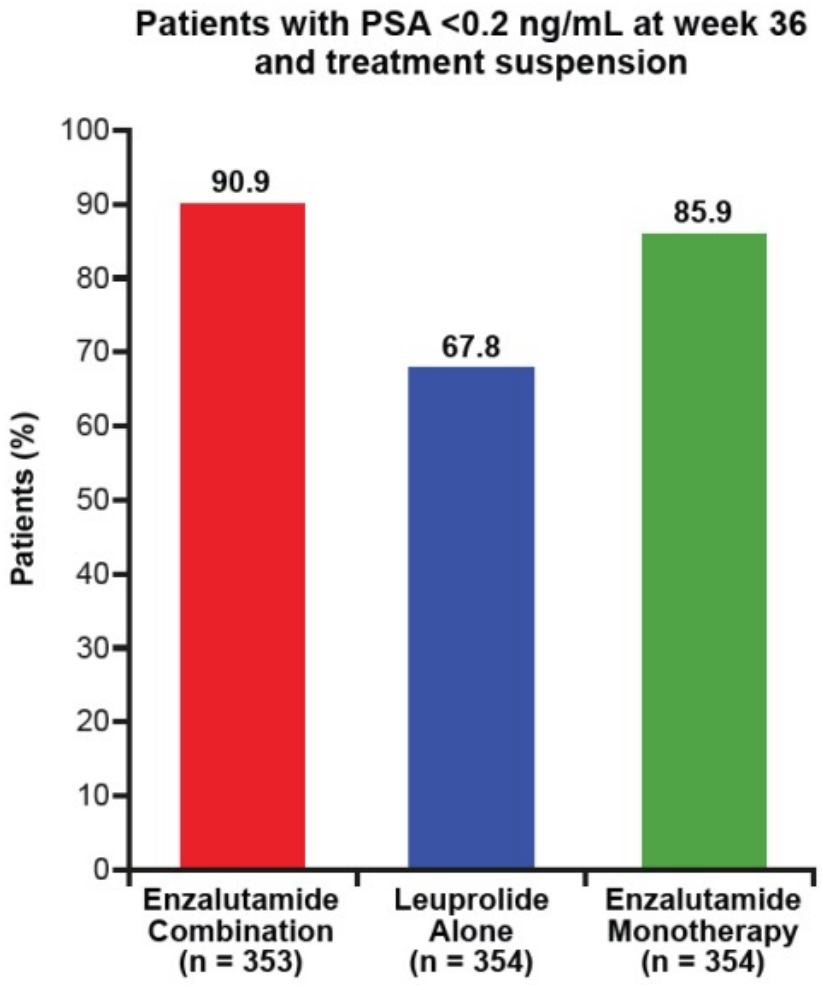
A Secondary End Points, Enzalutamide plus Leuprolide vs. Leuprolide Alone

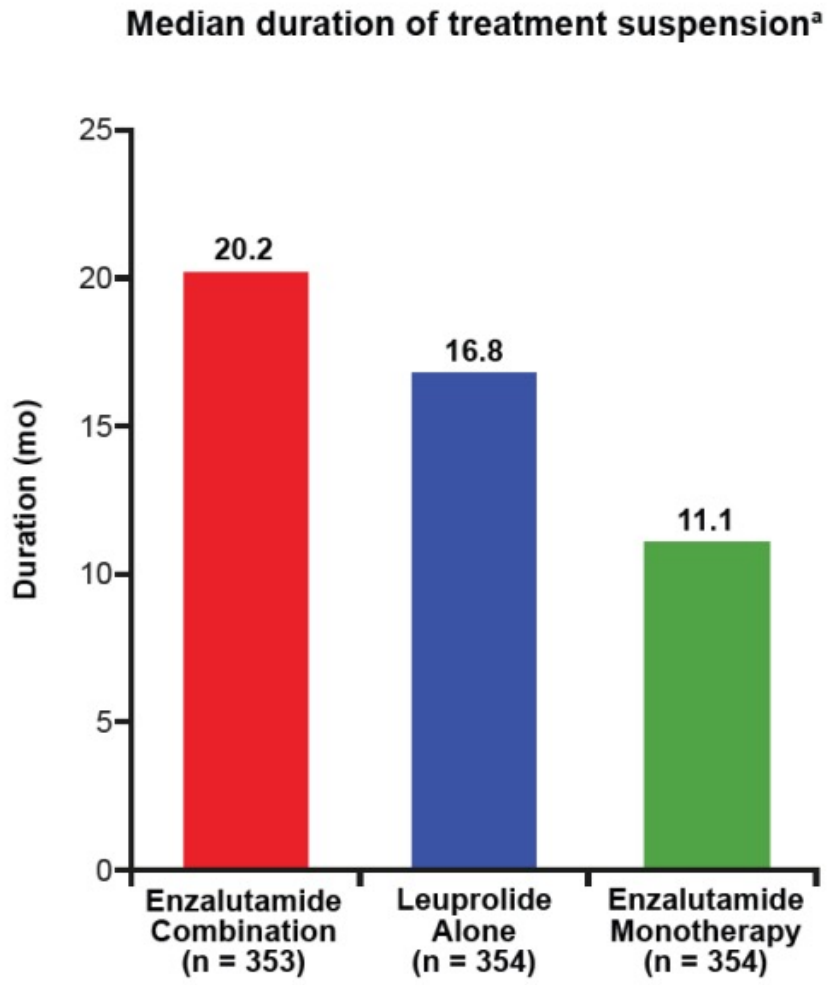
End Point	Enzalutamide+ Leuprolide (no. of patients)	Leuprolide Alone (no. of patients)	Enzalutamide+ Leuprolide (no. of events)	Leuprolide Alone (no. of events)	Hazard Ratio (95% CI)	Two-Sided P Value
Metastasis-free survival (primary end point)	355	358	45	92	0.42 (0.30–0.61)	<0.001
Overall survival	355	358	33	55	0.59 (0.38–0.91)	0.02
PSA progression	355	358	8	93	0.07 (0.03–0.14)	<0.001
First use of new antineoplastic therapy	355	358	58	140	0.36 (0.26–0.49)	<0.001
Distant metastasis	355	358	30	59	0.44 (0.28–0.69)	
Resumption of any hormonal therapy	321	240	256	217	0.69 (0.58–0.83)	
Castration resistance	355	358	14	120	0.09 (0.05–0.16)	
Symptomatic progression	355	358	104	169	0.55 (0.43–0.70)	
First symptomatic skeletal event	355	358	9	32	0.26 (0.13–0.55)	
First deterioration in FACT-P total score	355	358	257	248	1.14 (0.95–1.36)	



Freedland, et al. NEJM, 2023.

EMBARK



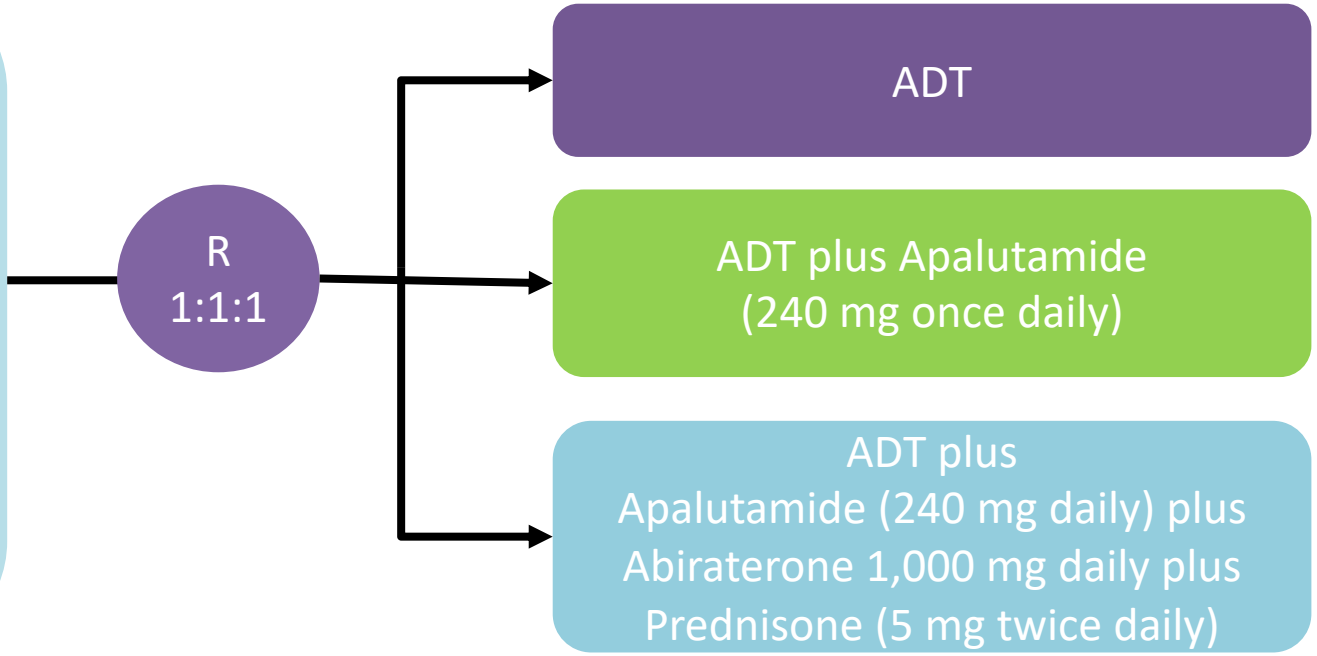


Freedland, et al. NEJM, 2023.

PRESTO

Key Eligibility Criteria

- Prior Radical Prostatectomy
- Salvage RT or no planned RT.
- No metastatic disease on CT/Bone Scan
- PET positive patients were allowed.
- PSA ≥ 0.5ng/mL
- PSADT ≤ 9 months
- Testosterone ≥ 150 ng/dL



- **52 weeks treatment**
- **Stratified by PSADT**
- **Primary Outcome: PSA recurrence**
- **Secondary Outcomes: safety, patient-reported quality of life, time to testosterone recovery, metastasis-free survival and time to castration resistance**

Aggarwal,et al. J Clin Oncol 42:1114-1123, 2024

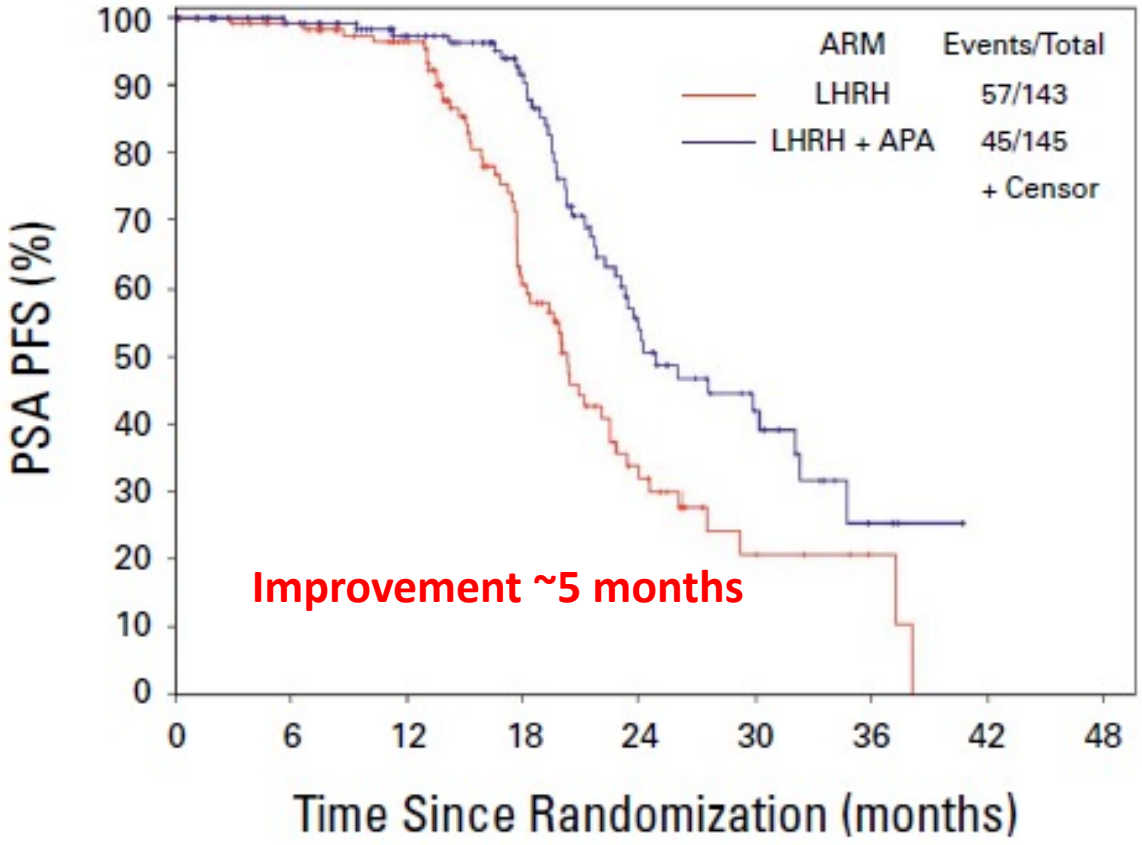
PRESTO

- 503 men with biochemical recurrence after local therapy (no mets)
  - ~ 166 in each arm
- 383 completed treatment
- 63 still on treatment

- Median Follow up was 21.5 months
- At 5 years of follow-up
  - Improve Biochemical Recurrence Free Survival for Apalutamide arms

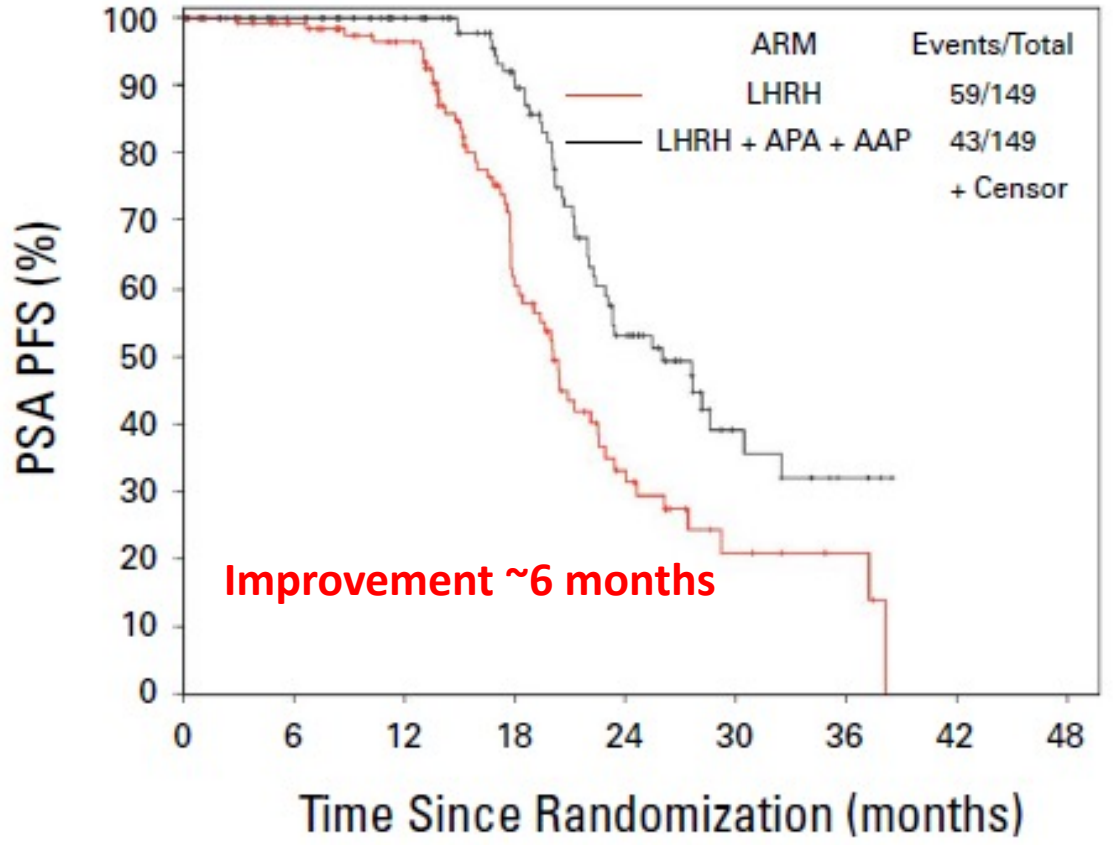
Aggarwal,et al. J Clin Oncol 42:1114-1123, 2024

PRESTO



Time to BCR

ADT +Appa - 24.9 mos [95% CI, 23.3 to 32.3]
ADT - 20.3 mos [95% CI, 18.2 to 22.9]
HR, 0.52 [95% CI, 0.35 to 0.77]; P=0.00047)



Time to BCR

ADT +Appa + Abby - 26.0 mos [95%CI, 22.9 to 32.5]
ADT - 20.0 mos [95% CI, 18.2 to 22.5
HR, 0.48 [95% CI, 0.32 to 0.71]; P=0.00008

Hormone Sensitive Biochemical Recurrence

- Biochemical recurrence - local therapy first.
  - RT with ADT
  - Intensification of ADT with Apalutamide and/or Abiraterone with RT
  - STAMPEDE Trial and FORMULA-509 Trial
- Treatment Intensity Different
  - EMBARK – shorter and trial of Enzalutamide alone
  - PRESTO – Longer and more intense with ADT, Apalutamide and Abiraterone.
- Endpoints different.
- Similar conclusions – next generation ADT works in high-risk patients

Non-metastatic CRPC

Three Trials

- PROSPER (enzalutamide + ADT v ADT) - n=1,401
- SPARTAN (apalutamide + ADT v ADT) - n=1,207
- ARAMIS (darolutamide + ADT v ADT) - n= 1,509

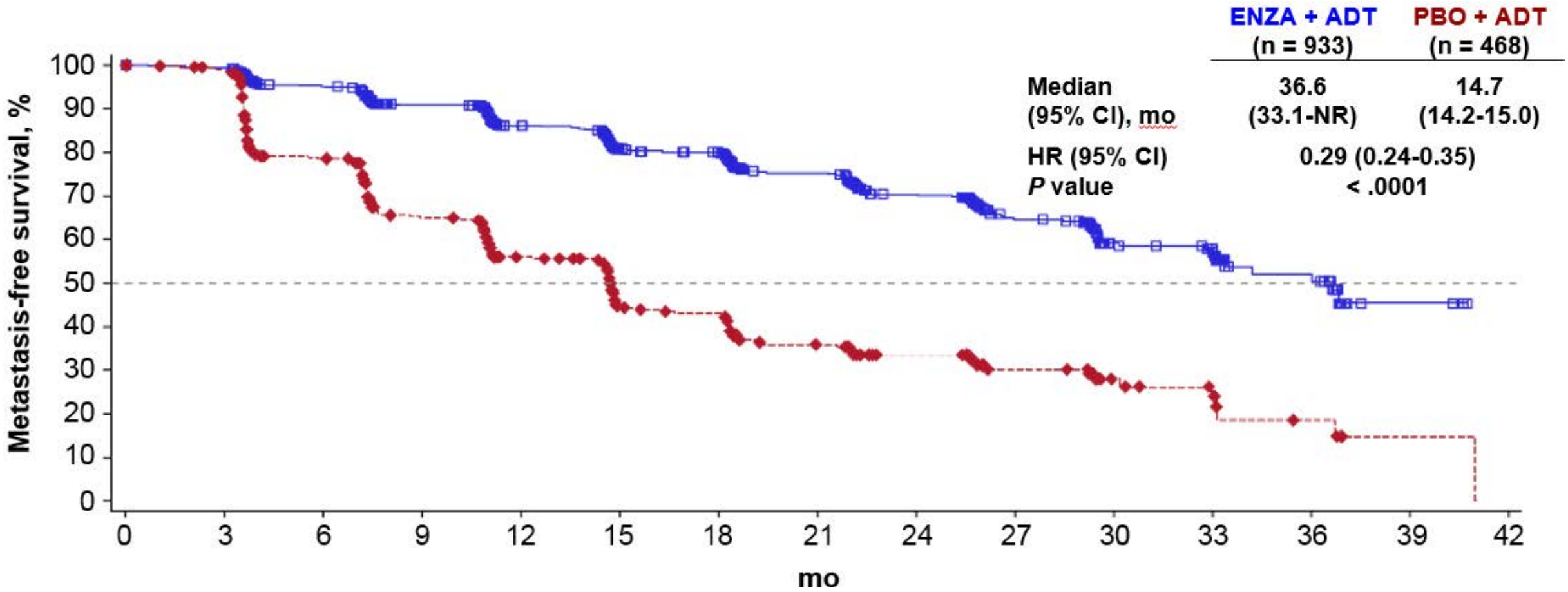
- Eligibility
  - Rising PSA despite castrate testosterone level (≤ 50 ng/dL)
  - Baseline PSA ≥ 2 ng/mL
  - PSA doubling time ≤ 10 months
  - No evidence of metastatic disease by conventional bone scan and CT/MRI
  - Pelvic lymph nodes up to 1.5 cm allowed (up to 2.0 cm in SPARTAN)
- 2:1 randomization

Non-metastatic CRPC

- Metastasis-free survival (primary endpoint):
  - PROSPER [HR=0.29 (0.24-0.35)]
  - SPARTAN [HR=0.28 (0.23-0.35)]
  - ARAMIS [HR=0.41 (0.34-0.50)]

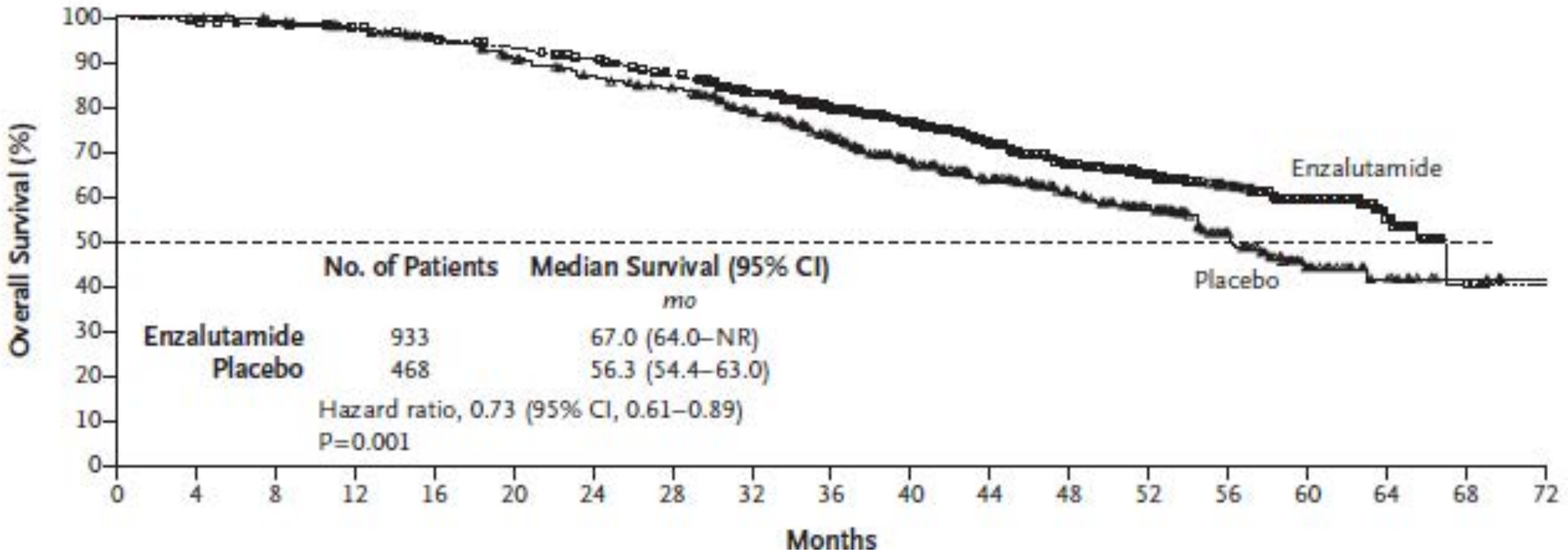
- Overall Survival (secondary endpoint):
  - PROSPER [HR=0.73 (0.61-0.89)]
  - SPARTAN [HR=0.78 (0.64-0.96)]
  - ARAMIS [HR=0.69 (0.53-0.88)]

PROSPER- Enzalutamide



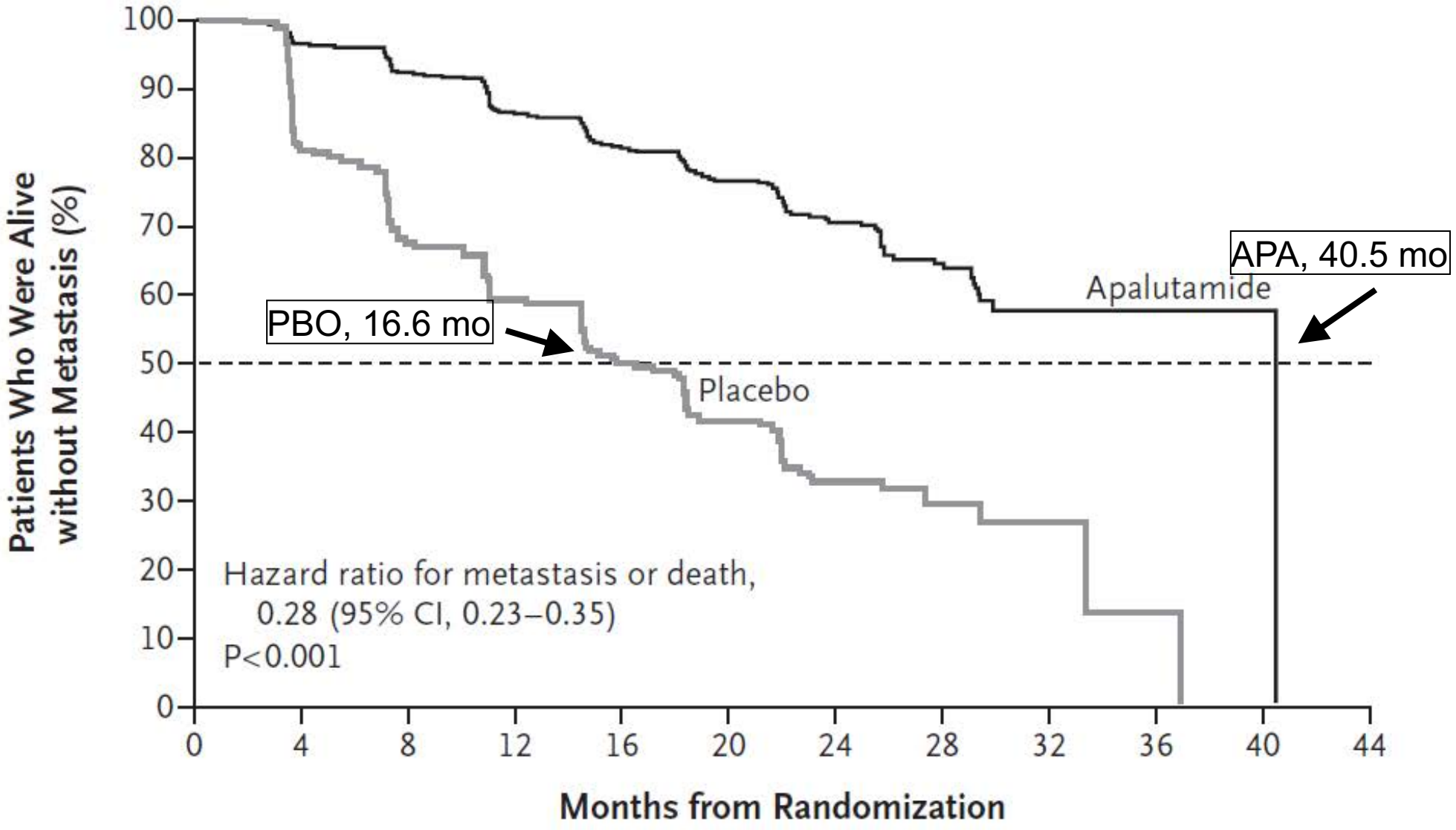
Hussain et al, NEJM, 378(26):2465-2474, 2018

PROSPER- Enzalutamide



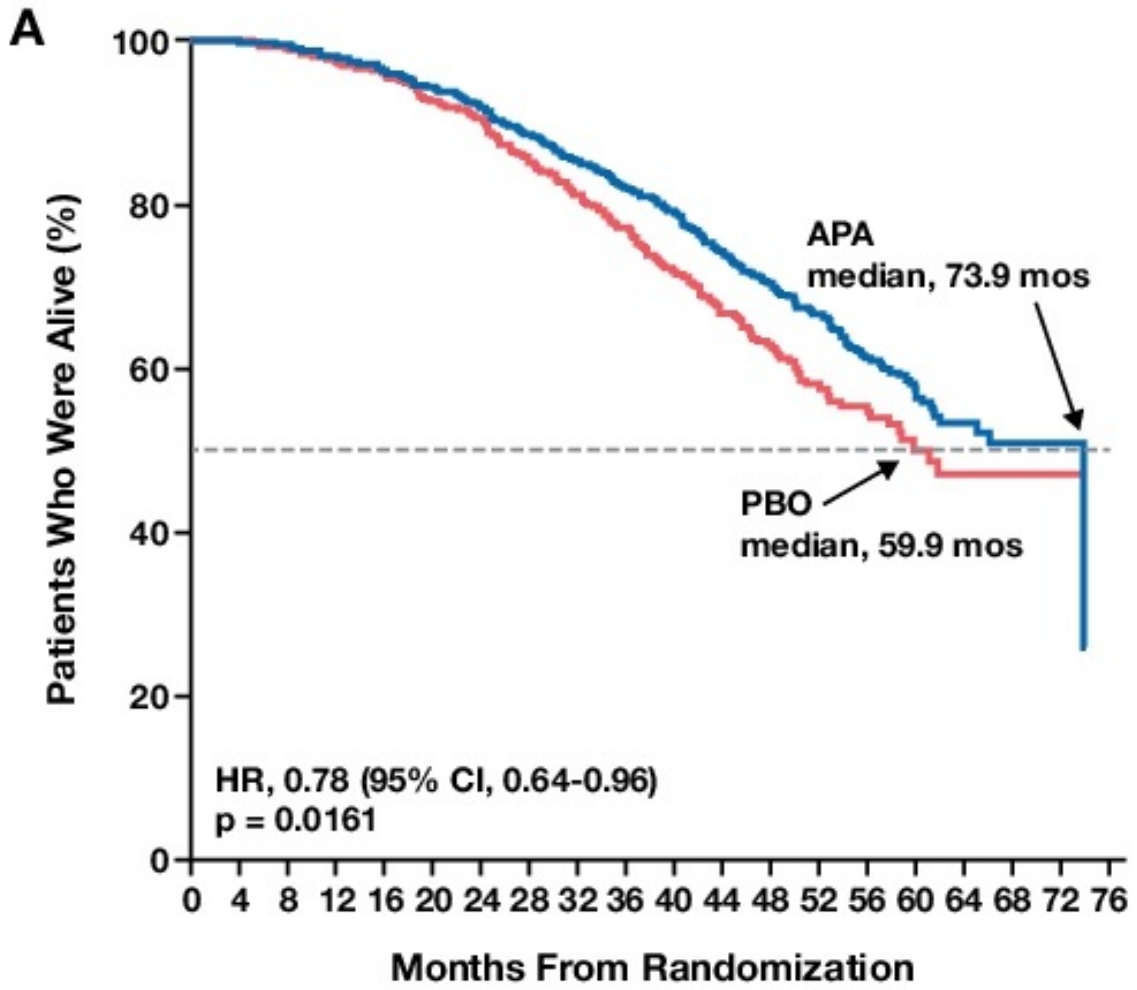
Sternberg, et al, NEJM, 382:2197-206, 2020

SPARTAN - Apalutamide



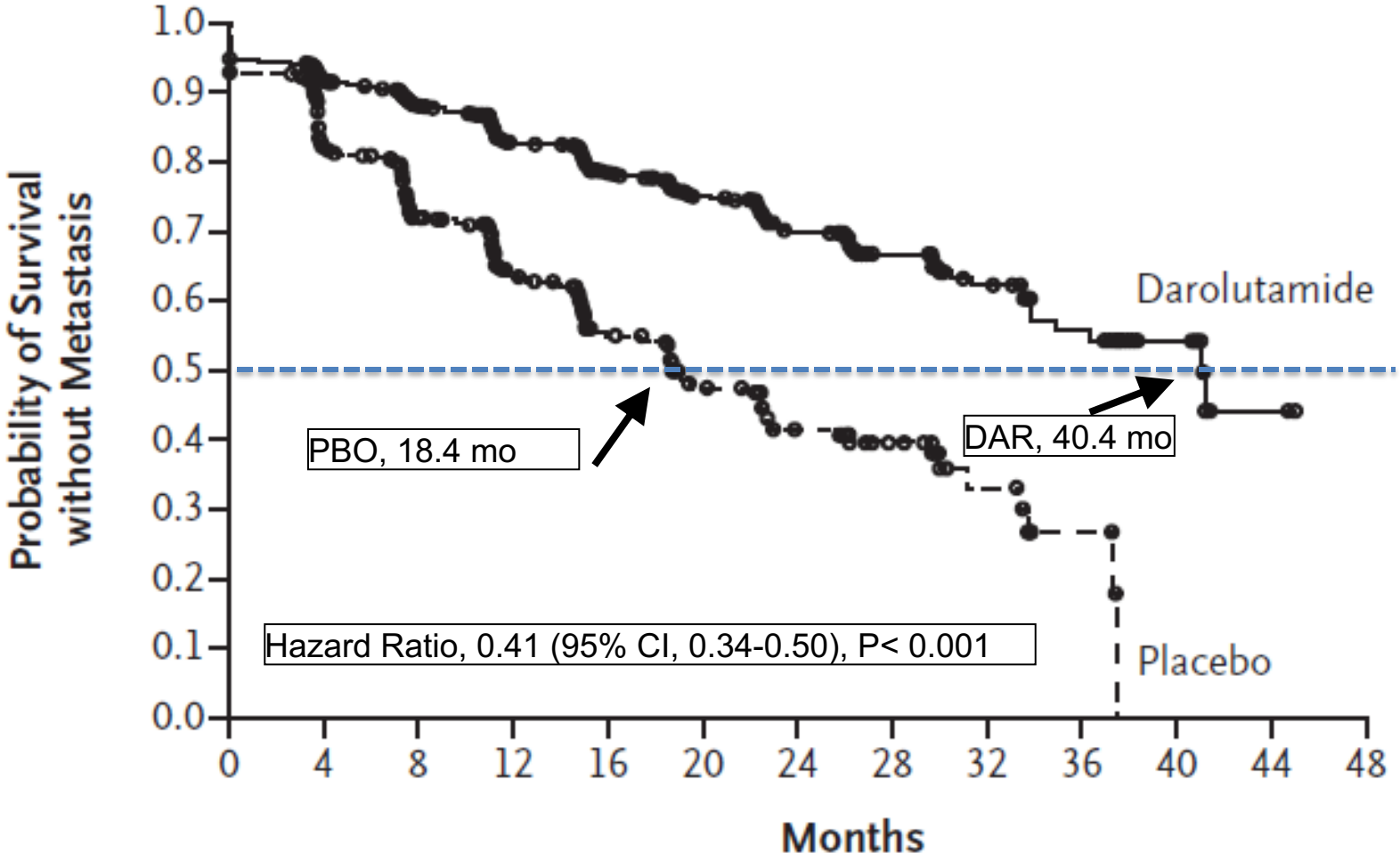
Smith et al, NEJM, 2018

SPARTAN - Apalutamide



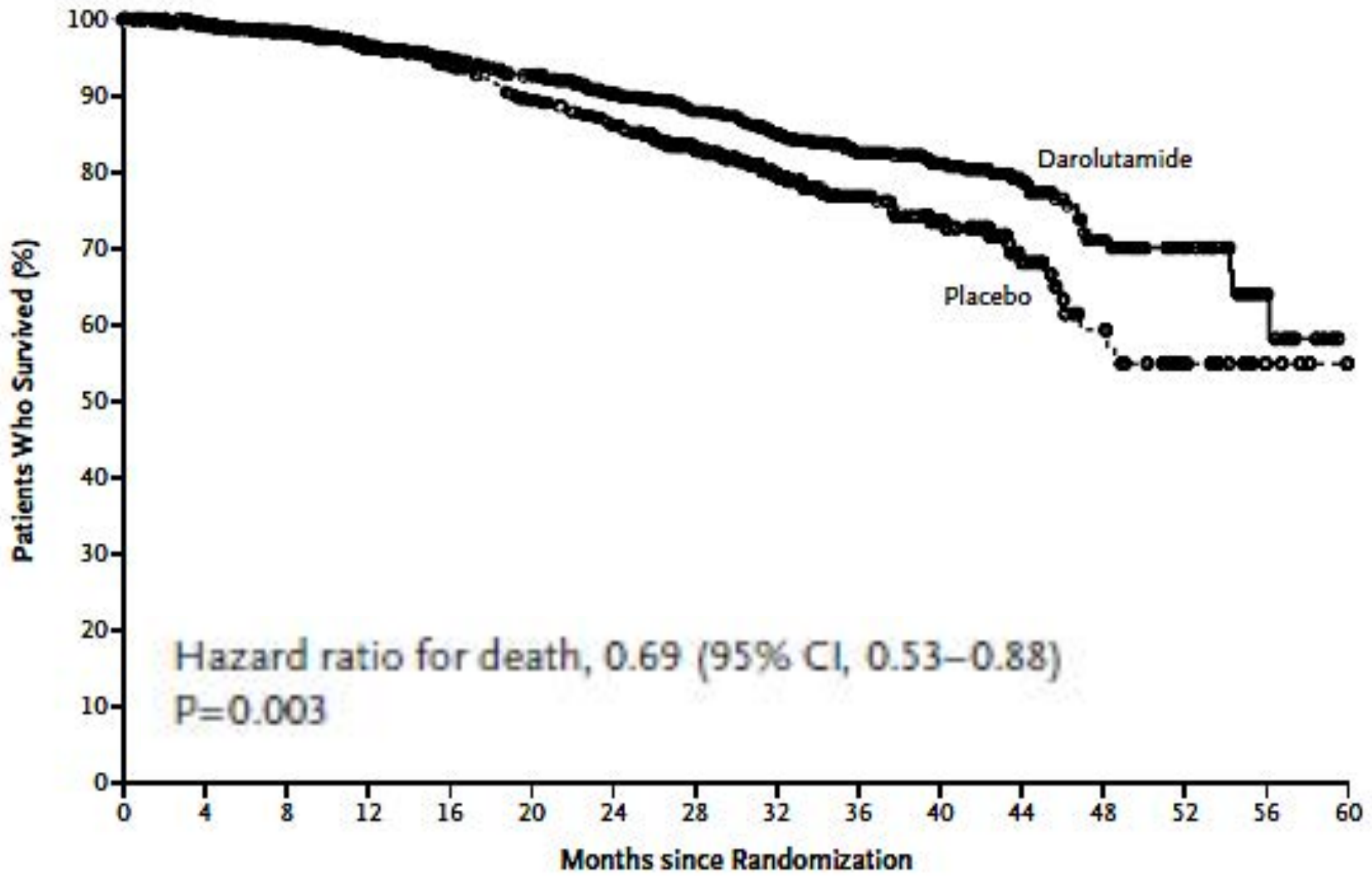
Smith et al, European Urology, 2021

ARAMIS - Darolutamide



Fizazi, et al, NEJM, 380:1235-46, 2019

ARAMIS - Darolutamide



Fizazi, et al, NEJM, 383:1040-9, 2020

Take Home nmCRPC

- Three drugs decrease MFS and OS
- Toxicity maybe less with Darolutamide
  - Discontinuation for adverse events (AEs)
    - 8.9% with Darolutamide versus 8.7% with placebo
    - 10.6% with Apalutamide versus 7% with placebo
    - 10% with Enzalutamide versus 6% with placebo
  - No increase in falls and fractures with Darolutamide
  - Increases were seen with Enzalutamide and Apalutamide
  - Overall, no difference in Grade 3 toxicity (~75% v 25%)

Future Studies

- ARASTEP: Darolutamide + ADT in nmHSPC
  - Similar to EMBARK
- PRIMORDIUM: Apalutamide + ADT in nmHSPC
  - PET imaging as primary end point

Future Directions

- nmCPRC is disappearing
  - Conventional ADT for nmHSPC is not guideline supported
  - Trials (EMARK/PRESTO) mean nmCRPC is going to be different
  - PET imaging is redefining metastatic disease
- nmHSPC is going to be redefined
  - Rapid PSAD
  - PET positive v. negative
  - Biological Markers (DDR, PSMA positive)

MODULE 2: Side Effects and Other Practical Considerations with Hormonal Therapy for Nonmetastatic Prostate Cancer — Dr Klotz

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Consulting Faculty Comments

ADT intensification for patients with biochemical recurrence

Neil Love, MD

David S Morris, MD

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QUESTIONS FOR THE FACULTY

David S Morris, MD

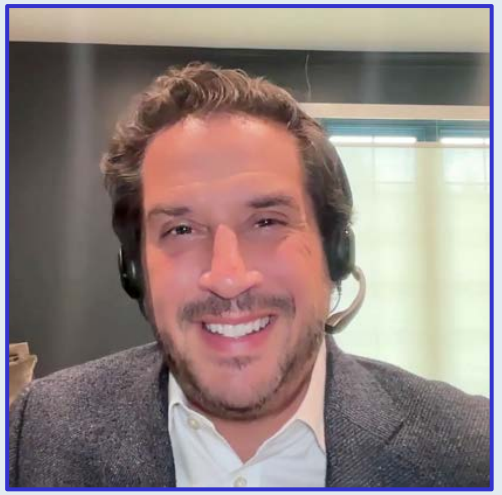
How important is it to have patients with PSA-only recurrence complete full pelvic therapy and all potential salvage options before initiating an EMBARK-like treatment approach?

What is your approach to treatment holidays for patients with high-risk biochemical recurrence who are receiving ADT combined with enzalutamide? Are you considering intermittent combination therapy?

Consulting Faculty Comments

Practical application of the EMBARK data to the management of high-risk biochemical recurrence

Neil Love, MD



Jason Hafron, MD

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QUESTIONS FOR THE FACULTY

Jason Hafron, MD

In which situations are you considering enzalutamide and ADT for patients with biochemical recurrence after definitive local therapy? What about enzalutamide monotherapy?

What is your experience with the enzalutamide-associated side effects of hot flashes and sexual dysfunction? Does testosterone make a difference in the adverse event profile?

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Practical Considerations with Hormonal Therapy for Nonmetastatic Prostate Cancer

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Initial considerations re ‘ADT for non-metastatic Pca’

- PSMA PET has resulted in dramatic stage migration
  - PSA-only failure (once PSA > 0.5) disappearing
- Evidence for a specific PSA threshold for initiating ADT scant
  - EORTC-30891: PSA 20 ng in men < 70, 50 ng in men ≥ 70 yrs
  - TOAD (Duschenes): Modest benefit of ADT pre mets but no PSA levels
  - Survival benefit of early ADT modest at best, less so weighed against known adverse effects of ADT
- Intermittent ADT supported by multiple randomized trials, but still controversial 38 years after first report: Klotz L, Whitmore W, Cancer 1986
- Unclear if PSMA positive nodal oligomets ≧ nodal mets on conventional imaging (lead time bias)

Tolerability profile of enzalutamide +/- ADT in EMBARK

- Any fatigue ≈ 45% with Enza vs 33% with L
- Fatigue ≥ Grade 3: 4% Enza vs 1.4% L
- Enza + L similar to Enza alone

Gynecomastia 45% Enza alone, 8% E + L or L alone

Similar to prior reports in advanced disease

'The safety profile of enzalutamide was consistent with that shown in previous clinical studies, with no apparent detrimental effect on quality of life.'

Table 2. Adverse Events (Safety Population).*

Event	Enzalutamide + Leuprolide (N=353)		Leuprolide Alone (N=354)		Enzalutamide Monotherapy (N=354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)					
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
Adverse event leading to death†	6 (1.7)	—	3 (0.8)	—	8 (2.3)	—
Most common adverse events‡						
Hot flash	243 (68.8)§	2 (0.6)	203 (57.3)§	3 (0.8)	77 (21.8)§	1 (0.3)
Fatigue	151 (42.8)§	12 (3.4)	116 (32.8)§	5 (1.4)	165 (46.6)§	14 (4.0)
Arthralgia	97 (27.5)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	0
Constipation	46 (13.0)	0	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	7 (2.0)	44 (12.4)	3 (0.8)	45 (12.7)	6 (1.7)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Pain in arm or leg	41 (11.6)	1 (0.3)	36 (10.2)	0	40 (11.3)	0
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	1 (0.3)	37 (10.5)	0	41 (11.6)	0
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	2 (0.6)	28 (7.9)	1 (0.3)	36 (10.2)	3 (0.8)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	1 (0.3)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	1 (0.3)
Peripheral edema	27 (7.6)	0	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	3 (0.8)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

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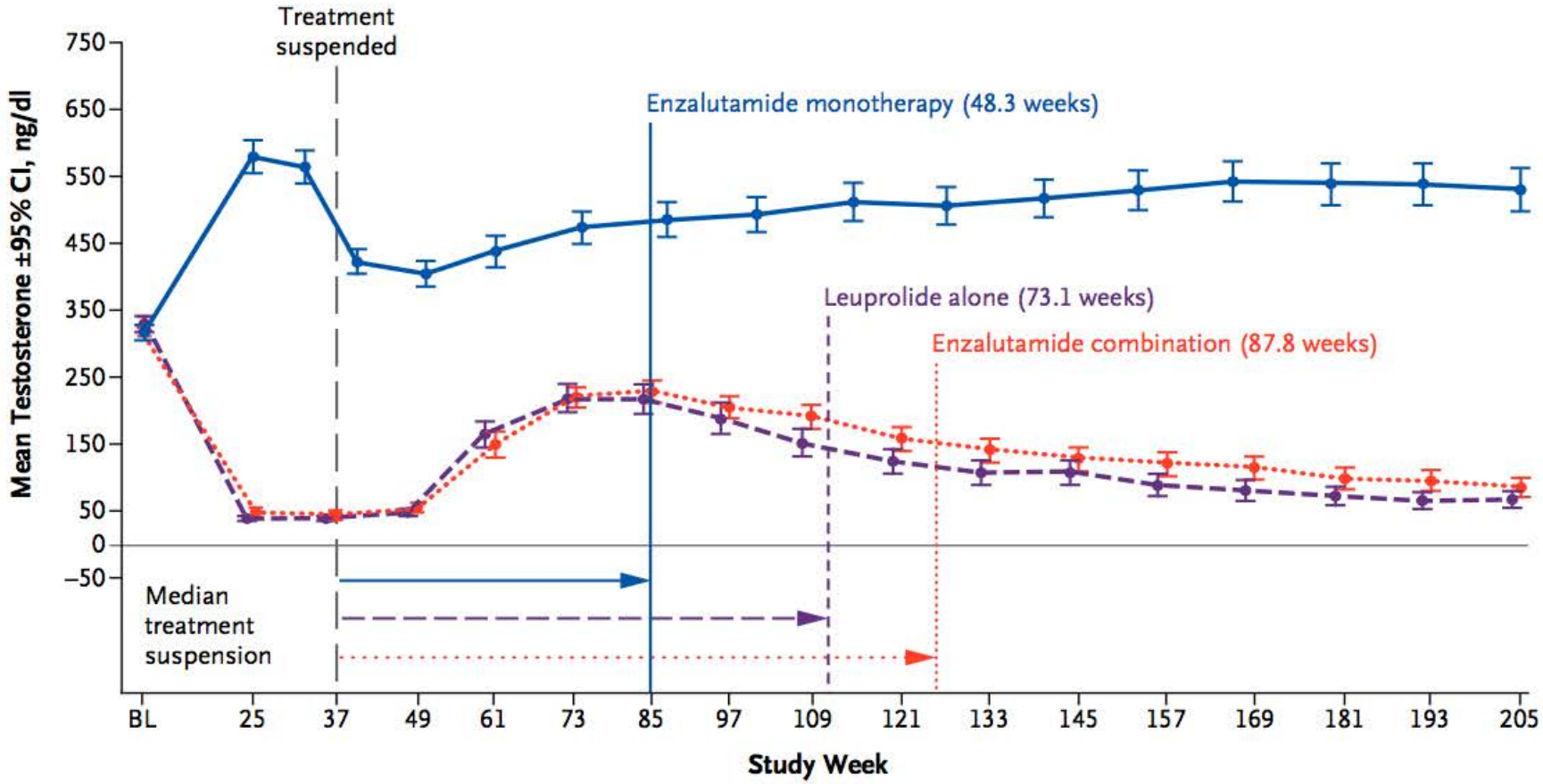


Number of Patients

Enzalutamide monotherapy	354	333	314	305	303	296	298	287	279	268	265	258	243	251	233	234	219
Enzalutamide combination	351	328	294	278	281	278	273	272	268	257	250	249	251	243	234	241	231
Leuprolide alone	354	329	304	291	286	281	266	253	247	238	232	222	219	213	210	192	193

Treatment: Treatment suspension; Enzalutamide monotherapy; Enzalutamide combination; Leuprolide alone; Clinically meaningful threshold

A

Enzalutamide Combination / Leuprolide Alone

BPI-SF Subdomains	No. of Events	Median (mo)	Hazard Ratio (95% CI)
Item 3 (worst pain in past 24 hours)	228/217	13.93/19.35	1.08 (0.89, 1.30
	133/151	80.00/66.27	0.82 (0.65, 1.04
Mean pain interference	229/217	19.32/19.71	1.07 (0.88, 1.29

● Time to First Clinically Meaningful Deterioration
◆ Time to Confirmed Clinically Meaningful Deterioration

B1

Enzalutamide Combination / Leuprolide Alone

FACT-P Subdomains	No. of Events	Median (mo)
Physical well-being	270/250	5.59/13.77
	206/182	24.84/49.84
Social/family well-being	213/208	16.59/13.86
	134/145	NE/66.37
Emotional well-being	191/168	32.99/47.05
	119/105	NE/NE
Functional well-being	263/254	8.18/10.87
	218/201	27.63/33.22
Prostate cancer pain subscale score	264/266	11.04/8.41
	193/196	35.91/30.39
Prostate cancer subscale score	287/274	5.55/5.75
	229/223	16.82/19.35
FACT-G total score	254/245	5.75/11.24
	190/179	38.64/47.01
FACT-P trial outcome index	256/241	8.15/13.83
	205/195	27.76/38.67
FACT advanced prostate symptom index	240/237	11.20/13.93
	171/163	49.94/63.21
FACT-P total score	257/248	8.31/11.10
	194/192	38.77/36.53

● Time to First Clinically Meanin
◆ Time to Confirmed Clinically M

0.6 0.8 1 1.2

Favors Enzalutamide Combination | Favors Leupro Alone

B2

Enzalutamide Monotherapy / Leu

FACT-P Subdomains	No. of Events	Media
Physical well-being	269/250	5.75/
	209/182	27.56
Social/family well-being	212/208	13.86
	137/145	79.87
Emotional well-being	199/168	33.12
	128/105	82.8
Functional well-being	266/254	8.41/
	204/201	38.34
Prostate cancer pain subscale score	262/266	8.74
	208/196	30.42
Prostate cancer subscale score	286/274	5.55
	248/223	14.00
FACT-G total score	257/245	8.34/
	199/179	33.58
FACT-P trial outcome index	266/241	8.44/
	216/195	33.18
FACT advanced prostate symptom index	270/237	8.44/
	199/163	35.94
FACT-P total score	263/248	8.38/
	207/192	30.55

C1

Enzalutamide Combination / Leuprolide Alone

QLQ-PR25 Subdomains	No. of Events	Median (mo)	Hazard Ratio (95% CI)
Sexual activity	236/216	2.86/2.89	1.12 (0.93, 1.35)
	223/202	2.96/2.99	1.09 (0.89, 1.32)
Sexual functioning	32/33	38.67/27.66	0.84 (0.50, 1.40)
	25/25	69.98/47.11	0.97 (0.54, 1.76)
Urinary symptoms	266/272	5.55/5.62	1.02 (0.86, 1.21)
	203/221	24.87/16.76	0.91 (0.75, 1.11)
Bowel symptoms/ function	242/248	11.01/11.07	1.03 (0.86, 1.23)
	175/177	44.25/47.15	0.99 (0.80, 1.22)
Hormonal treatment-related symptoms	312/322	2.83/2.83	1.09 (0.93, 1.28)
	296/297	2.86/2.89	1.19 (1.01, 1.40)
Incontinence aid	55/51	19.38/19.52	0.92 (0.63, 1.36)
	37/34	82.86/77.63	0.92 (0.57, 1.49)
Modified urinary symptoms	278/288	3.06/5.39	1.00 (0.85, 1.18)
	227/244	8.31/8.54	0.96 (0.80, 1.16)

● Time to First Clinically Meaningful Deterioration
◆ Time to Confirmed Clinically Meaningful Deterioration

0.4 0.6 0.8 1 1.2 1.4 1.6 1.8

Favors Enzalutamide Combination | Favors Leuprolide Alone

C2

Enzalutamide Monotherapy / Leuprolide Alone

QLQ-PR25 Subdomains	No. of Events	Median (mo)	Hazard ratio (95% CI)
Sexual activity	213/216	2.89/2.89	0.92 (0.76, 1.11)
	191/202	5.55/2.99	0.76 (0.62, 0.94)
Sexual functioning	56/33	22.34/27.66	1.46 (0.93, 2.29)
	45/25	44.19/47.11	1.47 (0.86, 2.49)
Urinary symptoms	267/272	8.34/5.62	0.83 (0.70, 0.99)
	210/221	24.74/16.76	0.91 (0.75, 1.10)
Bowel symptoms/ function	244/248	13.77/11.07	0.97 (0.81, 1.16)
	183/177	47.01/47.15	1.00 (0.82, 1.23)
Hormonal treatment-related symptoms	326/322	2.86/2.83	0.95 (0.81, 1.12)
	310/297	2.96/2.89	1.06 (0.90, 1.25)
Incontinence aid	59/51	38.60/19.52	0.94 (0.64, 1.38)
	45/34	66.23/77.63	1.12 (0.70, 1.79)
Modified urinary symptoms	280/288	5.59/5.39	0.85 (0.72, 1.00)
	231/244	13.90/8.54	0.88 (0.74, 1.06)

● Time to First Clinically Meaningful Deterioration
◆ Time to Confirmed Clinically Meaningful Deterioration

0.6 0.8 1 1.2 1.4 1.6 1.8 2 2.2 2.4 2.6

Favors Enzalutamide Monotherapy | Favors Leuprolide Alone

Sexual activity score

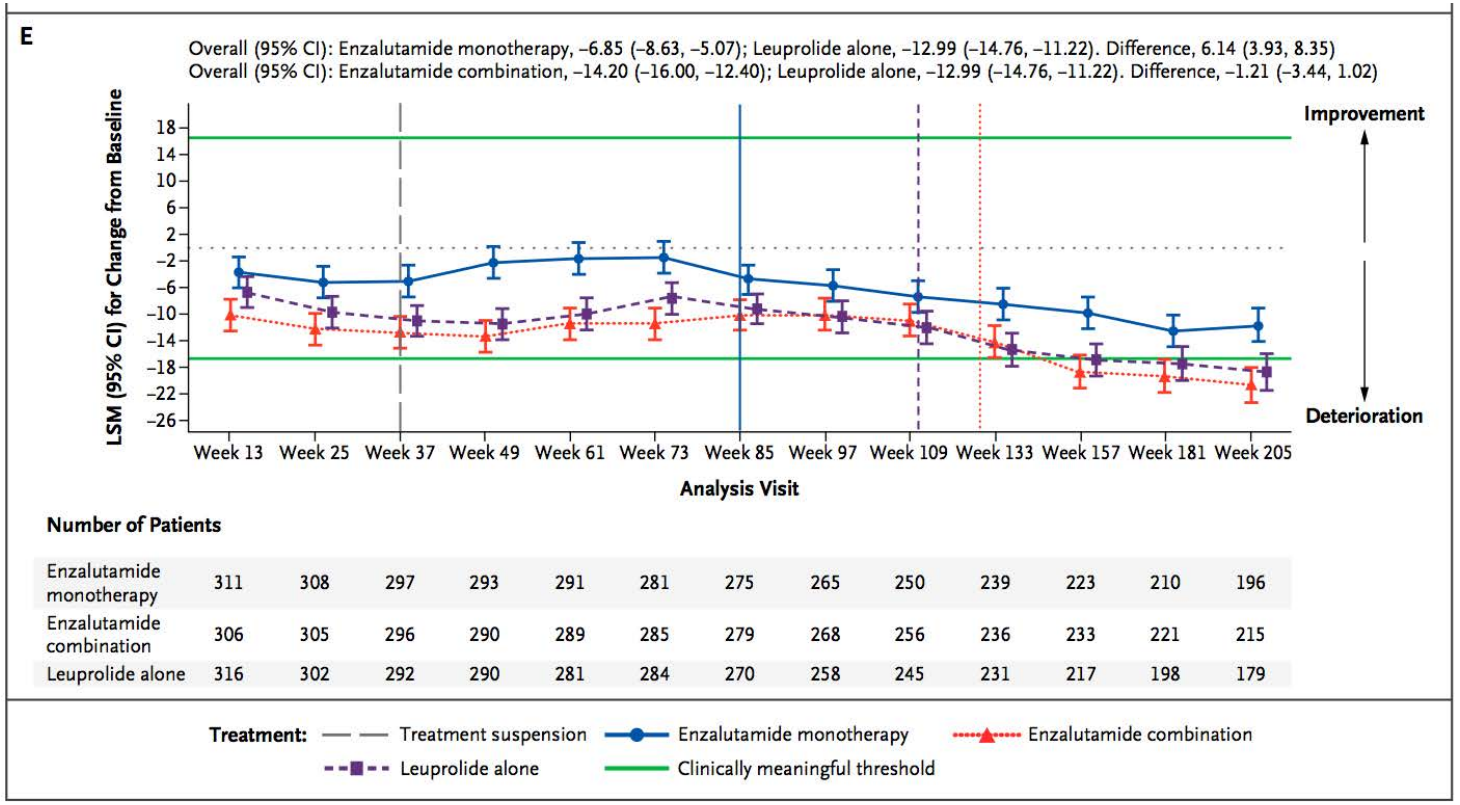
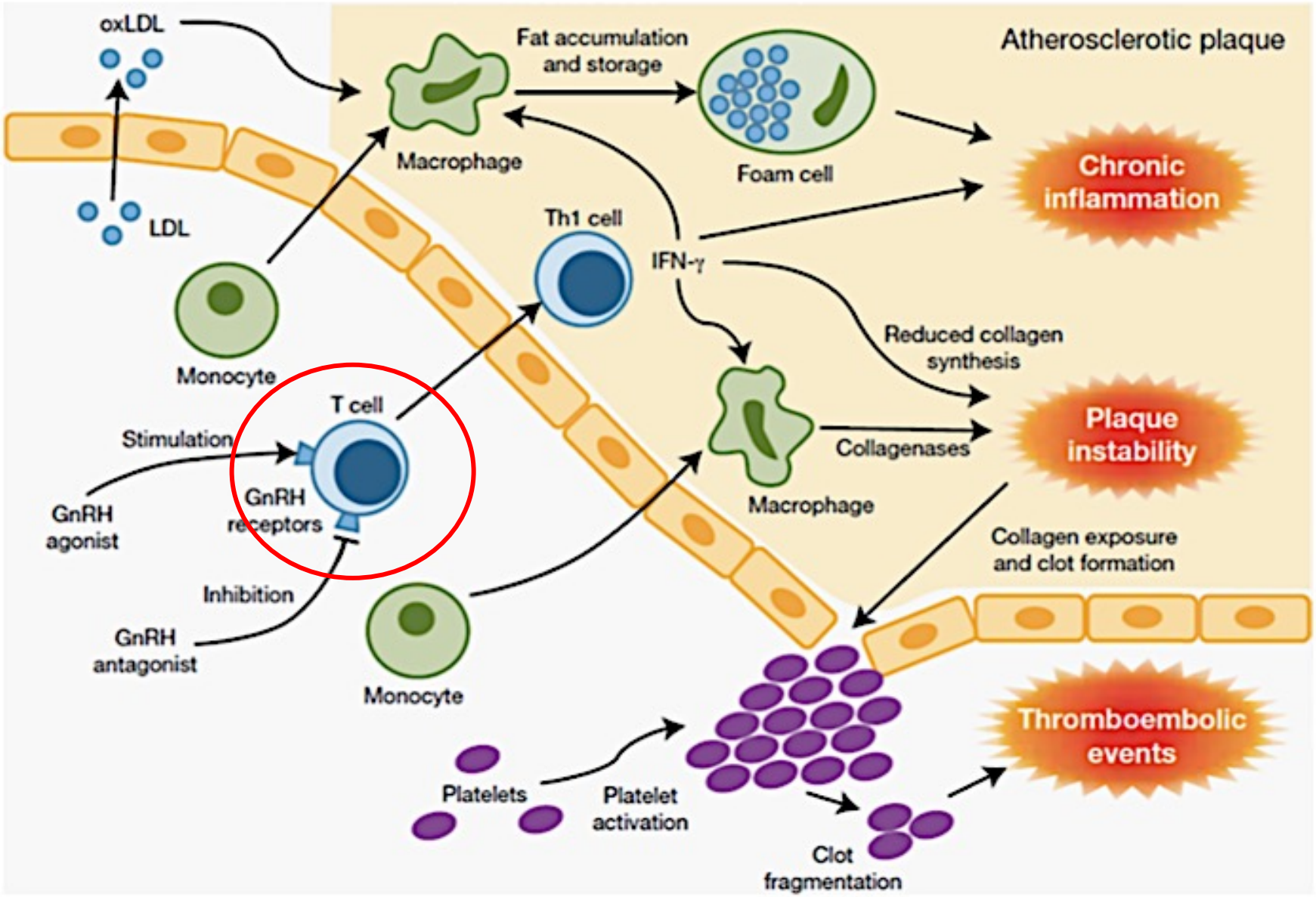


Figure 2. Continued.

Proposed mechanism for differential CV safety of LHRH agonists vs antagonists



Tivesten Å et al. *Urol Oncol* 2015;33(11):464-475.

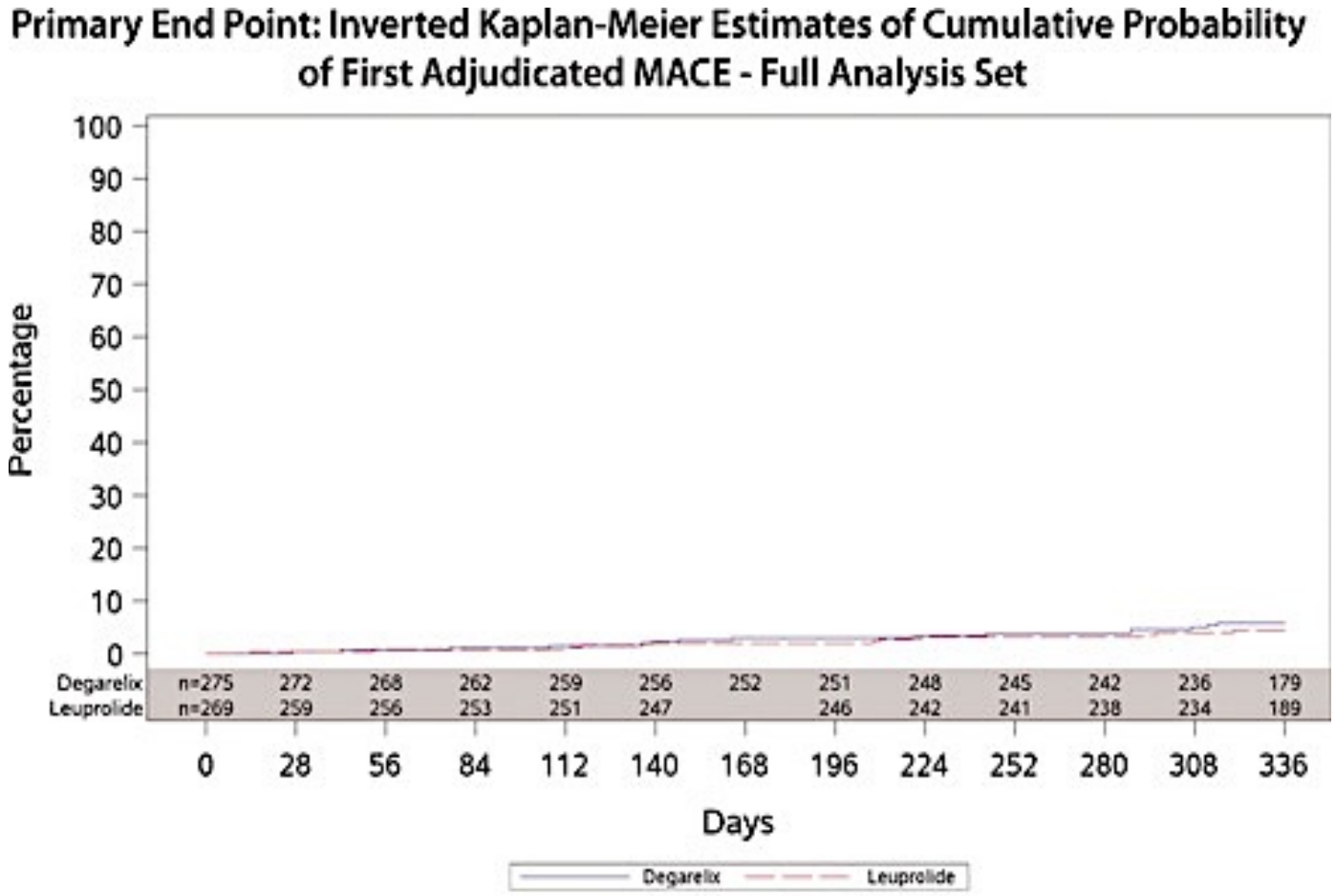
Adverse events: HERO study

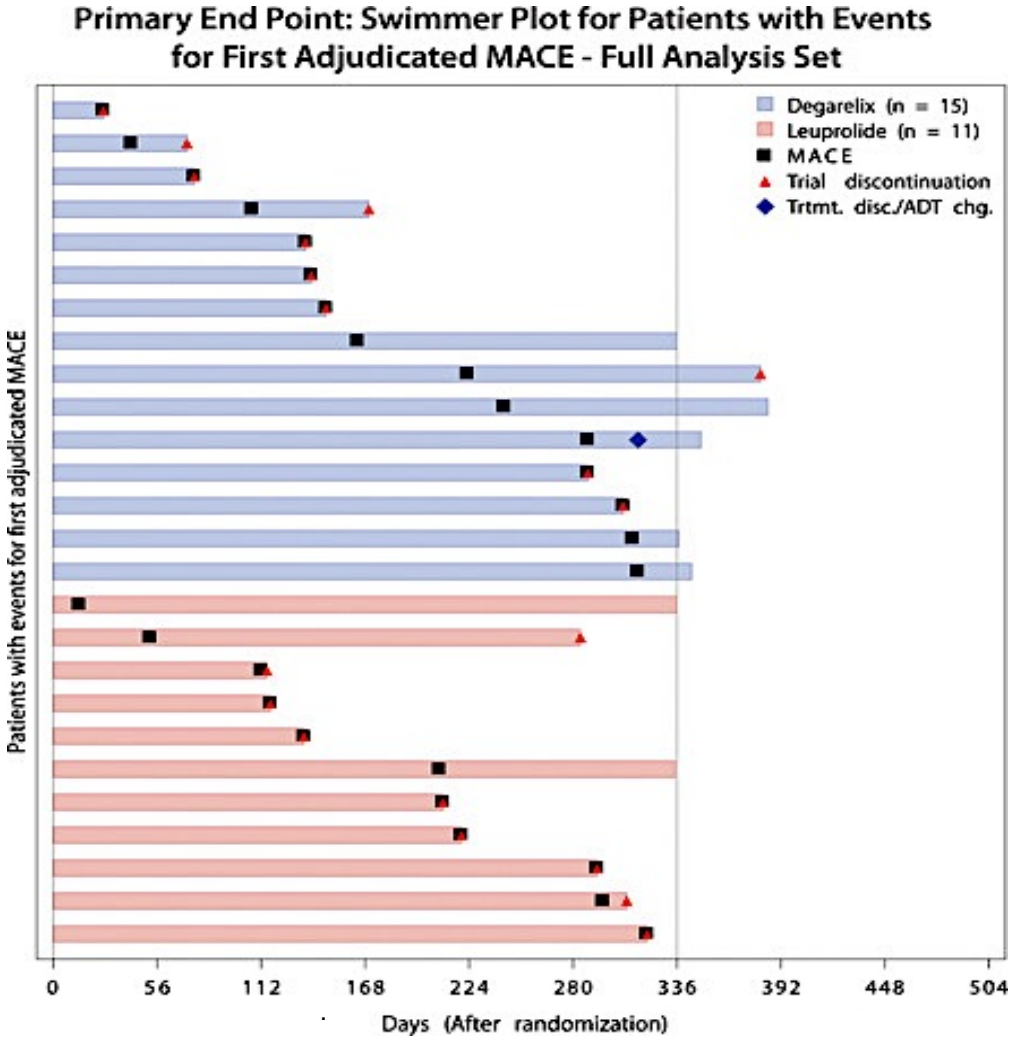
Event	Relugolix (N=622)		Leuprolide (N=308)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event	92.9%	18%	93.5%	20.5%
Serious adverse event	12.2%	9.8%	15.3%	11.4%
Fatal adverse event	1.1%	—	2.9%	—
MACE	2.9%	1.3%	6.2%	1.3%
No MACE history	2.8%	—	4.2%	—
With a history of MACE —	3.6%	—	17.8%	—

Shore N et al, NEJM 2020

Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Prostate Cancer: PRONOUNCE Study. R Lopes et al, Circulation 2021: 144:16; 1295

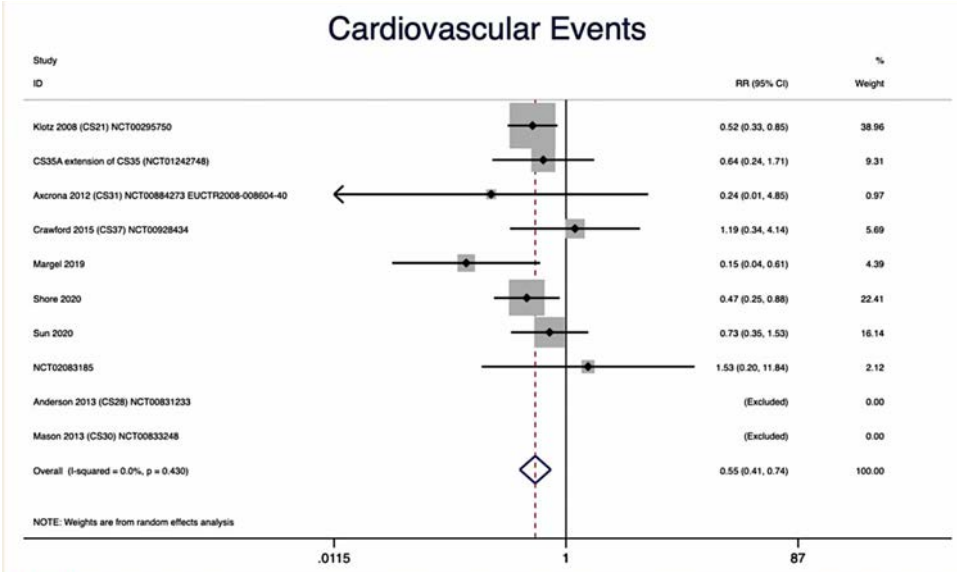
- N=545 men with pre-existing CV disease
- Planned 900; terminated early based on futility analysis

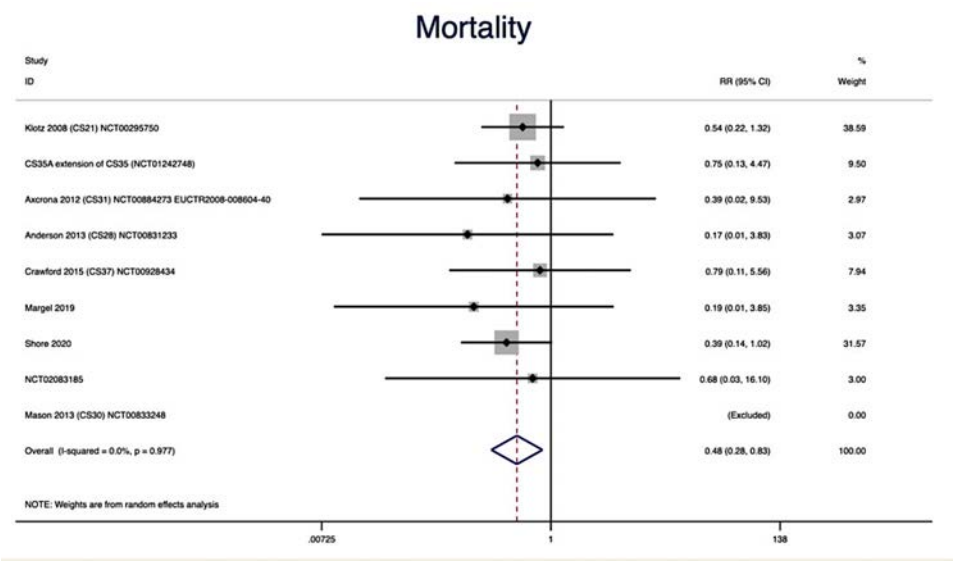


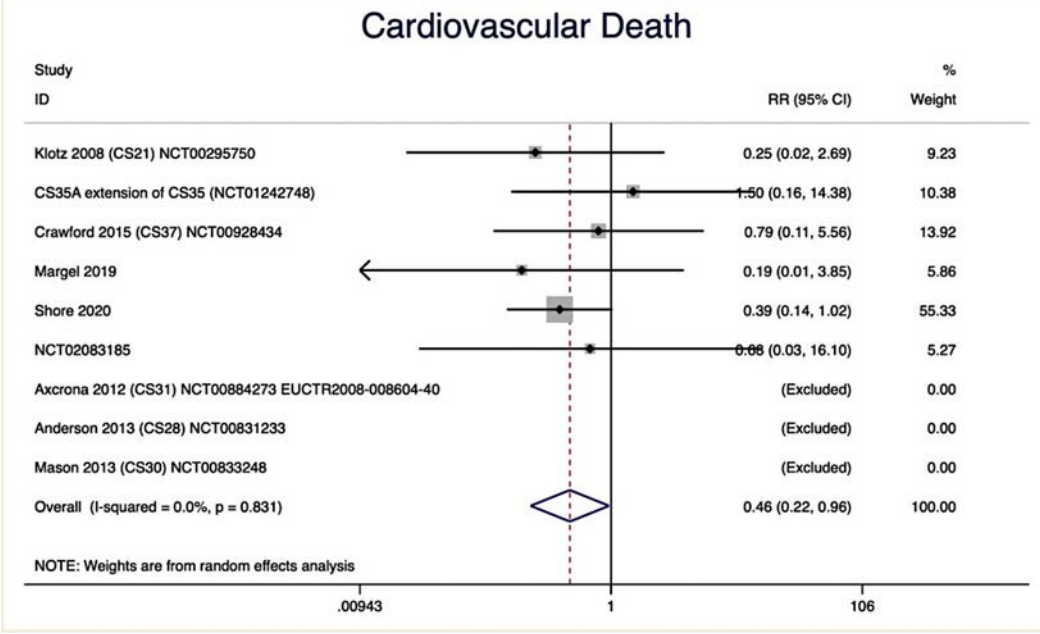


THE CARDIOVASCULAR EFFECTS OF GNRH ANTAGONISTS IN MEN WITH PROSTATE CANCER.

Cirne F, Klotz L, et al. Eur Heart J Cardiovasc Pharmacother. 2021







ADT and CV disease—bottom line

- ADT adversely affects CV health through multiple mechanisms
- Likely a greater impact in men with pre-existing CV disease
- Evidence for protective effect of antagonist vs agonist conflicting
  - Pre-clinical data compelling
  - Clinical data in both directions
  - We will likely never know the answer with certainty

Spectrum and frequency of CNS-related AEs (eg, seizure, cognitive decline, falls, fatigue) observed with hormonal therapy in patients with prostate cancer

- EMBARK: No difference in dizziness (11% all groups) or falls (15-21%) between 3 groups
- Seizures not reported (vs 1% in COU-AA studies)

Table 2. Adverse Events (Safety Population).*

Event	Enzalutamide + Leuprolide (N=353)		Leuprolide Alone (N=354)		Enzalutamide Monotherapy (N=354)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)					
Any adverse event	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related adverse event	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious adverse event	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious adverse event	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
Adverse event leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
Adverse event leading to permanent discontinuation of treatment	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
Adverse event leading to death†	6 (1.7)	—	3 (0.8)	—	8 (2.3)	—
Most common adverse events‡						
Hot flash	243 (68.8)§	2 (0.6)	203 (57.3)§	3 (0.8)	77 (21.8)§	1 (0.3)
Fatigue	151 (42.8)§	12 (3.4)	116 (32.8)§	5 (1.4)	165 (46.6)§	14 (4.0)
Arthralgia	97 (27.5)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Diarrhea	49 (13.9)	2 (0.6)	31 (8.8)	1 (0.3)	46 (13.0)	0
Constipation	46 (13.0)	0	31 (8.8)	0	34 (9.6)	1 (0.3)
Hematuria	42 (11.9)	7 (2.0)	44 (12.4)	3 (0.8)	45 (12.7)	6 (1.7)
Insomnia	42 (11.9)	2 (0.6)	37 (10.5)	0	25 (7.1)	0
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Pain in arm or leg	41 (11.6)	1 (0.3)	36 (10.2)	0	40 (11.3)	0
Asthenia	39 (11.0)	2 (0.6)	21 (5.9)	1 (0.3)	39 (11.0)	3 (0.8)
Dizziness	39 (11.0)	1 (0.3)	37 (10.5)	0	41 (11.6)	0
Headache	39 (11.0)	3 (0.8)	32 (9.0)	0	41 (11.6)	1 (0.3)
Urinary incontinence	34 (9.6)	2 (0.6)	28 (7.9)	1 (0.3)	36 (10.2)	3 (0.8)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)§	1 (0.3)
Coronavirus disease 2019	27 (7.6)	2 (0.6)	36 (10.2)	4 (1.1)	44 (12.4)	1 (0.3)
Peripheral edema	27 (7.6)	0	37 (10.5)	1 (0.3)	31 (8.8)	1 (0.3)
Urinary tract infection	27 (7.6)	1 (0.3)	26 (7.3)	2 (0.6)	37 (10.5)	3 (0.8)
Weight decreased	24 (6.8)	1 (0.3)	12 (3.4)	0	39 (11.0)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0
Breast tenderness	5 (1.4)	0	4 (1.1)	0	51 (14.4)	0

ADT associated with a decrease in BMD and fracture risk

Likely related to high FSH, low Estradiol

Annual loss of bone mass:

- 2 to 8% at the lumbar spine
- 0.75% loss in the general population of aging men

- Fracture rate positively associated with the cumulative ADT dose

Incidence of Osteoporosis in Men With PCa Receiving ADT:

50%	80%
4 years	10 years

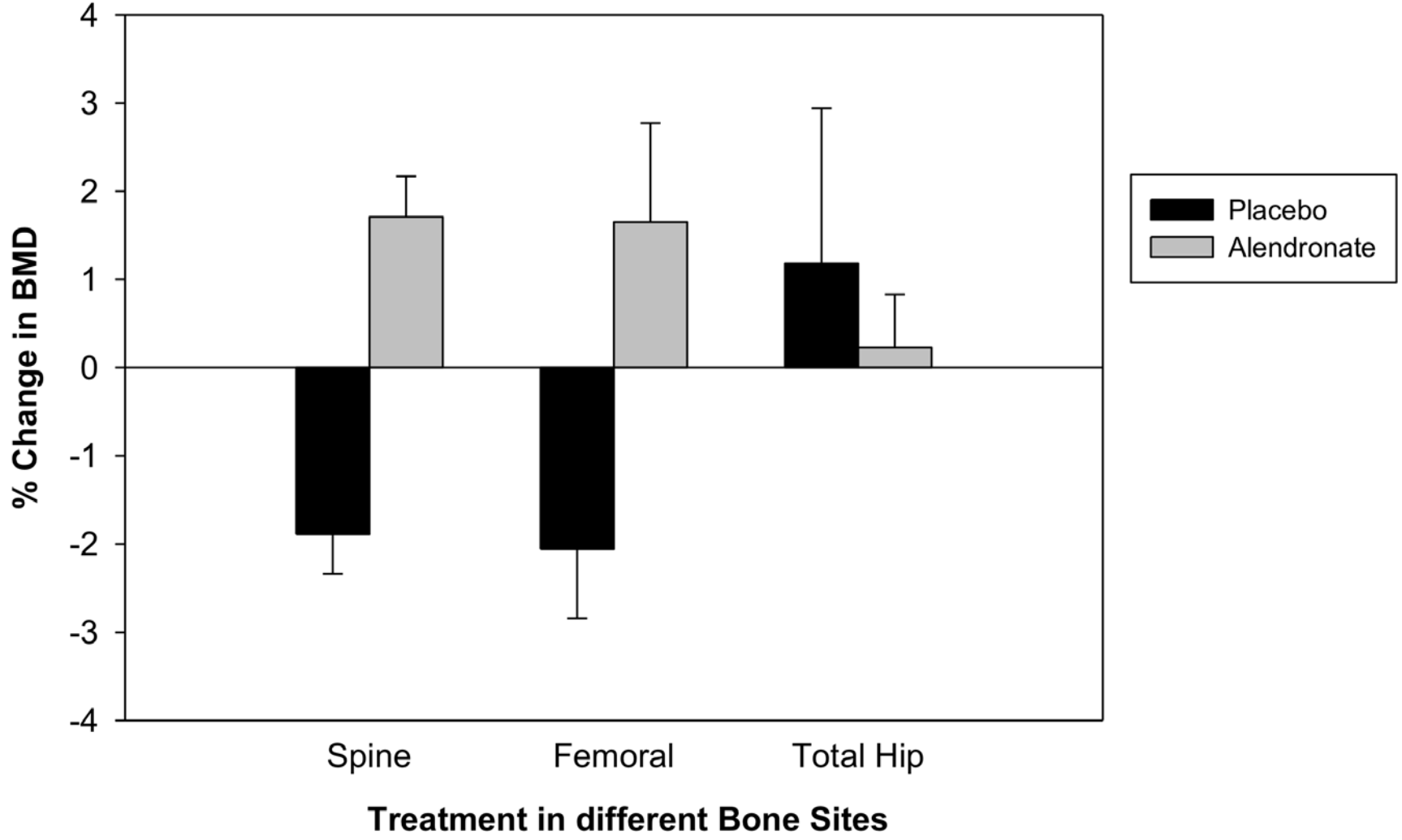
The mortality risk doubles after a fracture in men receiving ADT

1. Magee DE, Singal RK. *Can J Urol.* 2020;27(1S1):11-16. **2.** Cheung AS et al. *Endocr Relat Cancer*. 2014;21(5):R371-394. **3.** Nguyen C et al. *Pharmacotherapy*. 2018;38(10):999-1009. **4.** Rhee H et al. *BJU Int.* 2015;115(suppl 5):3-13.

BMD after 1 year of Leuprolide + Alendronate 70 mg/week vs placebo

Klotz L et al, Eur Urol 2013

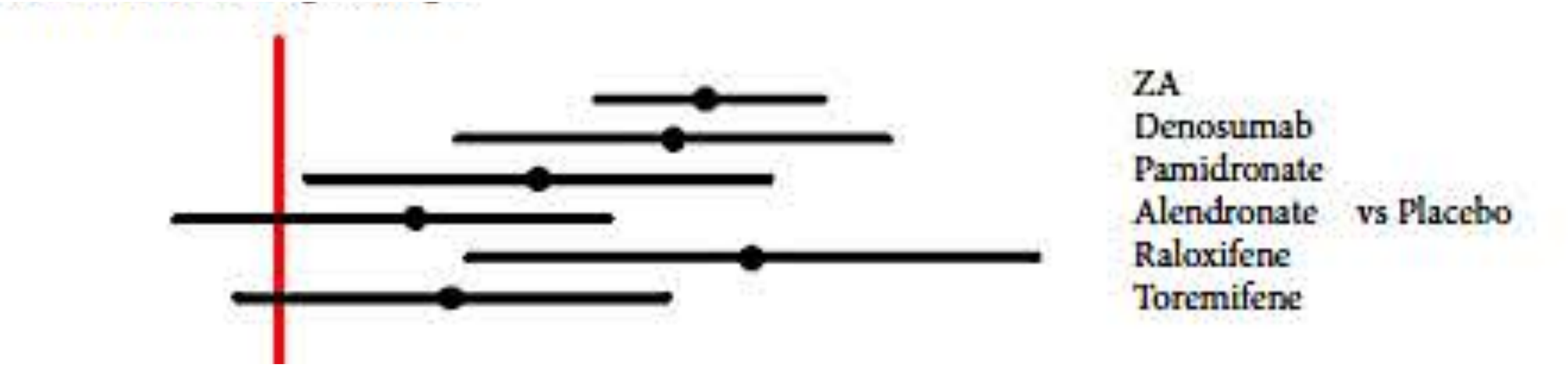
N=100



Efficacy of osteoporotic medications in men on ADT to reduce risk of fragility fractures—Meta-analysis. Poon Y et al, BJU Int 2018; 121: 17–28

Total hip: Mean % change in BMD

Placebo Bone targeted agent



All studies show gain of BMD (vs significant loss in placebo arm)

Recognition and Management of Decreased BMD

CONSIDER[2,3]:

- Baseline and periodic DEXA scan
- Regular aerobic, weight-bearing and resistance exercise
- Alcohol and smoking cessation
- Pre-treatment dental assessment and follow-up to reduce risk of osteonecrosis of jaw if RANK Ligand inhibitor used

Canadian guidelines:

- For men >70 years with T score of ≤-3.0, or established osteoporosis with fracture from minimal trauma
- Alendronate 70 mg weekly
- Denosumab 80 mg q 6 months
- Risedronate 35 mg weekly
- Zoledronic acid 4 mg q 6 month

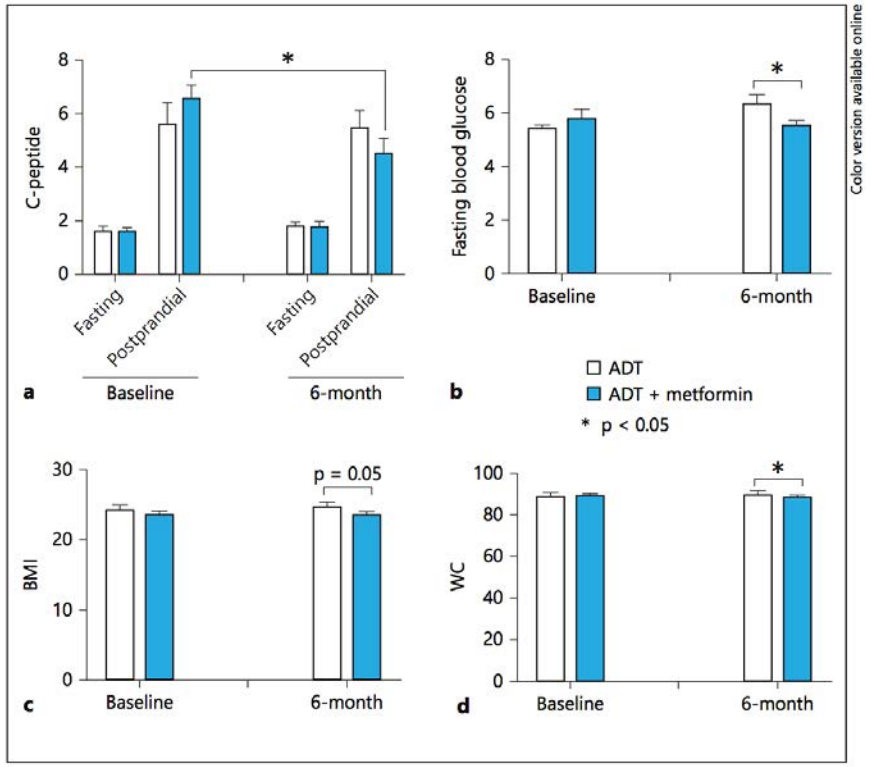
The National Osteoporosis Foundation recommendation[1]:

- Daily calcium intake of at least 600-1200 mg
- Daily vitamin D supplement of 800-1000 IU

1. Magee DE, Singal RK. *Can J Urol.* 2020;27(1S1):11-16. **2.** Rhee H et al. *BJU Int.* 2015;115(suppl 5):3-13. **3.** Cheung AS et al. *Endocr Relat Cancer*. 2014;21(5):R371-394.

Metformin with ADT—2 randomized trials

- **Zhu W, Urol Int. 2017;98(1):79-84**
- 62 men randomized between ADT and ADT + Metformin 500 mg TID x 6/12
- MET group had lower fasting glucose and waist circumference (WC)



- **Nobes J BJU Int. 2012 May;109(10):1495-502**
- 40 patients randomized to ADT +/- metformin 850-1700 mg/day + low Glycemic diet + exercise x 6 months
- Significant improvements in abdominal girth, weight, BMI, and BP in MET group
- Stay tuned: For data on semaglutide in ADT

The ‘ABCDEF’ for men on ADT

	Intervention	Comment
A	Awareness	Awareness of metabolic effects,
B	Bone Health	Alendronate 70 mg/wk or Denosumab 60-80 mg q 6/12
C	Cholesterol, Cigarettes	Statins—10-20 mg/day if healthy, ≥ 40 mg/day if history of hyperlipidemia Smoking cessation counselling, therapy
D	Discontinuation, Diet, Diabetes, Dementia	Intermittent ADT Diet rich in fruits, vegetables, grains, low fat Monitor glucose, Hb1Ac; Metformin
E	Exercise	150 minutes/week moderate intensity, 75 min week of vigorous exercise
F	Degarelix/Relugolix	May have a role if significant pre-existing CV disease and CV optimization not feasible

Unanswered questions:

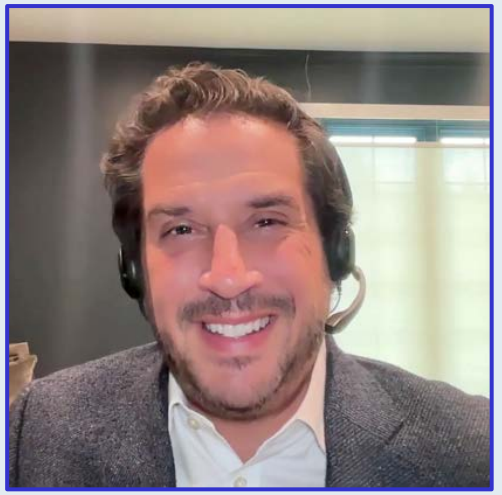
- Timing of ADT in PSA only recurrence
- Are oligomets on PSMA only = pre-PSMA PSA only recurrence or to N/M positive disease on conventional imaging?
- Can the EMBARK data be extrapolated to the other ARPIs?
- When and how to use intensified AR targeted therapy intermittently? What is the induction period and optimal threshold for re-treatment?
- Once intensified, always intensified?
- Role of ARPI monotherapy—should it be more widely used?
- What about lower risk PSA only recurrence—also a role for ADT + ARPI combination?
- Will biomarkers allow for personalized approach (HRR/PARPs, etc.)?

MODULE 3: Current and Future Approaches to Hormonal Therapy for Metastatic Prostate Cancer — Dr Aggarwal

Consulting Faculty Comments

Doublet versus triplet therapy for metastatic hormone-sensitive prostate cancer; role of radiation therapy in treating metastases

Neil Love, MD



Jason Hafron, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Jason Hafron, MD

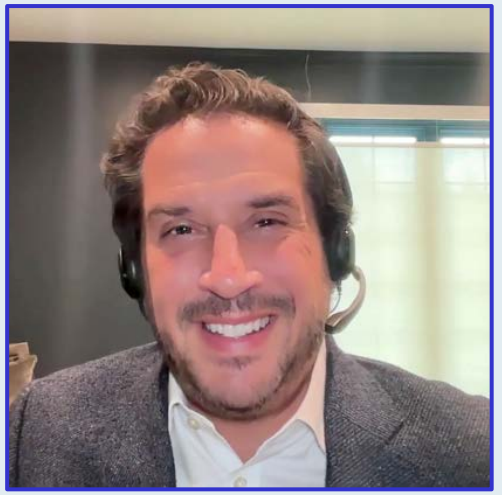
How do you decide between offering doublet versus triplet therapy to a patient with metastatic hormone-sensitive prostate cancer?

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Monitoring for abiraterone-associated side effects

Neil Love, MD



Jason Hafron, MD

RTP
RESEARCH
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QUESTIONS FOR THE FACULTY

Jason Hafron, MD

How do you monitor for side effects associated with abiraterone and prednisone?

RTP
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TO PRACTICE

UCSF Helen Diller Family Comprehensive Cancer Center

Current and Future Approaches to Hormonal Therapy for Metastatic Prostate Cancer

Rahul Aggarwal MD
Professor of Medicine
University of California San Francisco

Outline

- Doublet therapy for metastatic CSPC: Extended follow up from the phase 3 studies
- Triplet therapy – ARASENS and PEACE-1
- Targeting the PIK3-AKT-mTOR pathway in prostate cancer and ongoing studies of AKT inhibitor capivasertib

Definition of Low vs. High Volume Disease by Conventional Imaging

- ‘CHAARTED’ definition
  - Visceral metastases and/or 4 or more bone metastases with at least one outside axial column

- LATITUDE:
  - Two or more: Visceral metastases, ≥ 3 bone metastases, Gleason ≥ 8

Baseline Patient Characteristics of Phase 3 Studies of ADT Intensification in Metastatic CSPC

Study	De novo metastases at diagnosis (%)	High/Low Volume (%)	Prior docetaxel/ concomitant docetaxel (%)
LATITUDE	100	~79/21	0/0
TITAN	~83	~63/37	~10/0
ARCHES	~67	~63/37	~18/0

Fizazi K et al. *Lancet Oncol* 2019;20(5):686-700. Chi KN et al. *J Clin Oncol* 2021;39(20):2294-2303. Armstrong AJ et al. *J Clin Oncol* 2022;40(15):1616-1622.

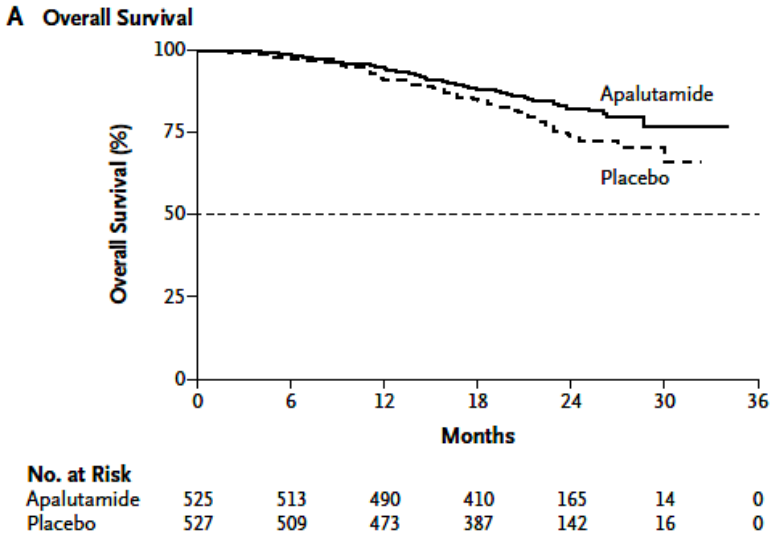
Intensification of ADT Improves Survival: Results with Extended Follow up

Study	Agent Added to ADT	No. of pts	Median Follow Up, months	Median OS, months Rx vs. Control	Landmark OS rates (%), Rx vs. Control	HR (95% CI)
LATITUDE	Abiraterone	1199	51.8	53.3 vs. 36.5	Not reported	0.66 (0.56-0.78)
TITAN	Apalutamide	1052	44.0	NR vs. 52.2	4 year OS: 65.1 vs. 51.8	0.65 (0.53-0.79)
ARCHES	Enzalutamide	1150	44.6	NR vs. NR	4 year OS: 71 vs. 57	0.66 (0.53-0.81)

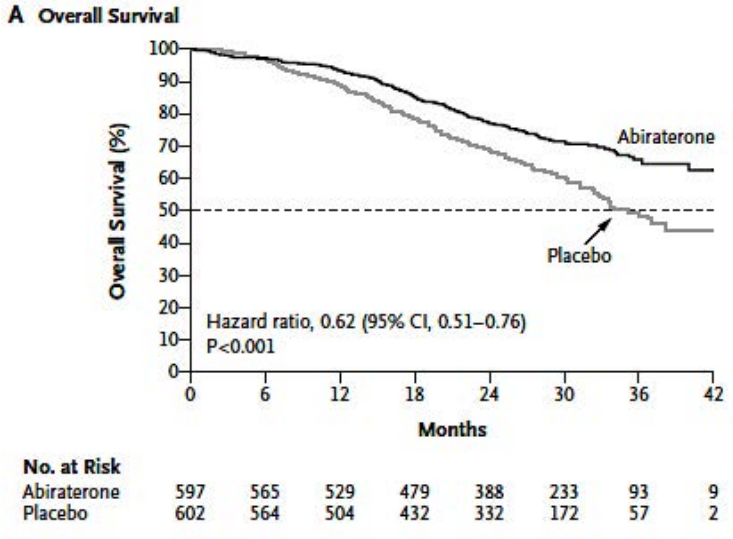
Fizazi K et al. *Lancet Oncol* 2019;20(5):686-700. Chi KN et al. *J Clin Oncol* 2021;39(20):2294-2303. Armstrong AJ et al. *J Clin Oncol* 2022;40(15):1616-1622.

Overall survival K-M Curves of Selected Studies of Intensified ADT in mCSPC

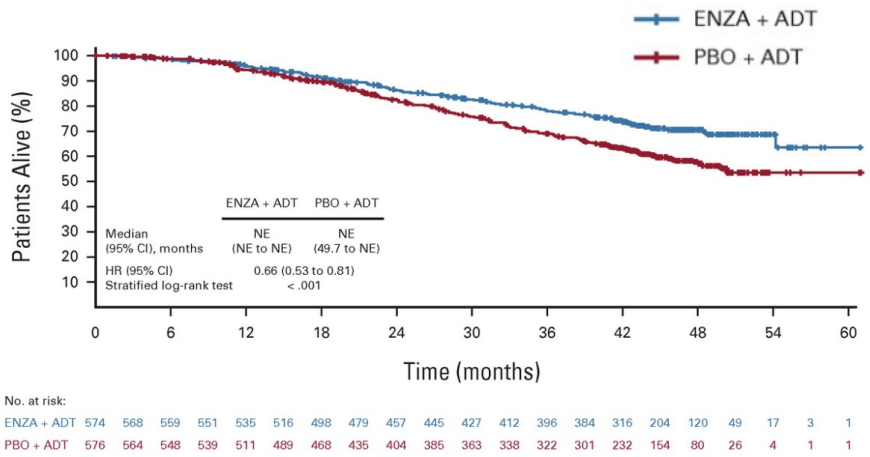
TITAN (ADT +/- apalutamide) (Chi K, et al. NEJM 2019)



LATITUDE (ADT +/- abiraterone) (Fizazi K, et al. NEJM 2017)



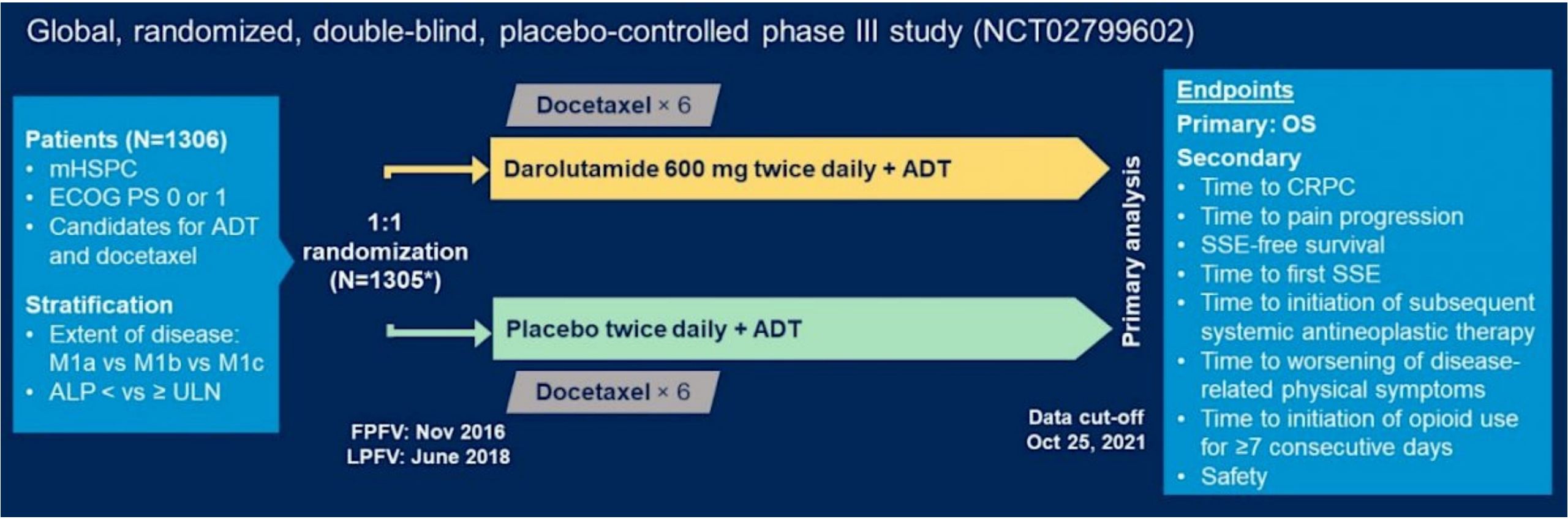
ARCHES (ADT +/- enzalutamide) (Armstrong A, et al. JCO 2022)



Outline

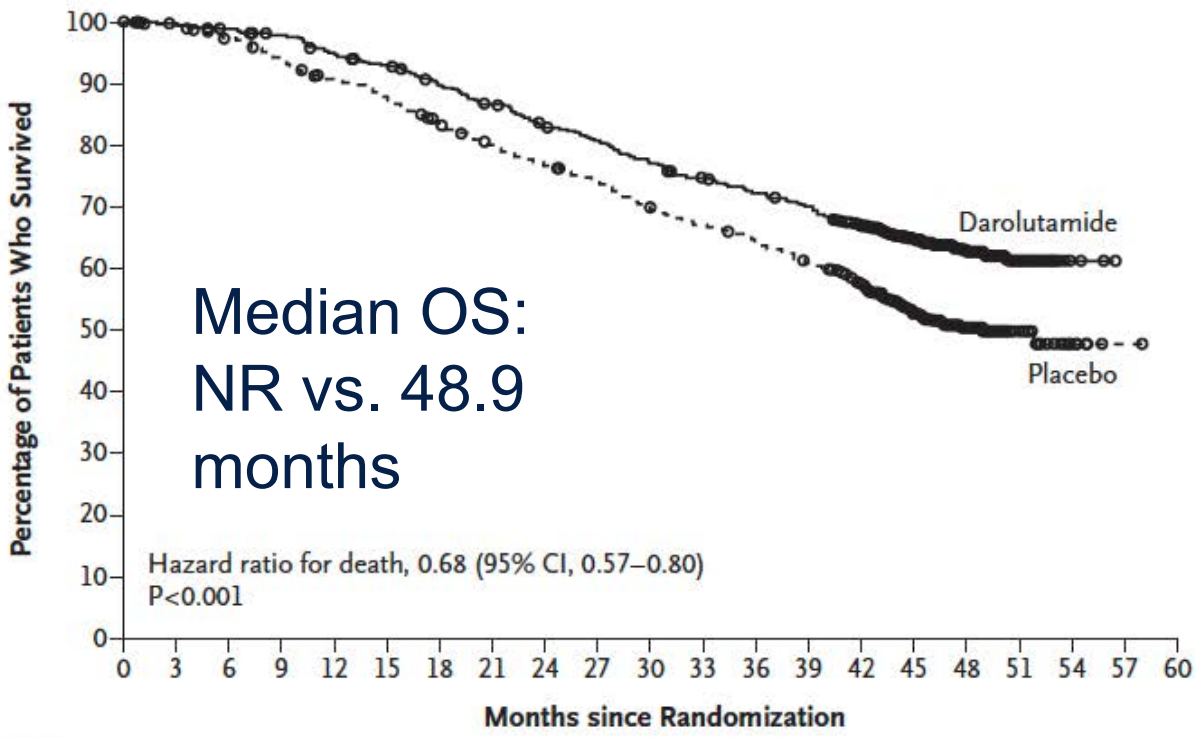
- Doublet therapy for metastatic CSPC: Extended follow up from the phase 3 studies
- Triplet therapy – ARASENS and PEACE-1
- Targeting the PIK3-AKT-mTOR pathway in prostate cancer and ongoing studies of AKT inhibitor capivasertib

ARASENS Phase 3 Study



Hussain MH et al. ASCO GU 2023;Abstract 15.

ARASENS Primary results



No. at Risk

Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

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)

Smith MR et al. *N Engl J Med* 2022;386(12):1132-1142.

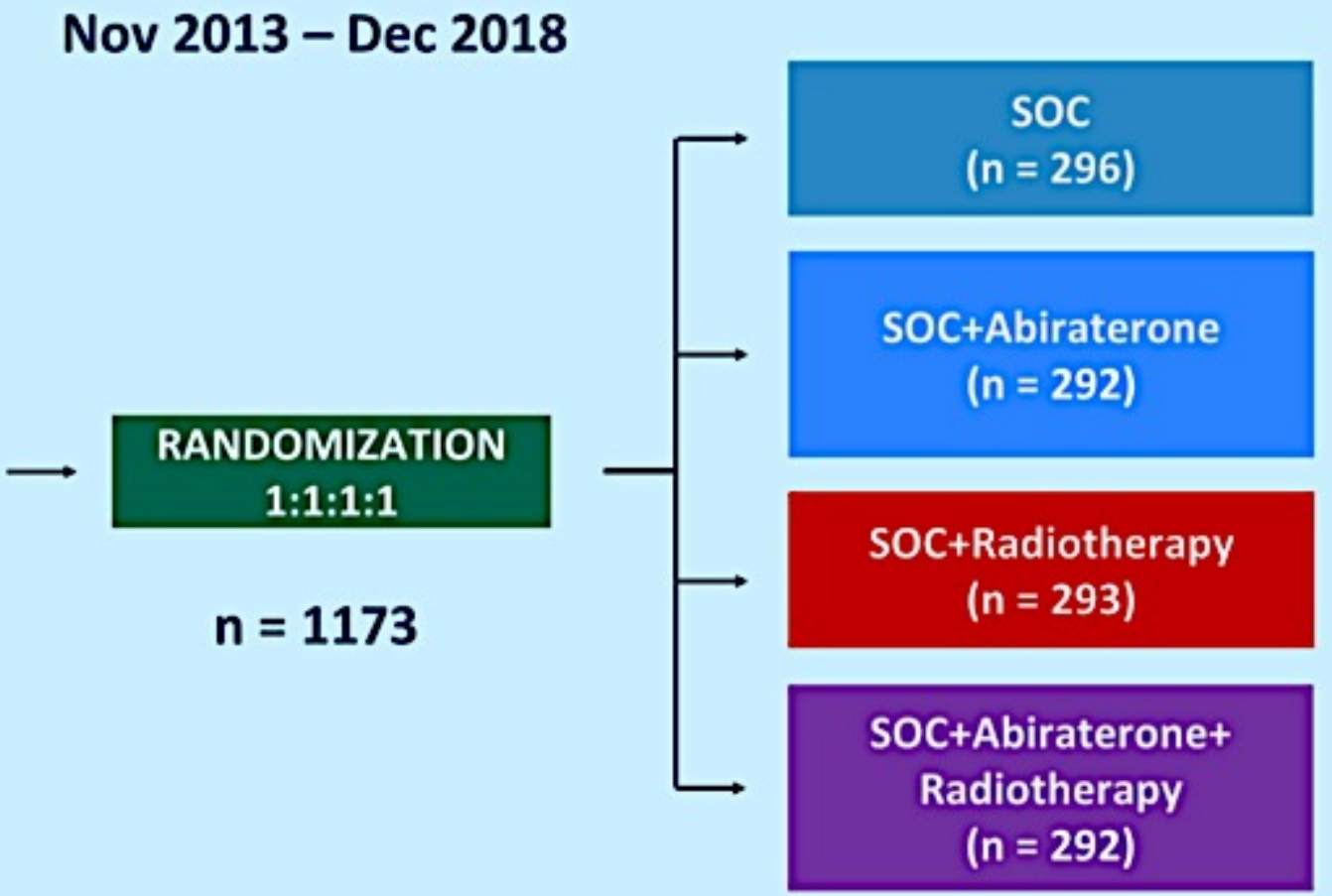
PEACE-1

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

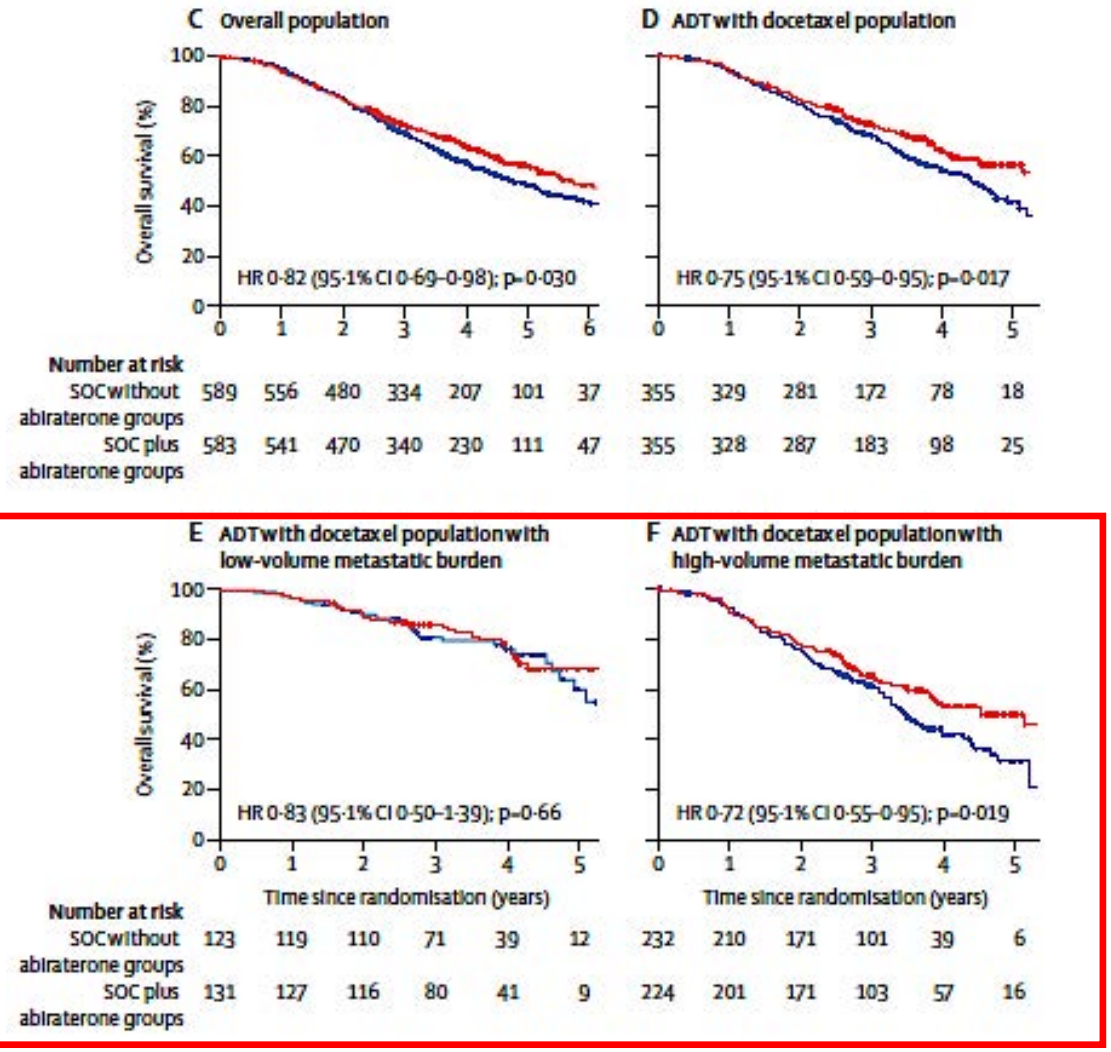
Permitted
ADT ≤ 3 months

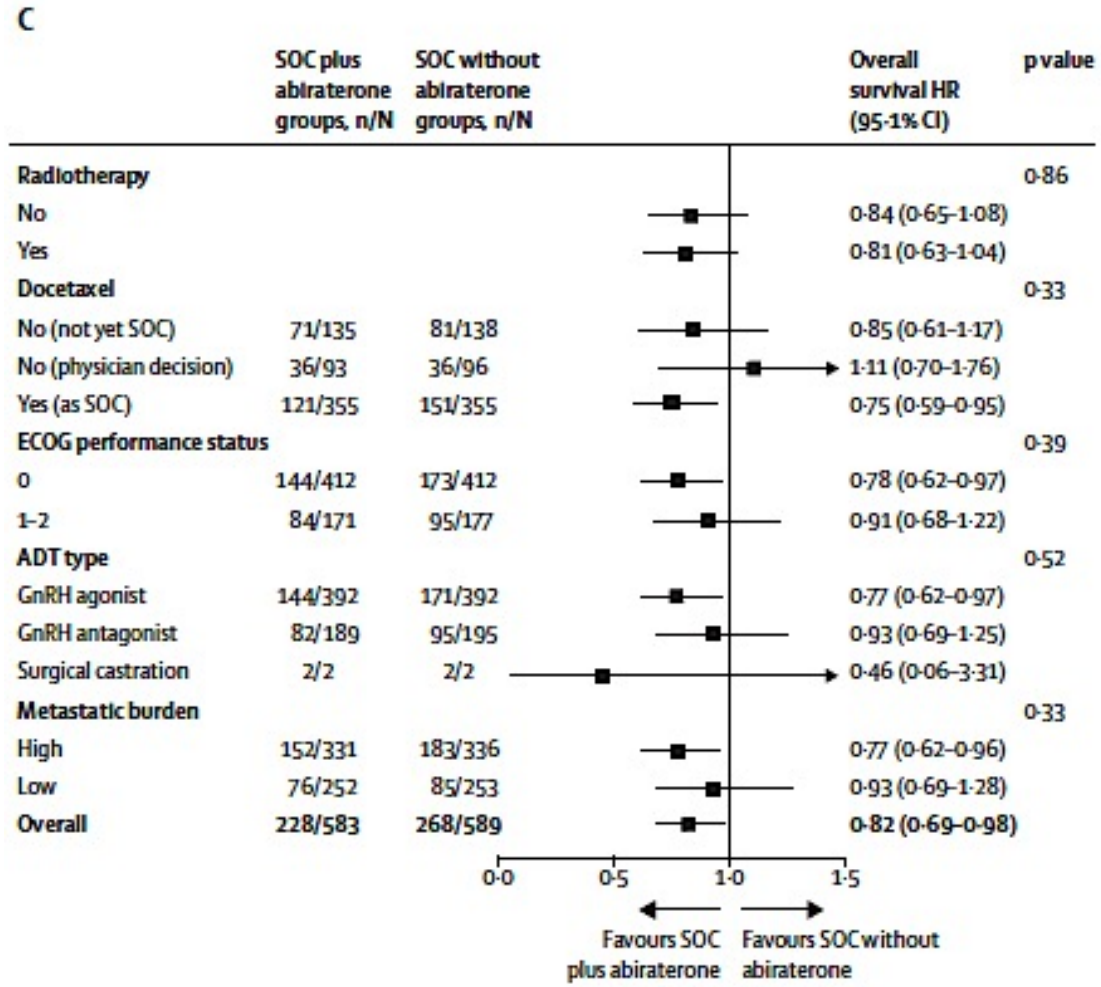
Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

PEACE-1





Fizazi K et al. *Lancet* 2022;399(10336):1695-1707.

So should we be doing ‘triplet’ therapy?

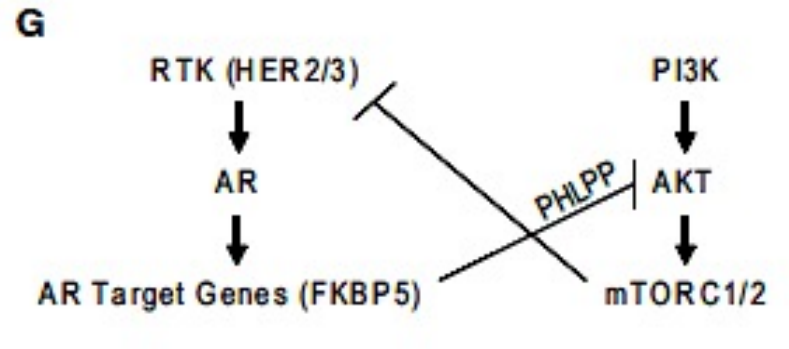
- We don’t have any prospective phase 3 survival data ADT + ARSI +/- taxane
- Reasons to consider triplet therapy:
  - Median survival times from PEACE-1 and ARASENS are compelling
  - Meta-analyses suggest potential benefit in high-volume patients
  - AR signaling inhibitor sensitivity can be heterogeneous in high grade tumors
  - Many patients don’t ever receive taxane chemotherapy in the mCRPC setting
- We need predictive biomarkers
  - ? PTEN/TP53/RB1
  - ? PAM50 classifier
  - ? Suboptimal PSA nadir/time to nadir
- Currently, I offer triplet therapy to de novo, high-volume mCSPC patients, particularly those with aggressive disease features

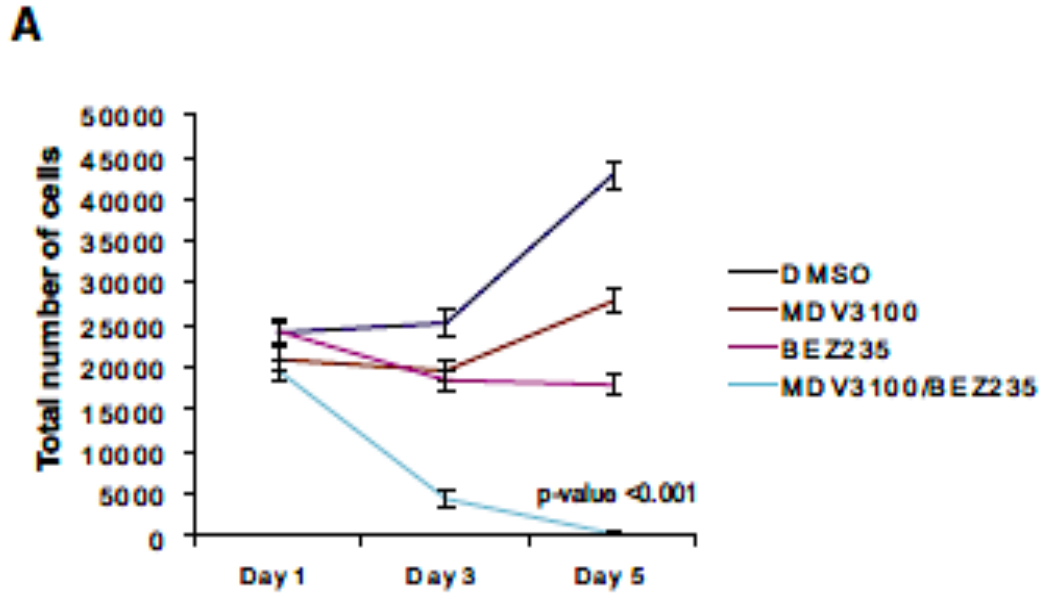
Outline

- Doublet therapy for metastatic CSPC: Extended follow up from the phase 3 studies
- Triplet therapy – ARASENS and PEACE-1
- Targeting the PIK3-AKT-mTOR pathway in prostate cancer and ongoing studies of AKT inhibitor capivasertib

Rationale for Targeting the PI3K-AKT-mTOR Axis in Prostate Cancer

- Genomic alterations in PI3K signaling pathway are the most frequent of any pathway in prostate cancer[1]
  - PTEN deletion
  - PIK3CA
  - AKT1 point mutations (e.g. E17K)
- Reciprocal cross-talk between the AR and PI3K signaling pathway[2]





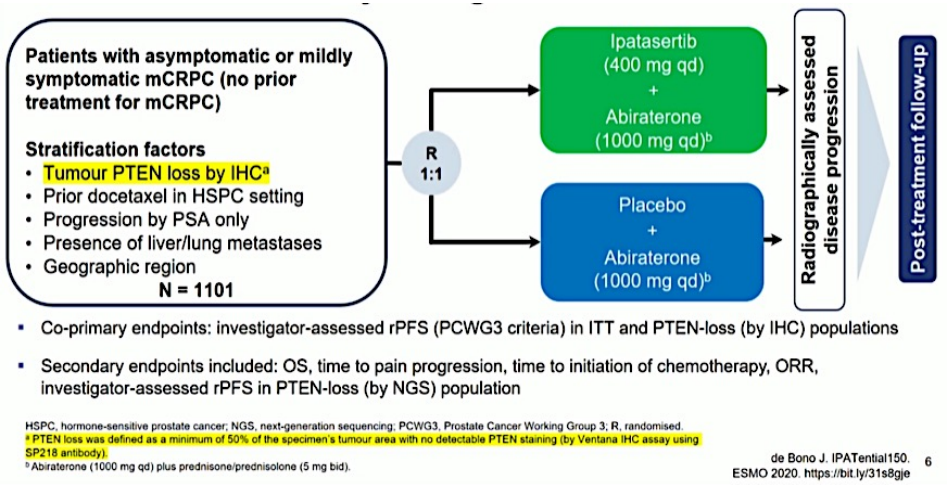
1. Abida W et al. PNAS 2019; 2. Carver B et al. Cancer Cell 2011

PI3K inhibitors have had limited success in prostate cancer cohorts

- Limited by narrow therapeutic index
- Toxicity profile not favorable
- Convergent bypass signaling pathways enable downstream AKT/mTOR activation

AKT inhibition is a promising therapeutic strategy in prostate cancer

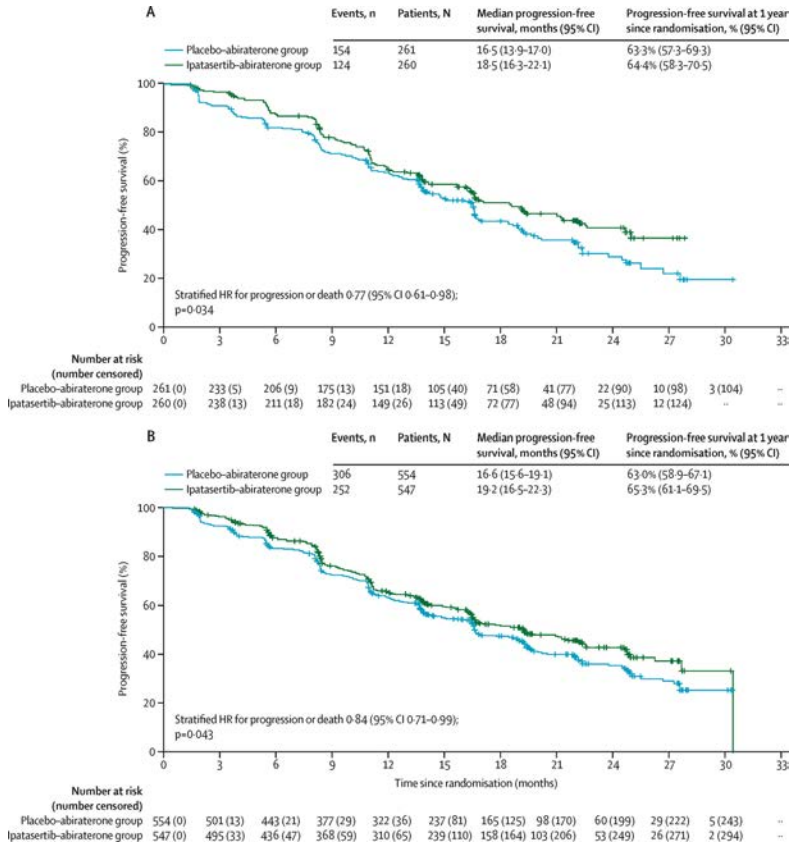
IPATential150 Trial

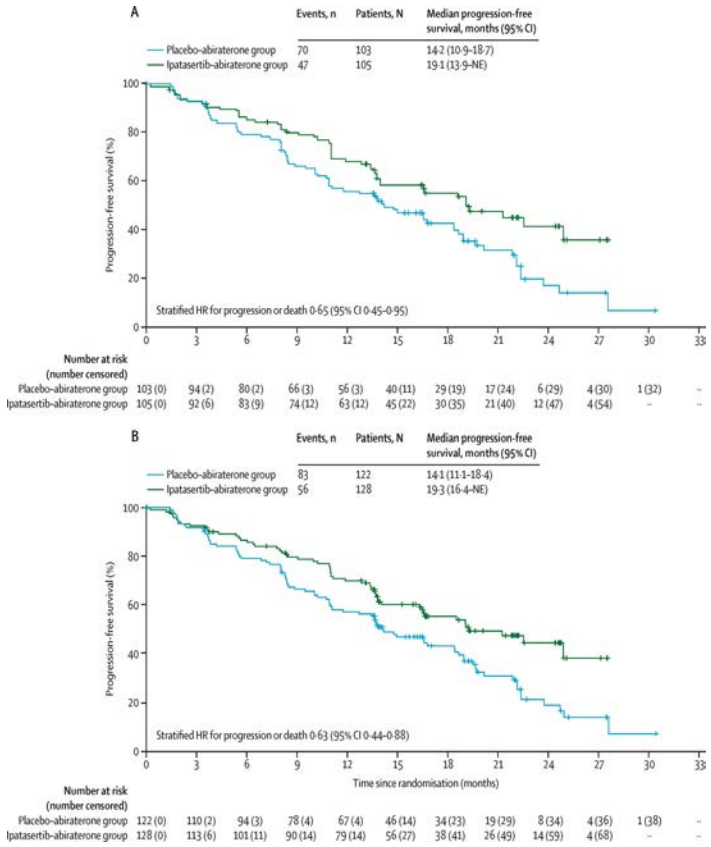


- Co-primary endpoints: investigator-assessed rPFS (PCWG3 criteria) in ITT and PTEN-loss (by IHC) populations
- Secondary endpoints included: OS, time to pain progression, time to initiation of chemotherapy, ORR, investigator-assessed rPFS in PTEN-loss (by NGS) population

HSPC, hormone-sensitive prostate cancer; NGS, next-generation sequencing; PCWG3, Prostate Cancer Working Group 3; R, randomised.
[a] PTEN loss was defined as a minimum of 50% of the specimen's tumour area with no detectable PTEN staining (by Ventana IHC assay using SP218 antibody).
[b] Abiraterone (1000 mg qd) plus prednisone/prednisolone (5 mg bid).

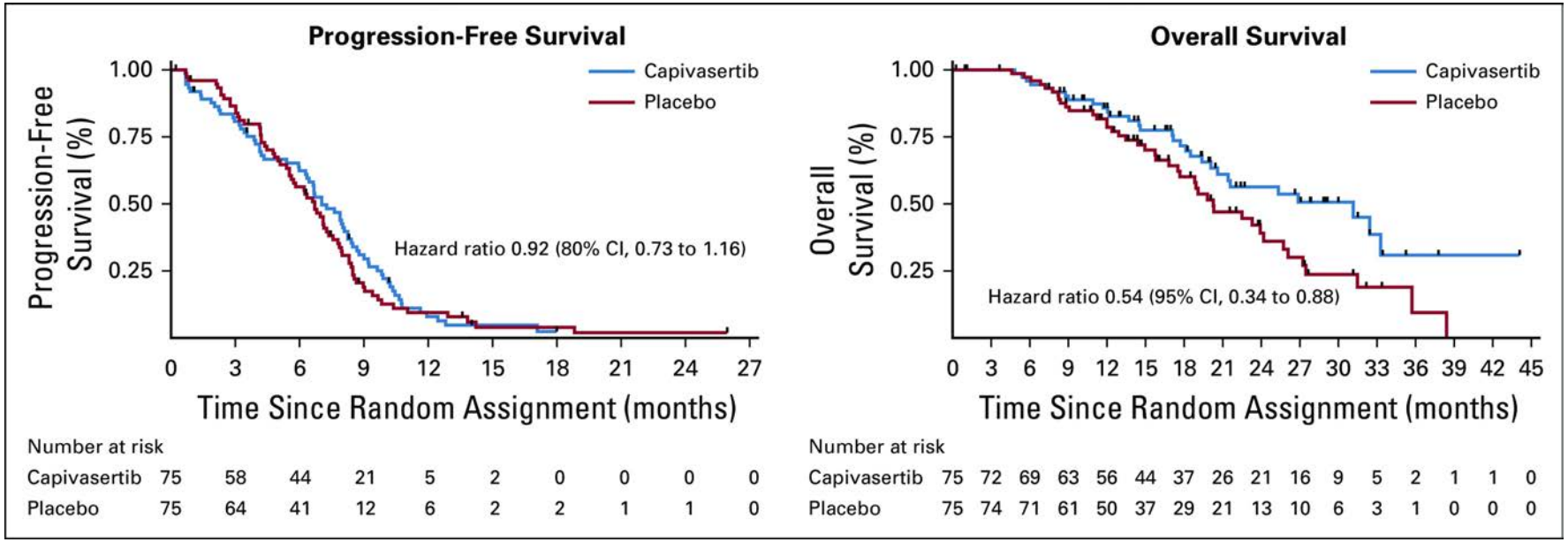
de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje 6

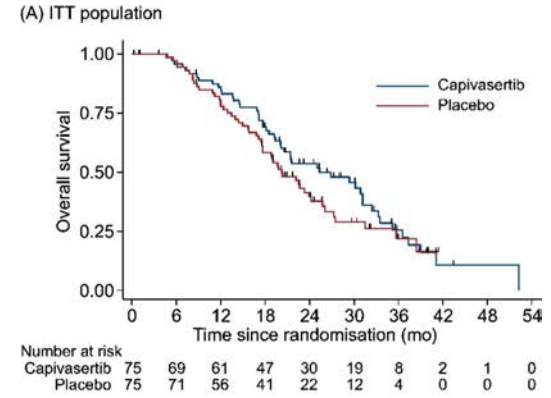


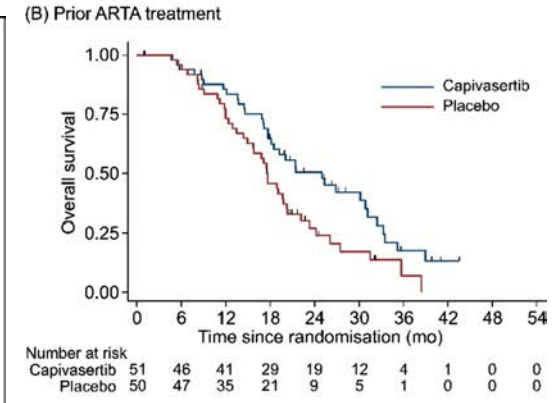


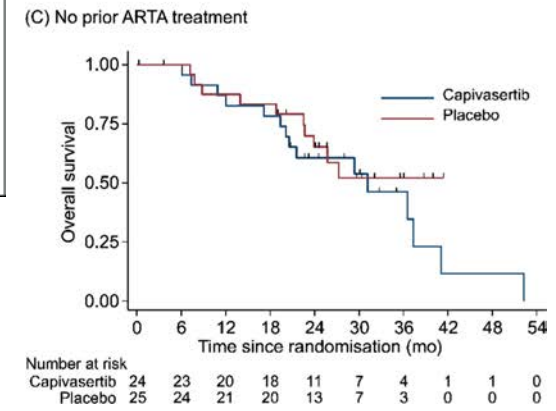
Sweeney C et al. The Lancet 2021

ProCAID Randomized Phase 2 docetaxel +/- capivasertib









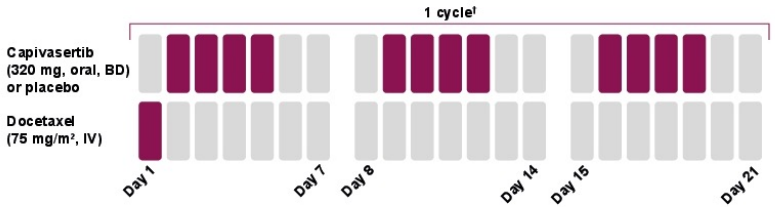
Crabb SJ et al. JCO 2021; Crabb SJ et al. Eur Urol 2022

CAPItello-280 Study

N≈790 randomized 1:1*

Capivasertib (320 mg orally, BD, 4 days on, 3 days off) plus docetaxel (75 mg/m² IV on Day 1 of each 21-day cycle for 6–10 cycles)†

Schedule of each 21-day dosing cycle



Matching placebo (320 mg orally, BD, 4 days on, 3 days off) plus docetaxel (75 mg/m² IV on Day 1 of each 21-day cycle for 6–10 cycles)†

*Stratification factors: the patient has received two or more lines of prior next-generation hormonal agents, with at least one line of next-generation hormonal agent used in CRPC setting (yes/no); the patient has visceral metastases (yes/no); geographic region (1. North America, Western Europe, and Australia; 2. Latin America and Eastern Europe; 3. Asia).
†Plus prednisone or prednisolone 5 mg BD or 10 mg QD, and a background of continued ADT.

Study endpoints

Primary

- **OS** defined as the time from randomization until the date of death due to any cause

Secondary

- **rPFS** defined as the time from randomization to radiographic progression according to RECIST v1.1 or PCWG3 criteria (investigator-assessed)
- **TTPP** defined as the time from randomization to clinically meaningful pain progression (2-point increase from baseline in BPI-SF Item 3 'worst pain' and/or the initiation of, or increase in, opioid use)
- **SSRE** defined as the time from randomization to use of radiation therapy for skeletal symptoms, new symptomatic pathological bone fractures, spinal cord compression, or surgical intervention for bone metastasis
- **Safety and tolerability**
- **Patient-reported outcomes** including physical functioning, urinary symptoms, pain, and HRQoL
- **Pharmacokinetic analysis**

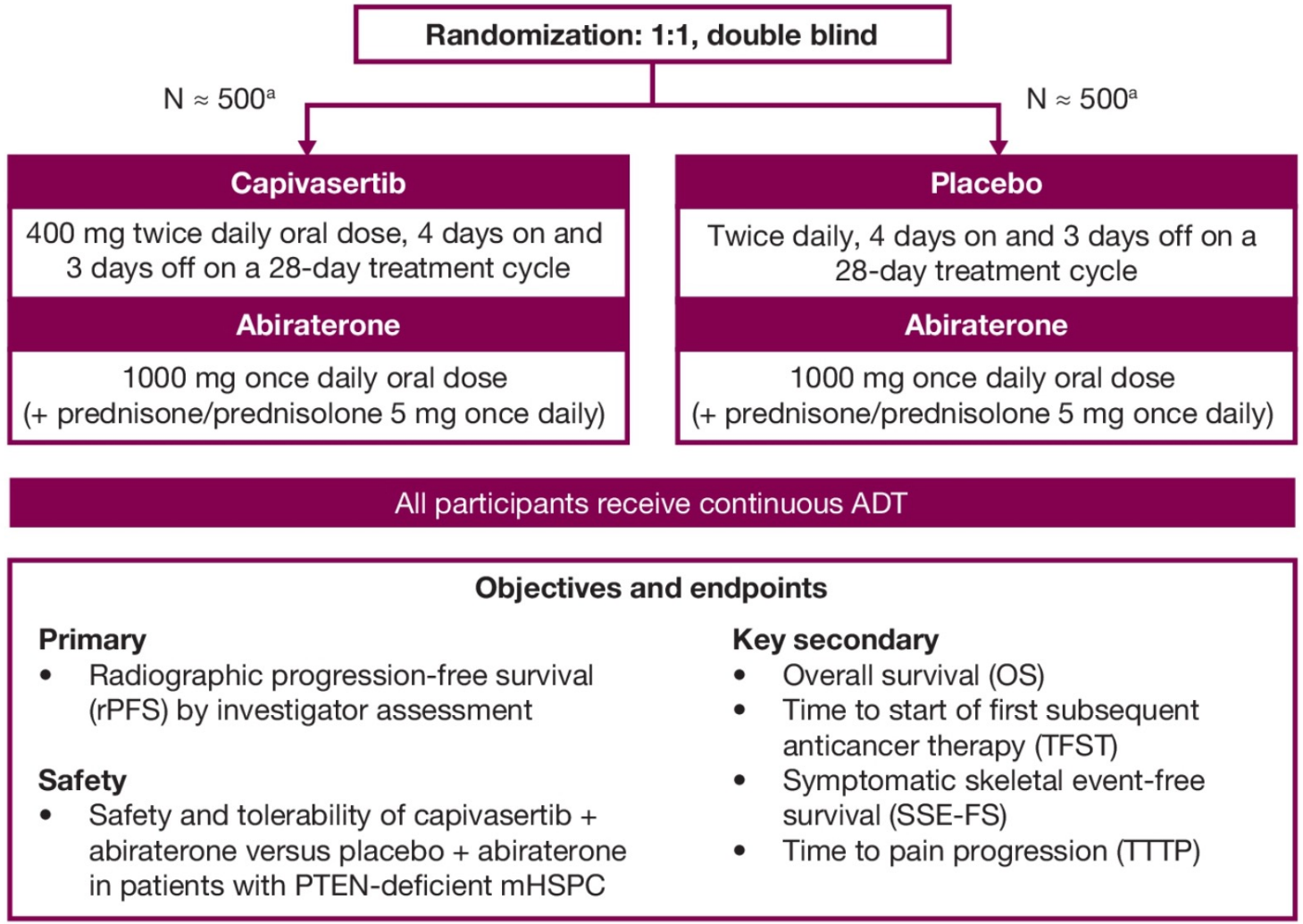
Crabb SJ et al. ASCO GU 2023;Abstract TPS287.

CAPItello-281 Study: AKT Inhibition in PTEN-deficient mCSPC

Inclusion criteria

- Adult males ≥ 18 years of age (≥ 20 years of age in Japan), with asymptomatic or mildly symptomatic mHSPC
- ECOG/WHO performance status of 0 or 1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks
- Histologically confirmed *de novo* (i.e., diagnosed within 3 months of randomization) mHSPC; adenocarcinoma must be the primary histological pattern and patients with small-cell tumors are not eligible
- Consent to provide a FFPE tissue block (preferred) or slides
- Valid PTEN IHC result indicating PTEN deficiency (centralized testing)
- Metastatic disease documented prior to randomization by clear evidence of ≥ 1 bone lesion and/or ≥ 1 soft tissue lesion
- Candidate for abiraterone and steroid therapy. Previous treatment with abiraterone and/or a steroid for *de novo* disease is allowed up to a maximum of 3 months (93 days) prior to randomization
- Ongoing ADT with GnRH analog (combination with first-generation androgen receptor antagonists, e.g., bicalutamide is allowed), or LHRH antagonist or bilateral orchiectomy

Figure 4. Trial design and outcome measures for CAPItello-281



Fizazi K et al. ASCO GU 2021;Abstract TPS178.

Summary

- Unequivocal benefit of ARSIs in mCSPC
  - Should be offered to every patient regardless of disease volume or if de novo versus recurrent disease
  - We need to address barriers to increase uptake in real world studies

- Triplet therapy has a role in higher risk mCSPC
  - Biomarkers needed to optimize patient selection

- Targeting the PI3K/AKT/mTOR signaling pathway may further improve outcomes in metastatic prostate cancer

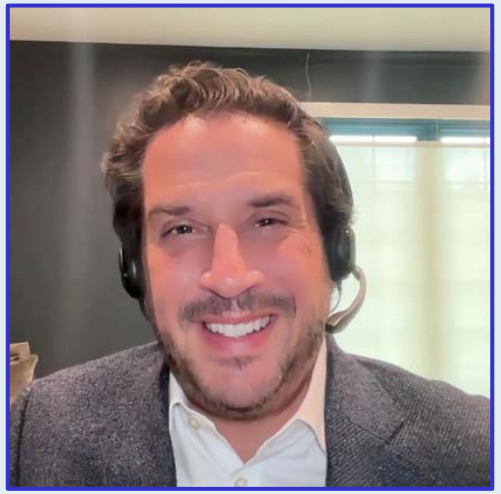
MODULE 4: New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr Srinivas

Consulting Faculty Comments

Selecting the optimal combination of AR and PARP inhibitors; potential use of PARP inhibitors outside the mCRPC setting

Neil Love, MD

David S Morris, MD



Jason Hafron, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

David S Morris, MD

How do you approach the selection of an AR inhibitor to pair with a PARP inhibitor for a patient with mCRPC who previously received an AR inhibitor in the hormone-sensitive setting?

Would you consider administering a PARP inhibitor to a patient with metastatic hormone-sensitive prostate cancer?

Jason Hafron, MD

How do you decide which PARP inhibitor to use for patients with mCRPC?

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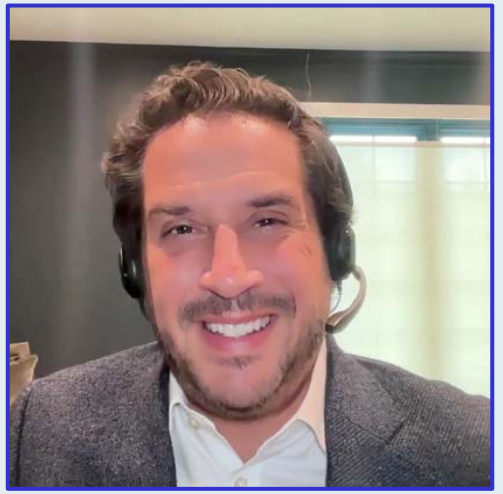
TO PRACTICE

Consulting Faculty Comments

Toxicity profiles of AR/PARP inhibitor combinations and management of common toxicities

Neil Love, MD

David S Morris, MD



Jason Hafron, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

David S Morris, MD

Have you noticed any clinical differences in terms of tolerability between the PARP/AR inhibitor combinations that are currently approved?

How do you typically manage anemia and what are your thresholds for modifying how you administer a PARP inhibitor to anemic patients?

Jason Hafron, MD

How do you typically address the fatigue and nausea that is commonly associated with PARP inhibitors?

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TO PRACTICE

New Considerations with the Use of PARP Inhibitors for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

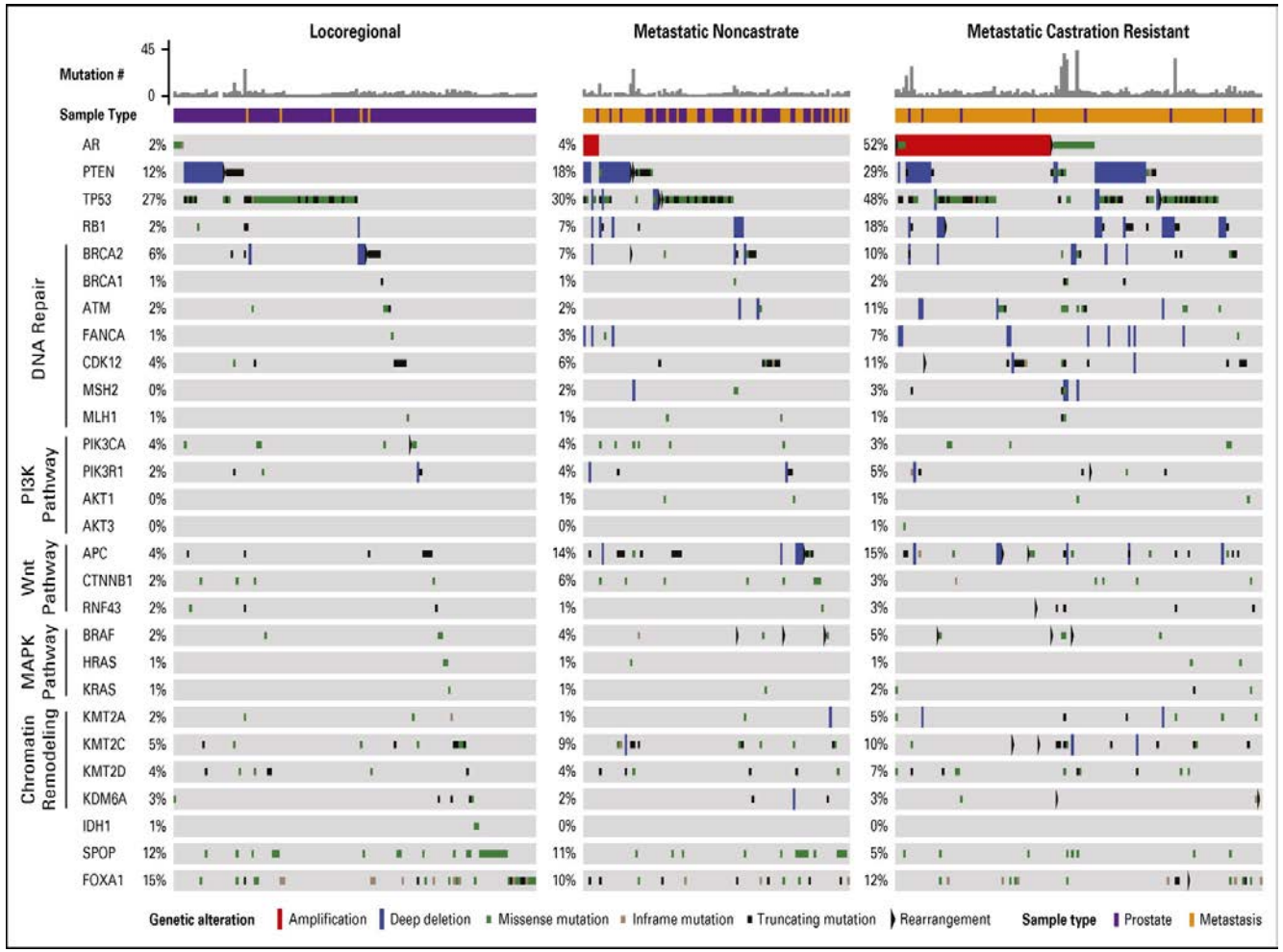
Sandy Srinivas, MD

Stanford University

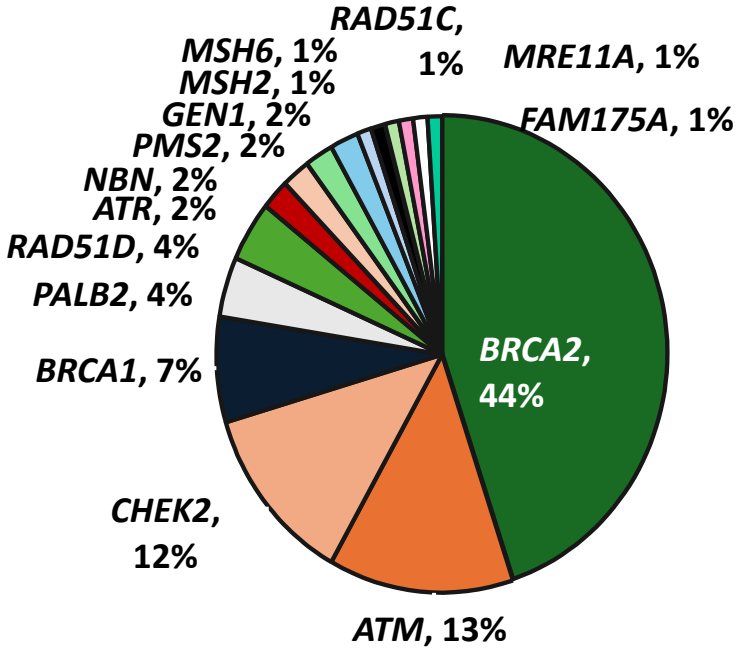
Mutational Landscape by Disease State

Genomic progression from localized disease to mCRPC

- *BRCA1*: 1% to 2%
- *BRCA2*: 6% to 10%
- *ATM*: 2% to 11%
- *FANCA*: 1% to 7%



Distribution of Presumed Pathogenic Germline Mutations



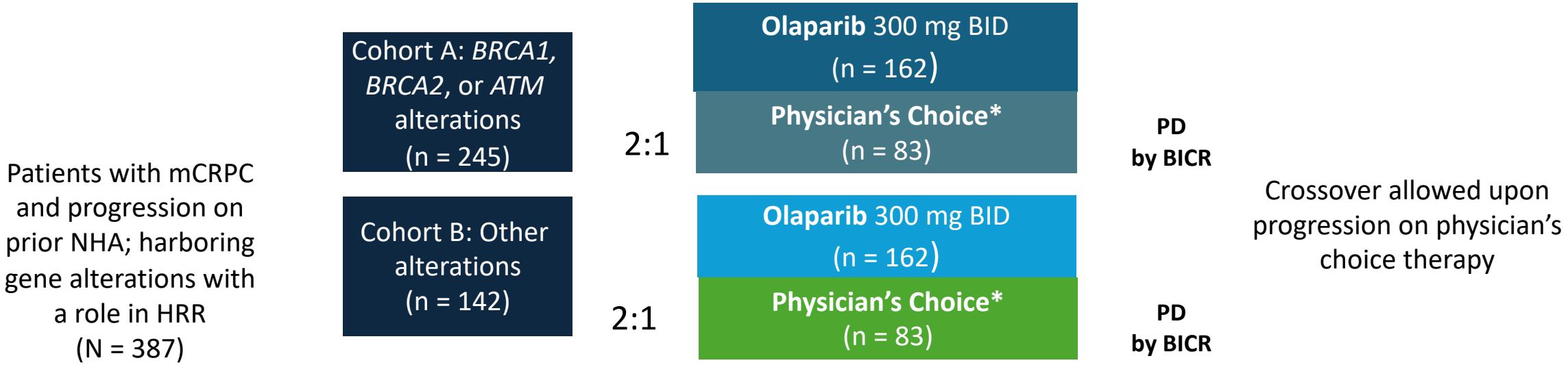
Actionable Mutations

Overall: 23%

Abida. JCO Precision Oncol. 2017;PO.17.00029; Pritchard. NEJM. 2016;375:443

Phase III PROfound: Olaparib vs Physician's Choice in Progressing Metastatic CRPC

Stratified by previous taxane (yes vs no) and measurable disease (yes vs no)



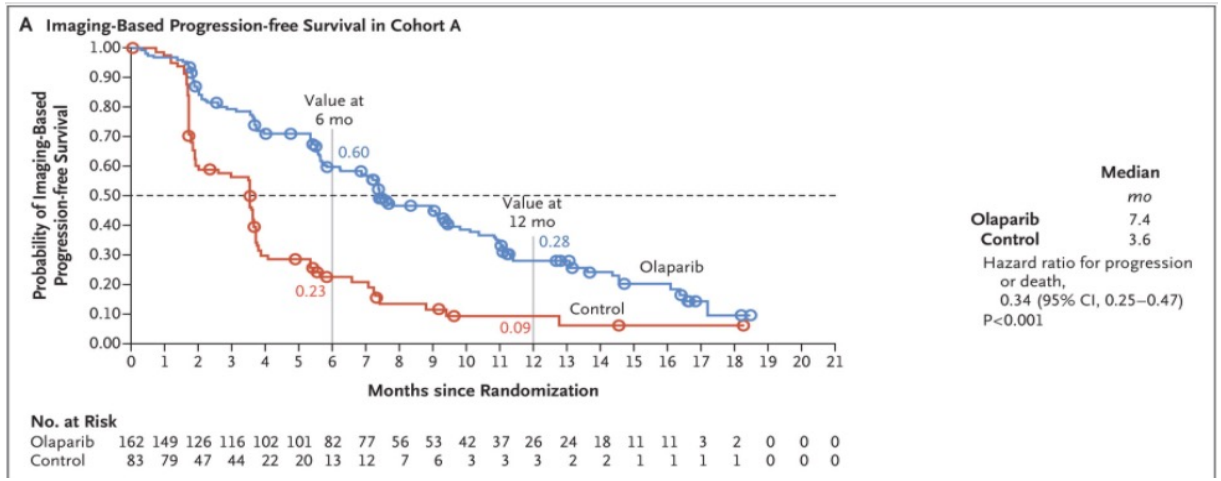
*Enzalutamide 160 mg QD or abiraterone acetate 100 mg QD plus prednisone 5 mg BID.

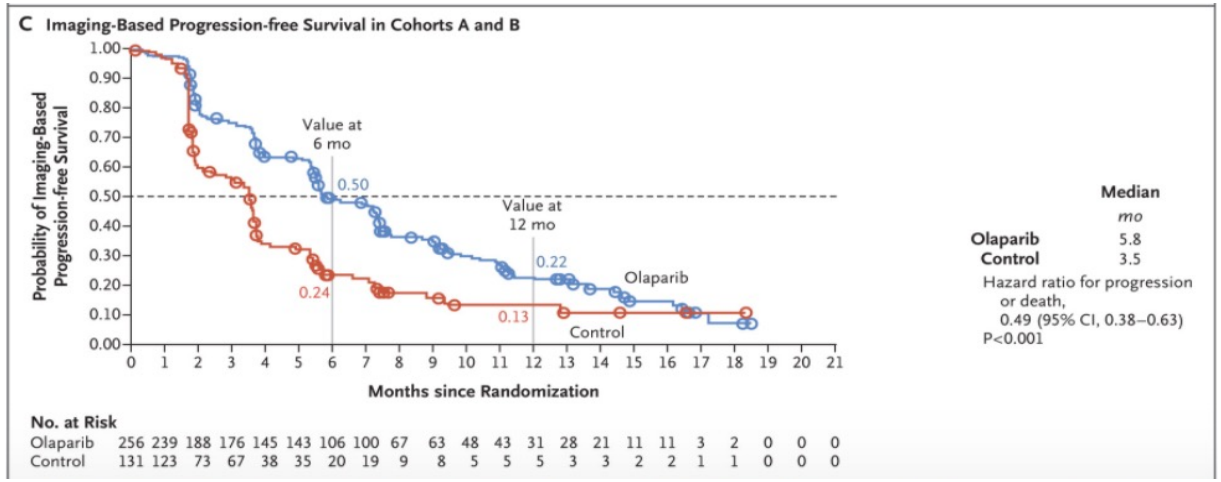
†***BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L.***

- Primary endpoint: radiographic PFS in Cohort A using RECIST 1.1 and PCWG3 by BICR
- Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in Cohort A, time to pain progression in Cohort A, OS in Cohort A

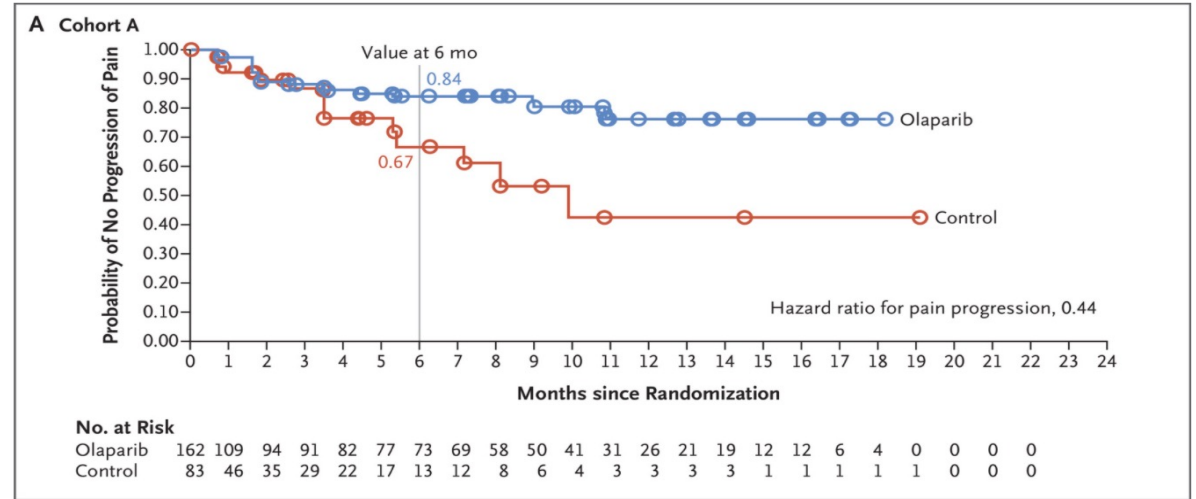
Hussain. NEJM 2020; de Bono. NEJM. 2020;382:2091.

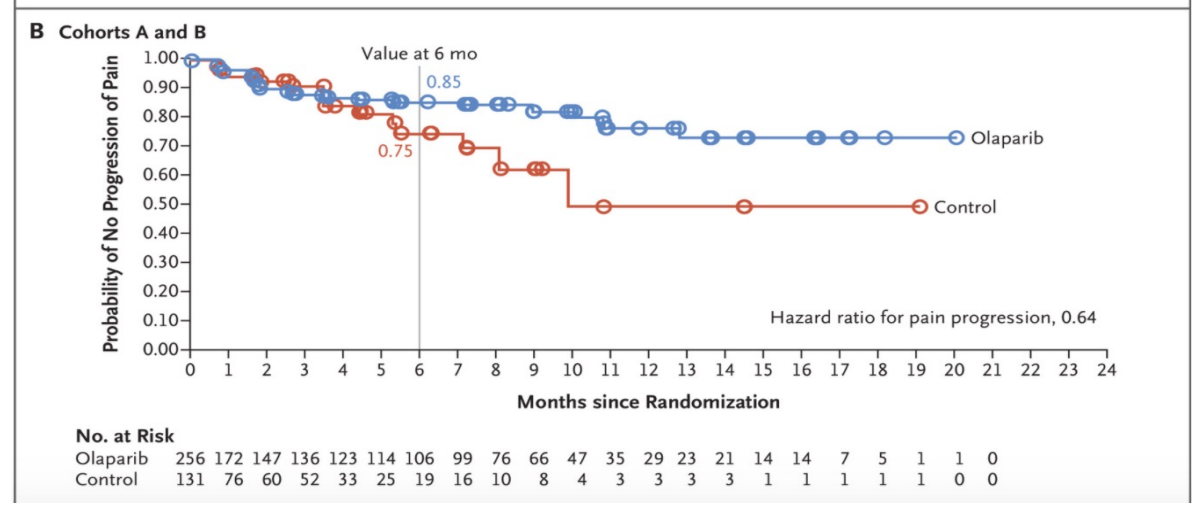
PROfound Primary Endpoint: rPFS





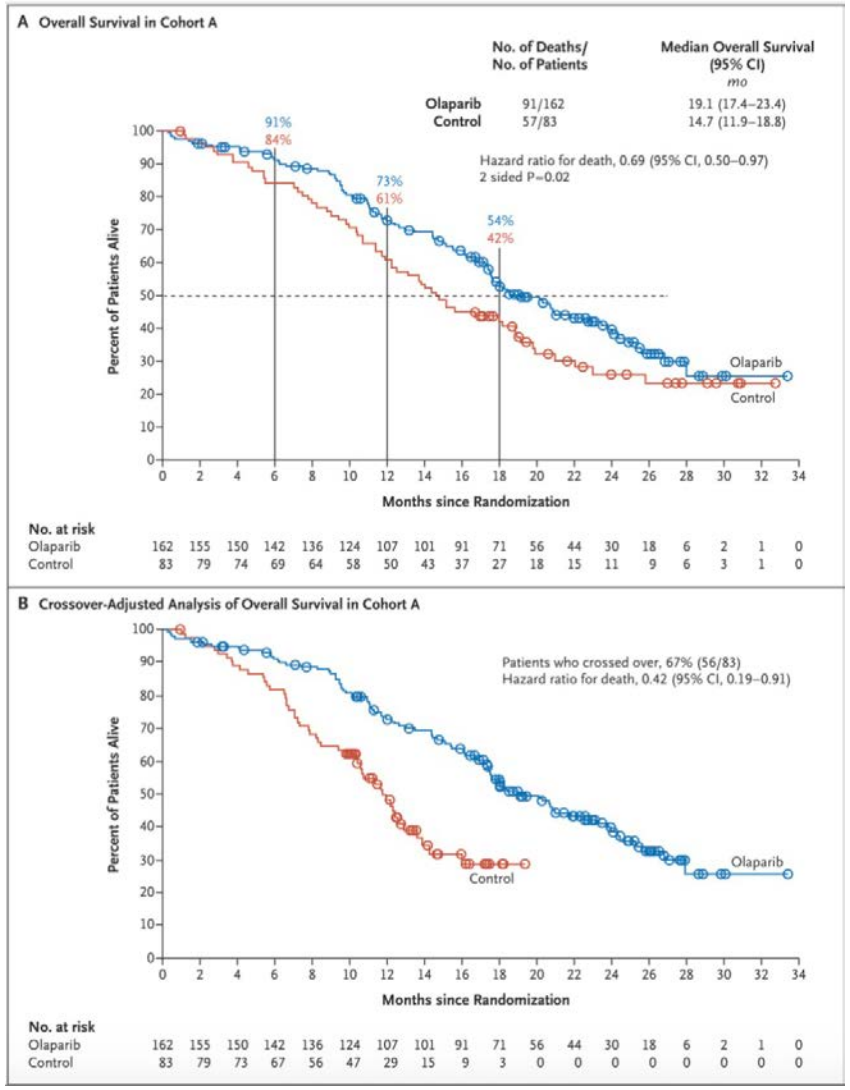
Sec EP: Pain Progression

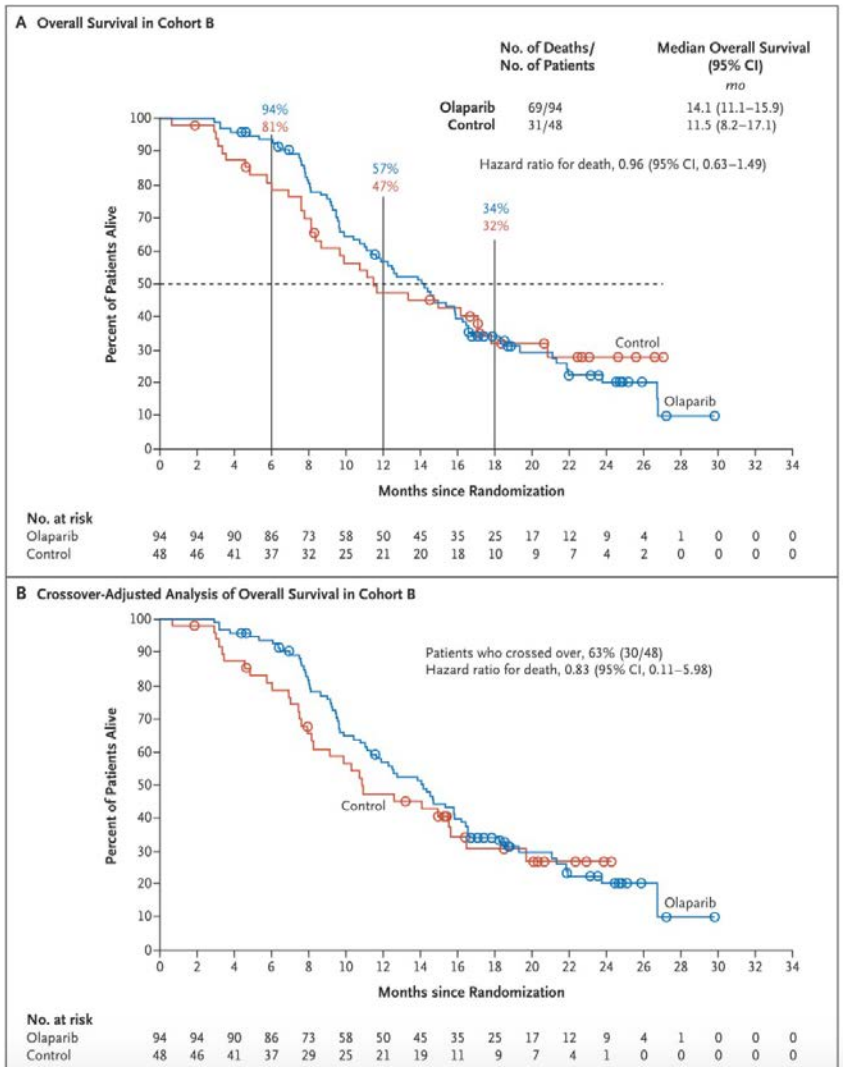


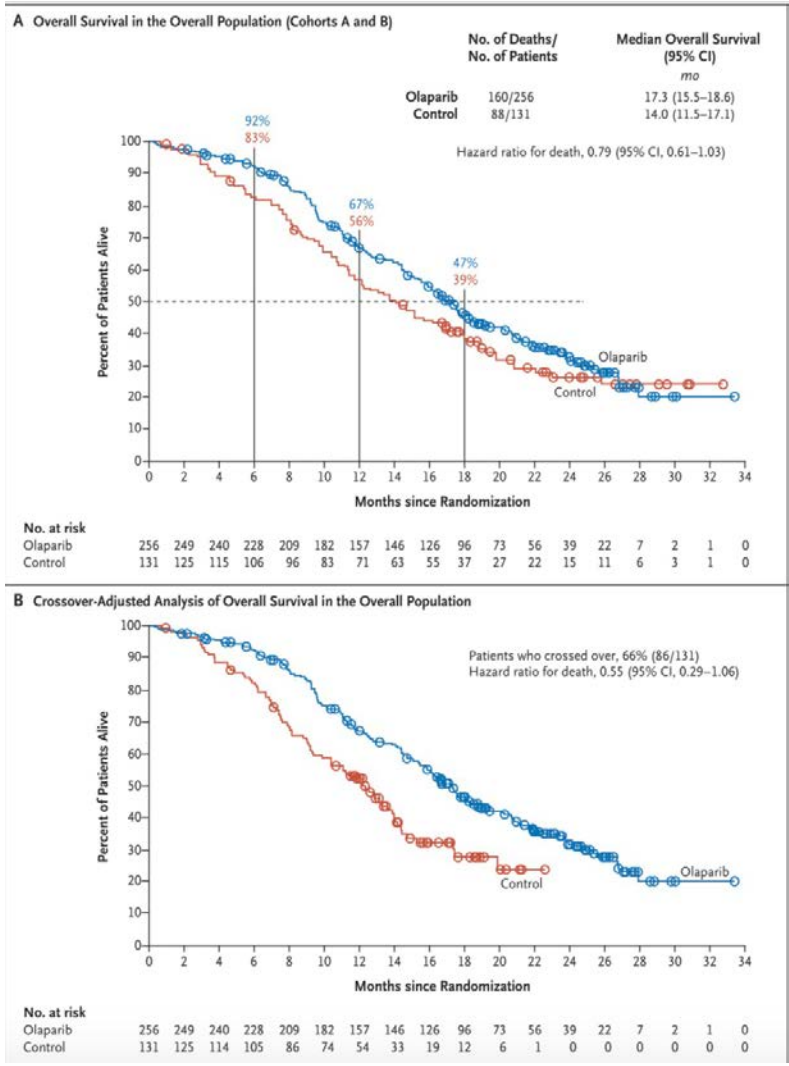


DeBono NEJM 2020

PROfound OS: Cohort A/B/Overall







FDA approval May 19, 2020, for patients with mCRPC and HRR mutations who have progressed after abiraterone or enzalutamide

TRITON3: **Rucaparib vs Physician's Choice in Progressing mCRPC With *BRCA1/2* or *ATM* Alterations**

- Randomized, ongoing, multicenter, open-label phase III study

*Stratification by ECOG PS (0 or 1), hepatic metastases (yes or no), and genetic alteration (*BRCA1, BRCA2, *or* ATM*)*

Patients with mCRPC; deleterious somatic or germline alteration in ***BRCA1/2* or *ATM***; progression on ARPI in any setting; ECOG PS 0/1; no prior PARPi or CT for CRPC
(N = 405)

2:1

Rucaparib 600 mg BID
x 28-day cycles
(n = 270)

Physician's Choice*
(n = 135)

Until radiographic progression or discontinuation for other reason

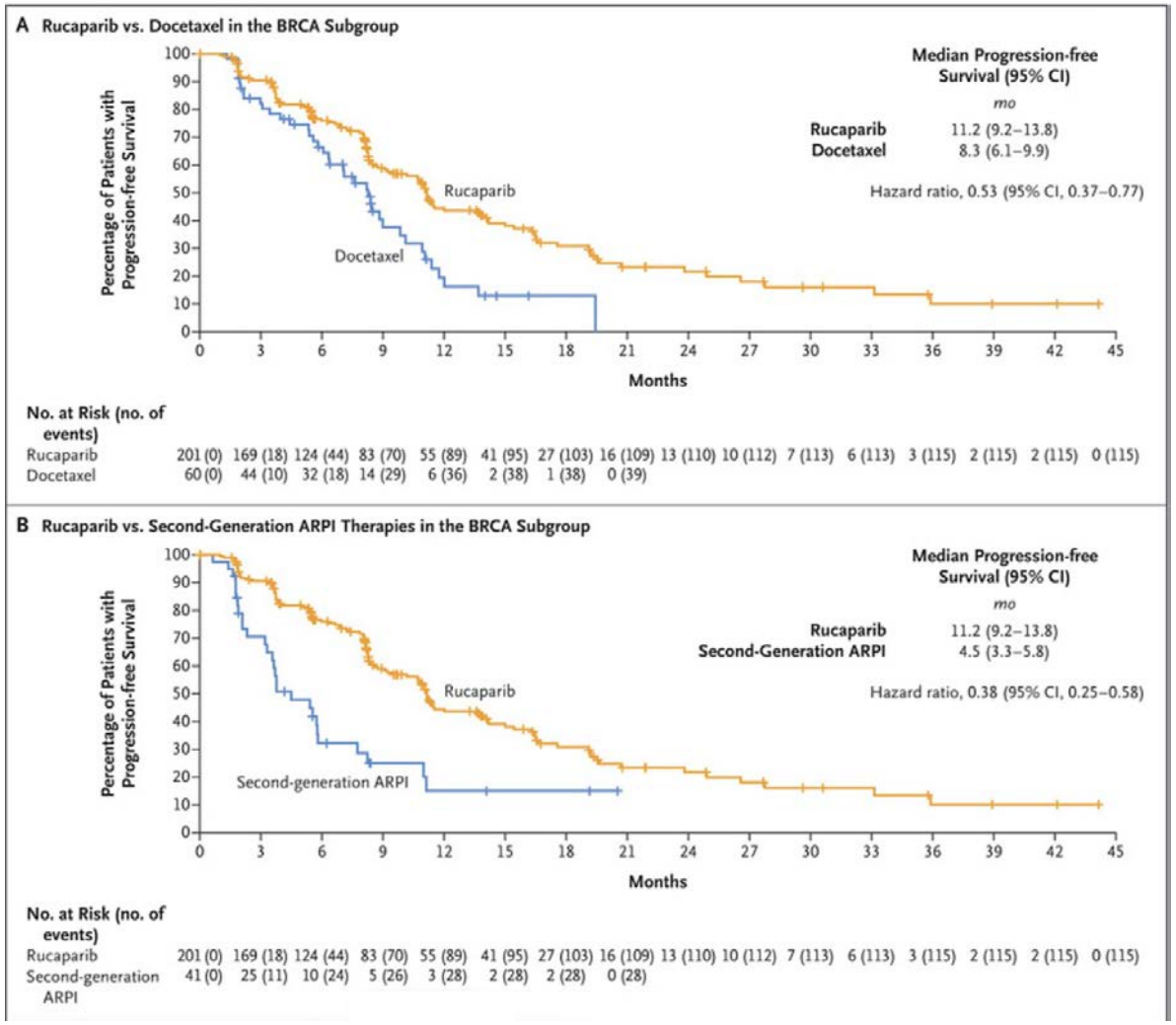
Crossover from CT to rucaparib optional following PD

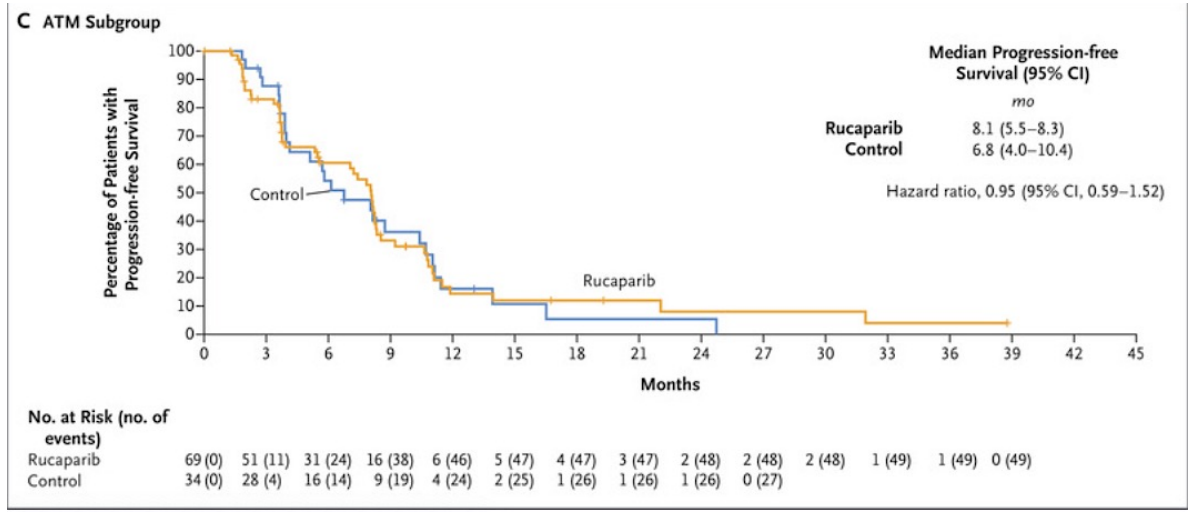
*Docetaxel 75 mg/m^2 in 21-day cycles (max 10 cycles) or abiraterone 1000 mg QD or enzalutamide 160 mg QD. Prednisone coadministered with docetaxel or abiraterone.

- **Primary endpoint:** rPFS by IRR
- **Key secondary endpoints:** OS, ORR by IRR
- **Subgroup analyses:** OS and rPFS for rucaparib vs docetaxel or second-generation ARPI

Bryce. ASCO GU 2023. Abstr 18. Fizazi. NEJM. 2023;388:719.

TRITON3: Results

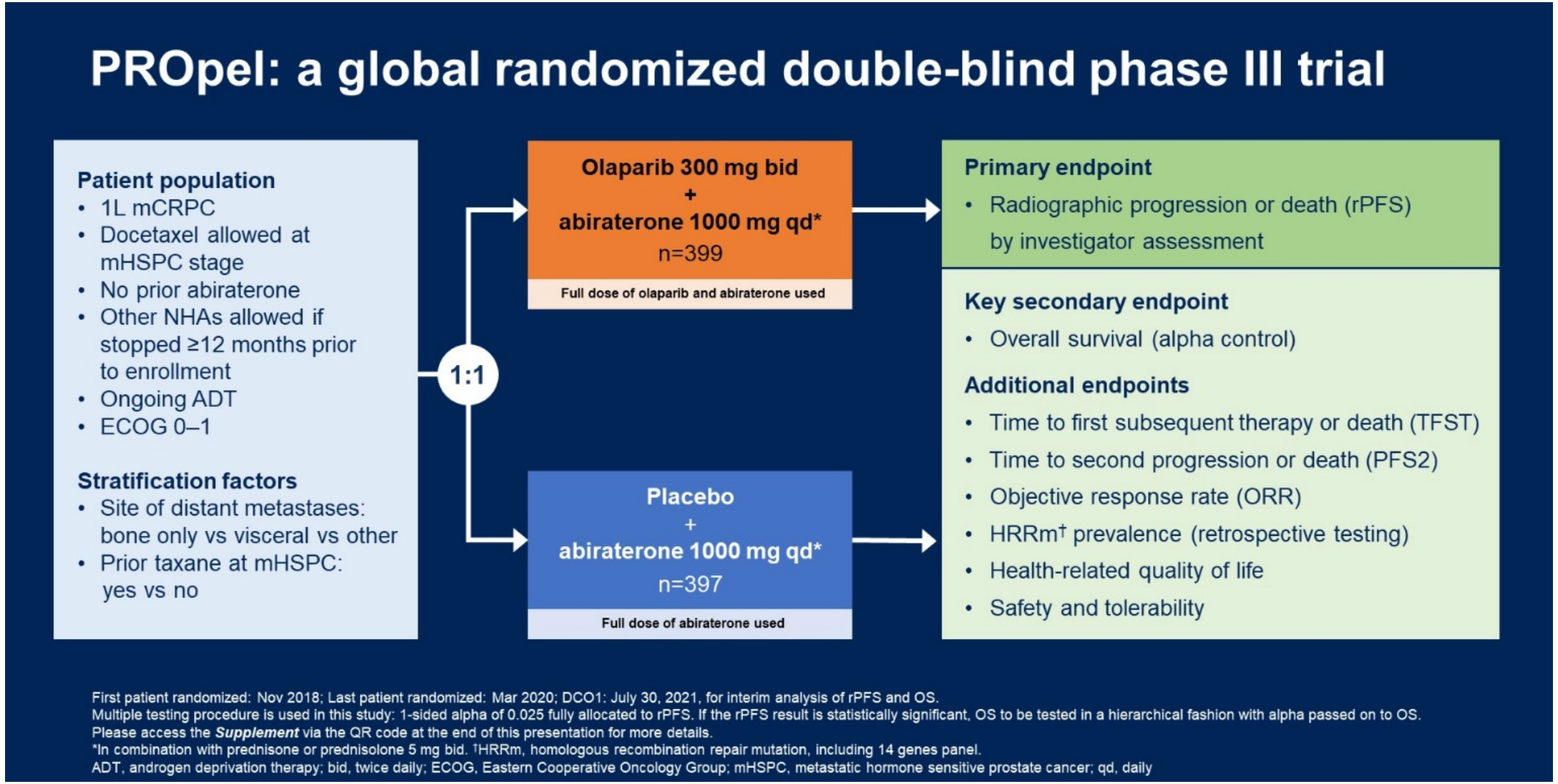




FDA accelerated approval May 15, 2020, post NHT/taxane-based chemotherapy in mCRPC with BRCA mutation based on Phase II TRITON2

Fizazi NEJM 2023

Combination #1: Abiraterone/Olaparib



Patient Characteristics: RESULTS; rPFS improved in all comers

PROpel: baseline patient characteristics

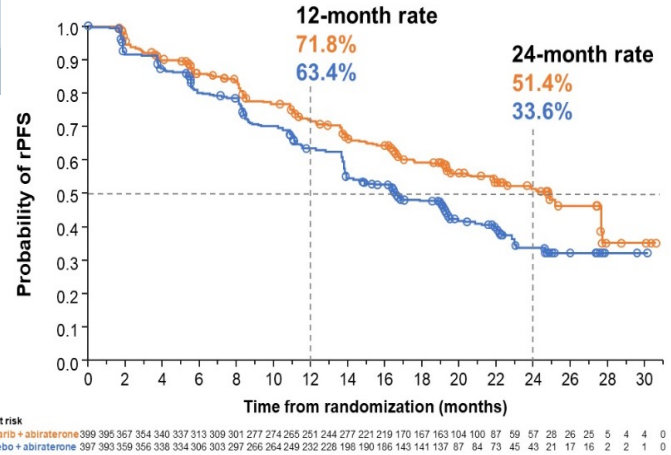
Well-balanced between treatment arms

	Olaparib + abiraterone (n=399)	Placebo + abiraterone (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 ≥ 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†		
HRRm	**111 (27.8)**	**115 (29.0)**
Non-HRRm	**279 (69.9)**	**273 (68.8)**
HRRm unknown	**9 (2.3)**	**9 (2.3)**

†The HRRm status of patients in PROpel was determined retrospectively using results from tumor tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved. Please access the Supplement via the QR code at the end of this presentation for more details.
BPI-SF, Brief Pain Inventory – Short Form; ctDNA, circulating tumor DNA; IQR, interquartile range; PSA, prostate-specific antigen.

PROpel primary endpoint: rPFS by investigator-assessment

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
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	

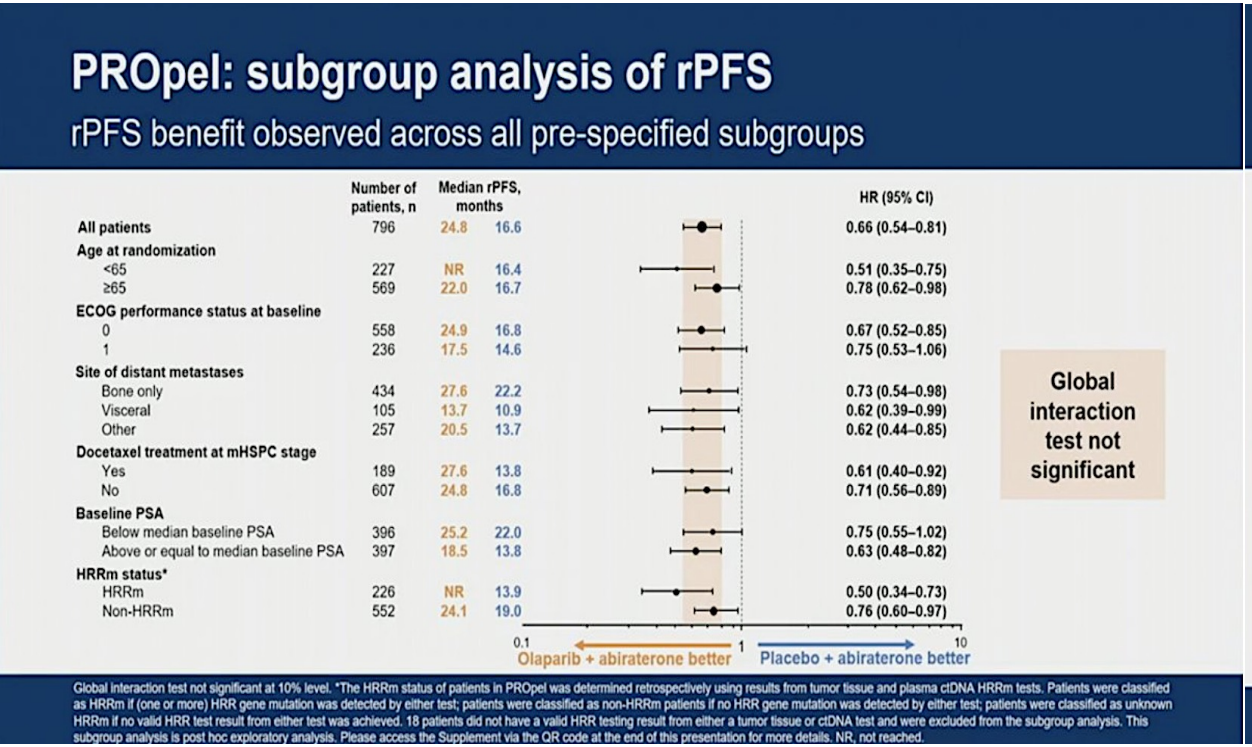
Pre-specified 2-sided alpha: 0.0324

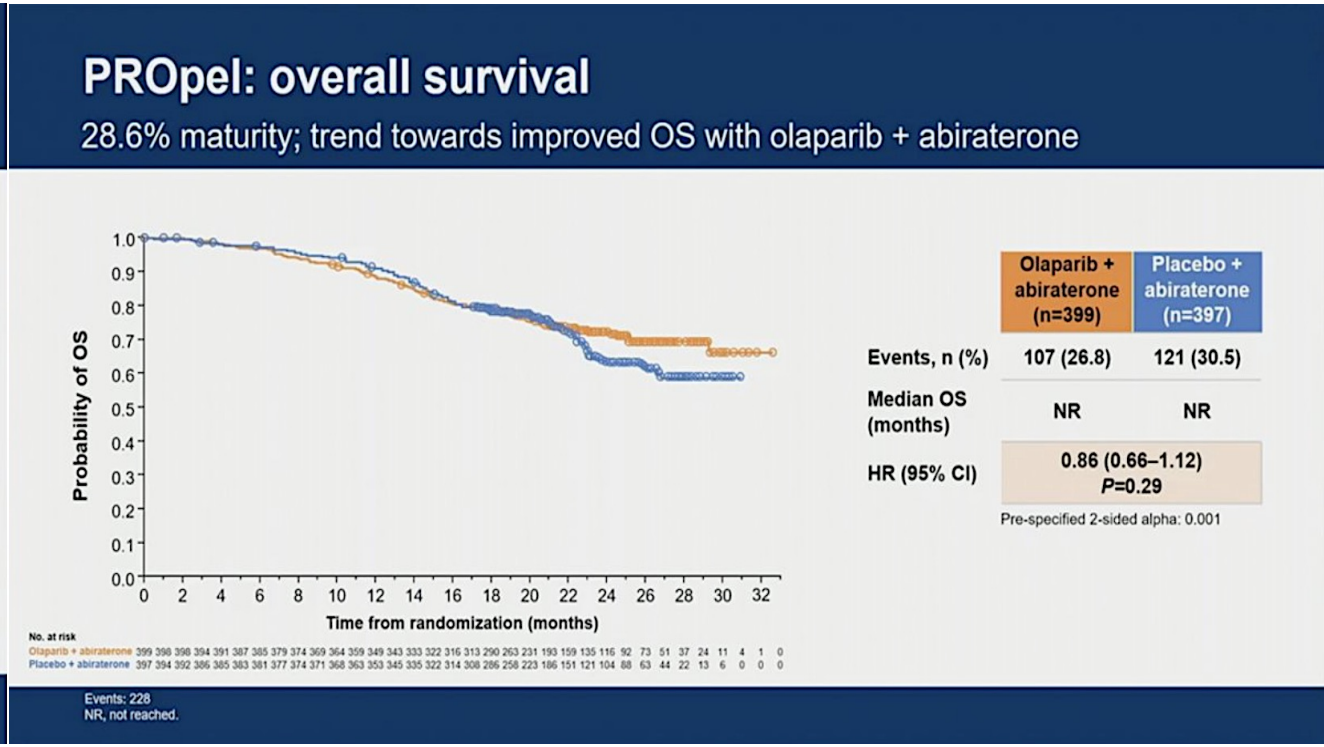
Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

Saad. ASCO GU 2022. Abstr 11. Clarke. NEJM Evidence. 2022.
Clarke ASCO GU 2023; Abst LBA16.

All groups benefit from the combo: HR better for HRRm





FDA did a post hoc analysis: 11% BRCA positive
BRCA Positive: HR 0.30; BRCA uncertain: 0.73; BRCA negative: 1.06
ODAC 4/28- unanimous vote for narrow indication; FDA approval for BRCA in mCRPC

Saad. ASCO GU 2022. Abstr 11. Clarke. NEJM Evidence. 2022. Clarke ASCO GU 2023; Abst LBA16.

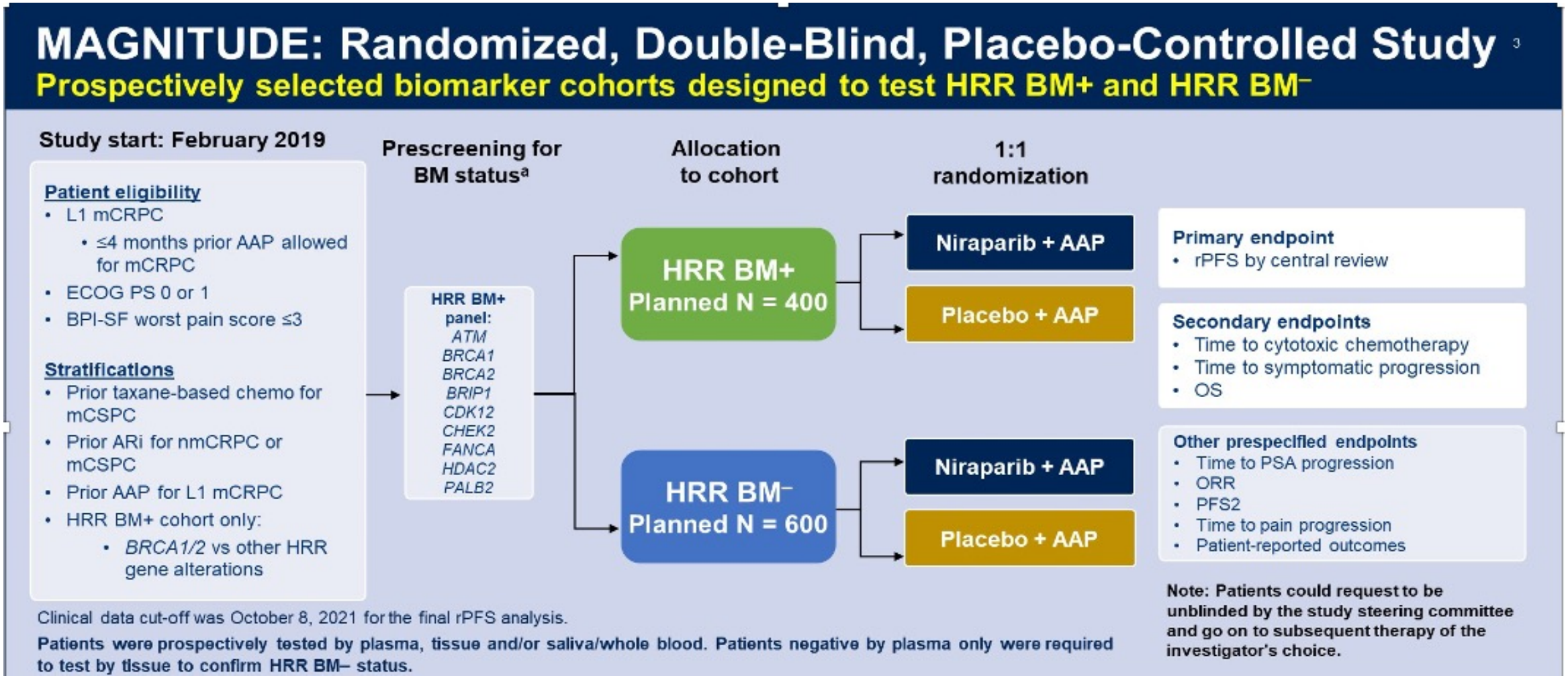
PROpel: AEs in >10% of Patients

AE, %	Abiraterone + Olaparib (n = 398)		Abiraterone + Placebo (n = 396)	
	Any	Gr ≥3	Any	Gr ≥3
Anemia	49.7	16.1	17.7	3.3
Fatigue/asthenia	38.7	2.5	30.3	1.5
Nausea	30.7	0.3	14.4	0.3
Back pain	21.6	1.0	19.9	1.5
Diarrhea	20.6	1.3	10.6	0.3
Constipation	18.6	0	14.9	0.3
Decreased appetite	16.6	1.0	7.8	0
Vomiting	15.6	1.5	9.3	0.3

AE, %	Abiraterone + Olaparib (n = 398)		Abiraterone + Placebo (n = 396)	
	Any	Gr ≥3	Any	Gr ≥3
Hypertension	15.3	3.8	18.7	4.5
Arthralgia	14.6	0	19.4	0.5
COVID-19	12.8	3.8	8.8	2.0
Peripheral edema	12.3	0	12.6	0.3
Dizziness	12.3	0	6.8	0
Urinary tract infection	11.6	2.5	8.8	1.0
Cough	11.8	0	7.3	0
Hot flush	8.8	0	12.9	0

Clarke. ASCO GU 2023. Abstr LBA16.

Combinations of PARPI with NHT: Niraparib/Abiraterone #2



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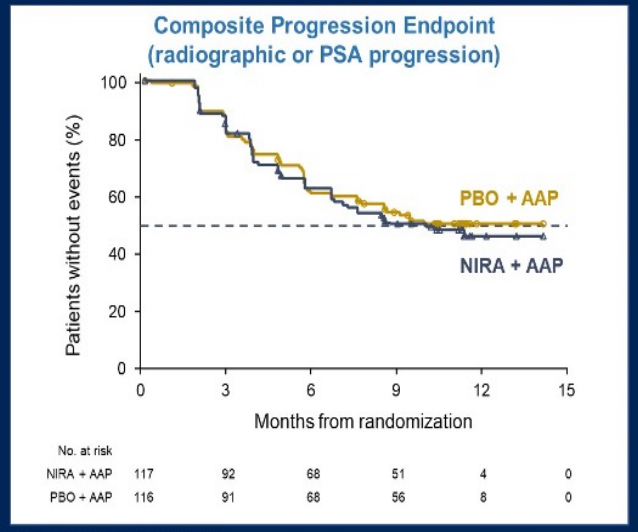
Results: NEGATIVE in HRR neg: Closed for futility

5

MAGNITUDE HRR BM⁻ : Prespecified Early Futility Analysis
No Benefit of NIRA + AAP in HRR BM⁻ Patients



- Composite endpoint[a] (N = 233)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

[b]Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

[a]rPFS or PSA progression, whichever occurred first
AAP, abiraterone acetate + prednisone/prednisolone; AE, adverse event; BM, biomarker; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; IDMC, independent data monitoring committee; mCRPC, metastatic castration-resistant prostate cancer; NIRA, niraparib; PBO, placebo; PSA, prostate specific antigen; rPFS, radiographic progression free survival

6

MAGNITUDE HRR BM+ Cohort: Patient Baseline Characteristics

	NIRA + AAP (n=212)	PBO + AAP (n=211)
Median age (range), yr	69 (45-100)	69 (43-88)
Biomarker alteration, n (%)		
BRCA2	86 (40.6)	88 (41.7)
BRCA1	12 (5.7)	4 (1.9)
ATM	43 (20.3)	42 (19.9)
CHEK2	18 (8.5)	20 (9.5)
PALB2	8 (3.8)	4 (1.9)
CDK12	5 (2.4)	8 (3.8)
FANCA, BRIP1 or HDAC2	11 (5.2)	13 (6.2)
Co-occurring alterations	29 (13.7)	32 (15.2)
BRCA containing co-occurring mutations	16 (7.5)	23 (10.9)
Median hemoglobin (range), g/L	129.0 (64.0-172.0)	131.0 (75.0-161.0)
Median LDH (range), enzyme U/L	199.0 (87.0-2959.0)	200.5 (77.0-1530.0)
ECOG, n (%) 0 / 1	130 (61.3) / 82 (38.7)	146 (69.2) / 65 (30.8)
Bone metastases, n (%)	183 (86.3)	170 (80.6)
Visceral metastases, n (%)	51 (24.1)	39 (18.5)
Liver	18 (8.5)	13 (6.2)
Lung	27 (12.7)	18 (8.5)
PSA at study entry (ug/L), median (range)	21.4 (0-4826.5)	17.4 (0.1-4400.0)
Prior taxane-based chemotherapy for nmCRPC/mCSPC, n (%)	41 (19.3)	44 (20.9)
Prior AR-targeted therapy for nmCRPC/mCSPC, n (%)	8 (3.8)	5 (2.4)
Prior AAP therapy for L1 mCRPC, n (%)	50 (23.6)	48 (22.7)

AAP, abiraterone acetate + prednisone/prednisolone; AR, androgen receptor; BM, biomarker; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; L1, first line; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NIRA, niraparib; nmCRPC, nonmetastatic castration-resistant prostate cancer; PDO, placebo; PSA, prostate-specific antigen.

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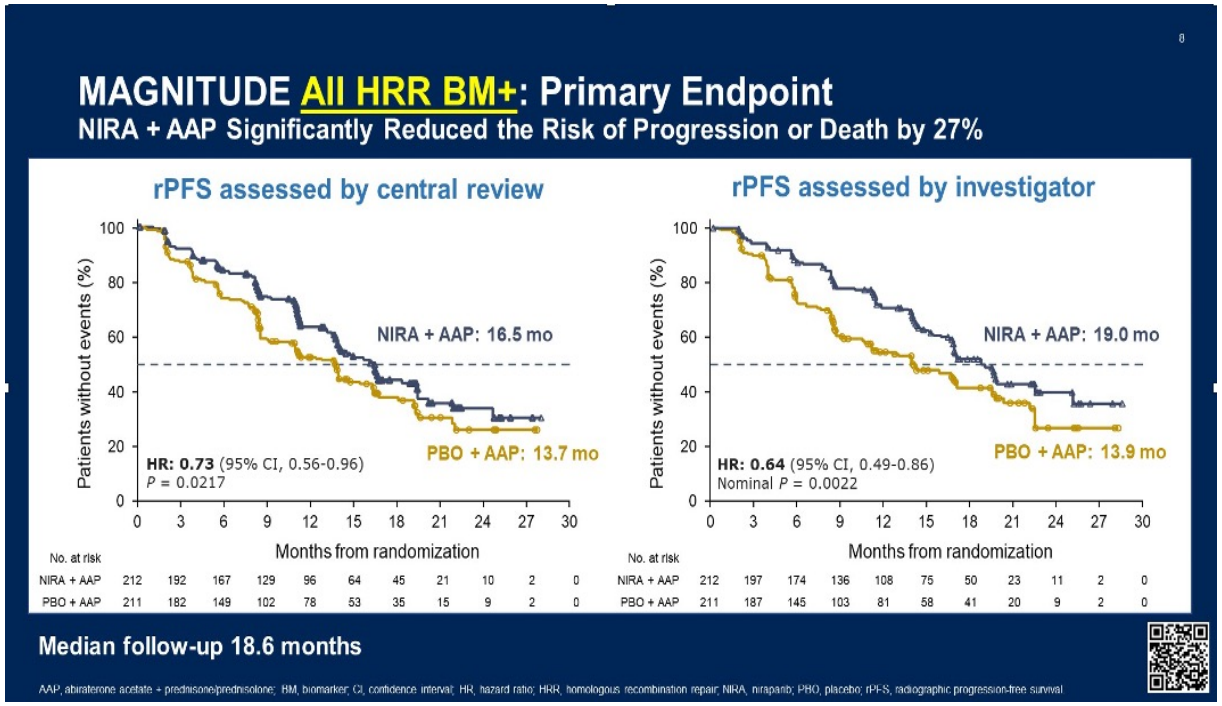
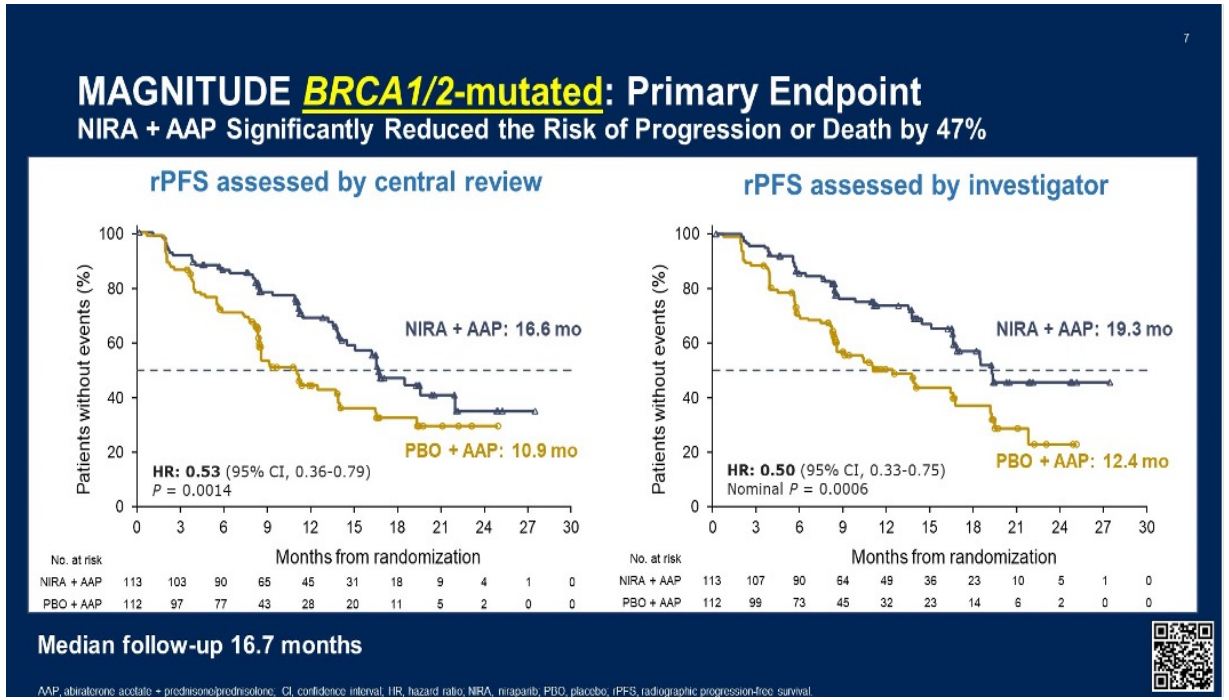
Biomarker Positive Cohorts: Improved rPFS in HRR + and in BRCA +

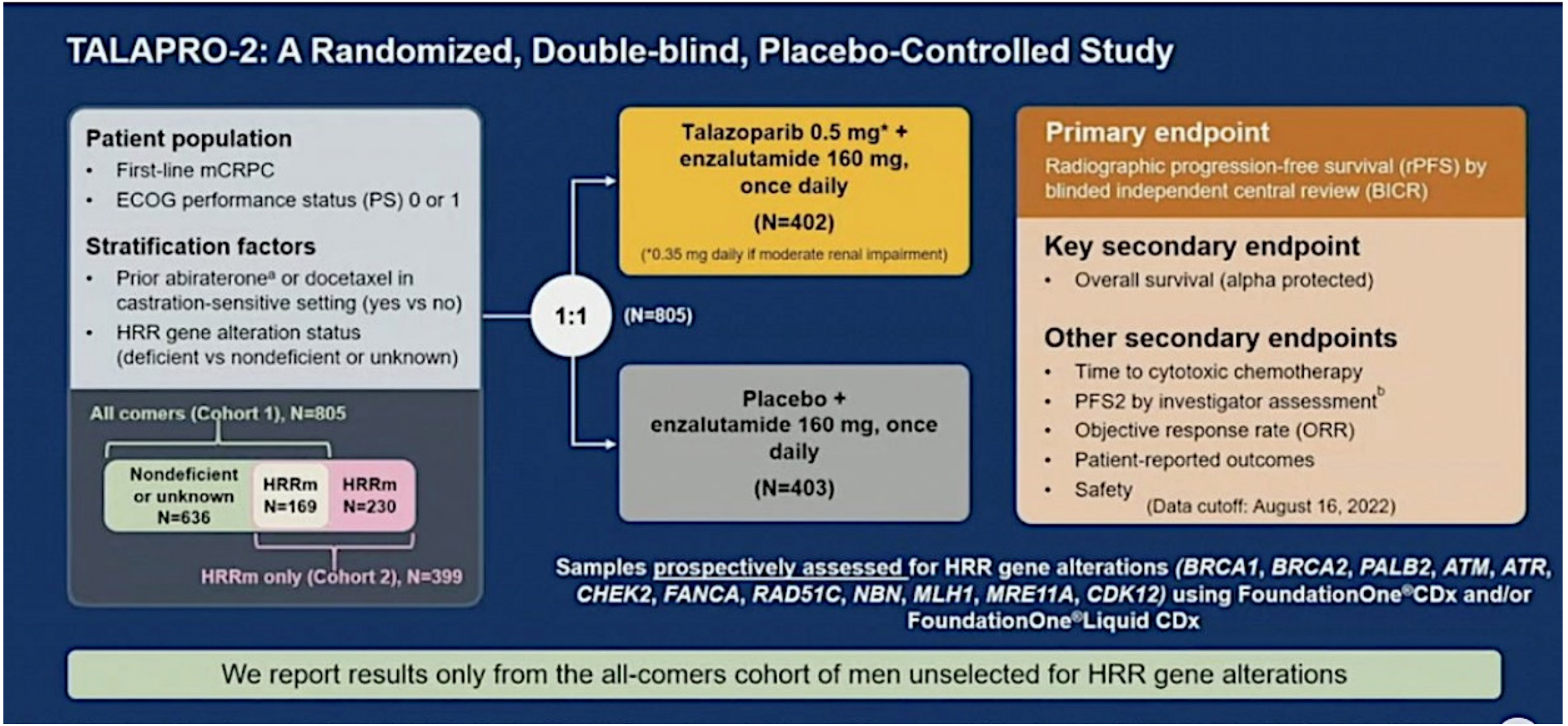




HR : Much better in the BRCA enriched population: BRCA prognostic biomarkers with worse outcome
COUGAR-302: Abiraterone in mCRPC- PFS 16 months. FDA approval for BRCA pts mCRPC

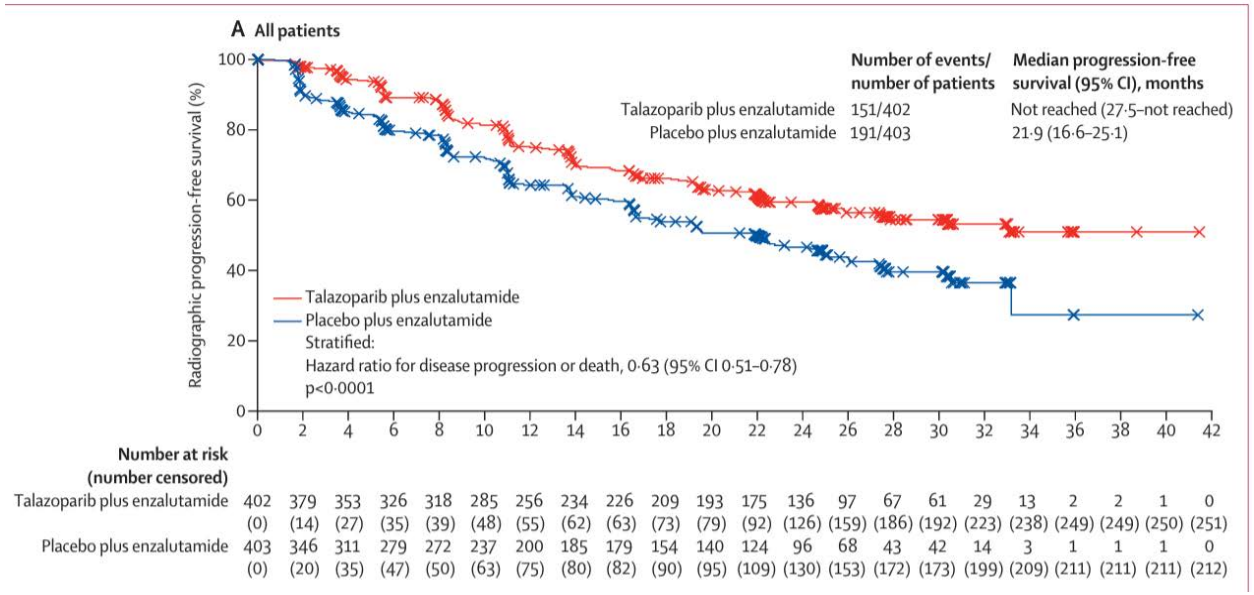
Chi, JCO 2023

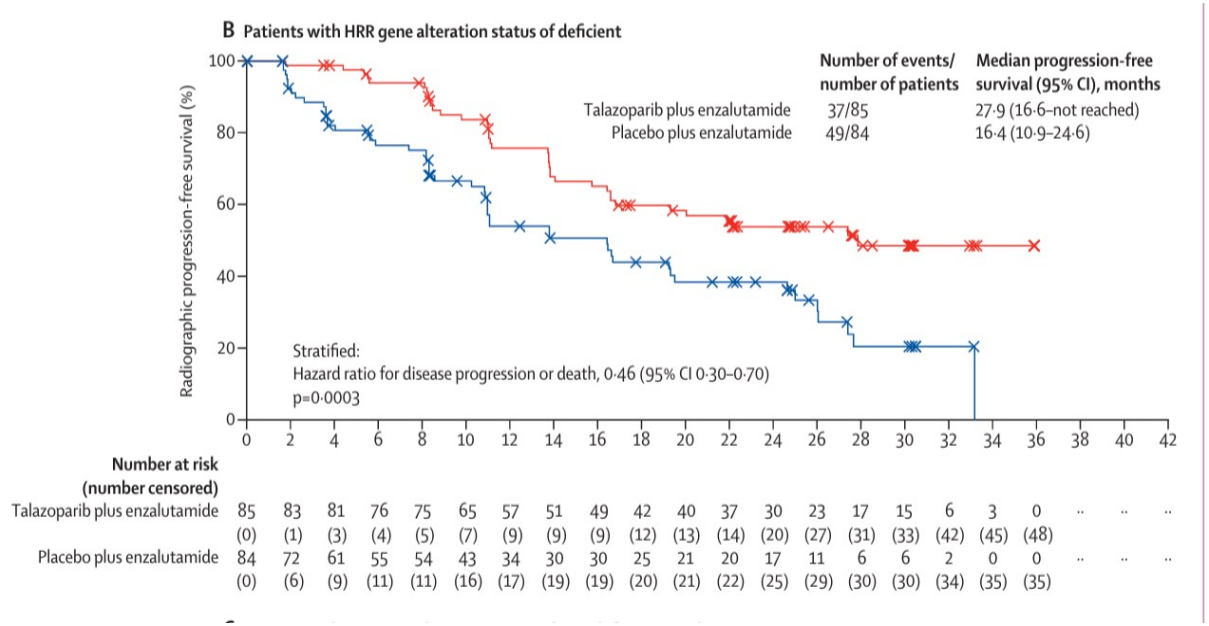
Combination #3: TALAPRO-2: Talazoparib



Agarwal Lancet Oncology 2023

Improvement in rPFS in ITT and in HRR





Agarwal Lancet 2023

TALAPRO-2: Safety

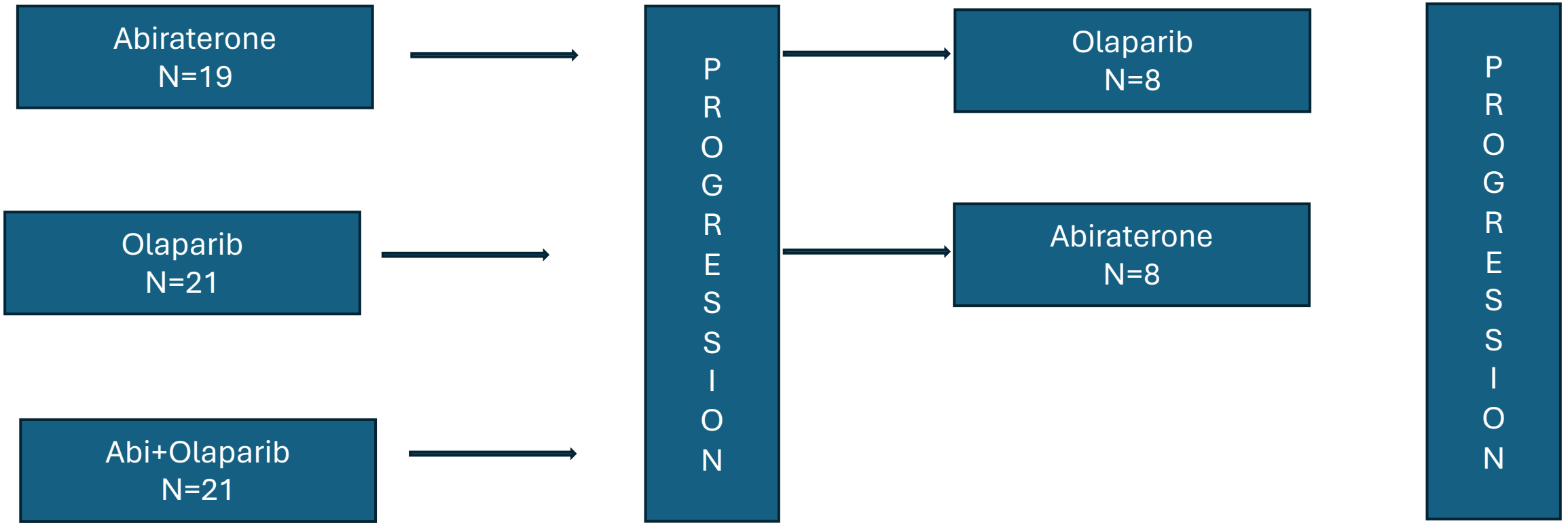
TEAE, n (%)	Talazoparib + Enzalutamide (n = 398)	Placebo + Enzalutamide (n = 401)
Any TEAE ▪ Treatment related	392 (98.5) 357 (89.7)	379 (94.5) 279 (69.6)
Serious AE Treatment related	157 (39.4) 78 (19.6)	107 (26.7) 12 (3.0)
Any grade 3-4 TEAE	286 (71.9)	163 (40.6)
Any grade 5 TEAE Treatment related	13 (3.3) 0	18 (4.5) 2 (0.5)
Dose interruption of talazoparib or placebo due to AE	300 (75.4)	94 (23.4)
Dose reduction of talazoparib or placebo due to AE	223 (56.0)	29 (7.2)
Discontinuation of talazoparib or placebo due to AE	76 (19.1)	49 (12.2)

Agarwal. ASCO GU 2023. Abstr LBA17.

PARP Combinations: No OS

	PROPEL	MAGNITUDE	TALAPRO-2
Genes	ATM, BRCA, BARD1, BRP1,CDK12,CHK1/2; FANCL, PALB2, RAD51B/C,D/54L	ATM, BRCA, BRP1, CDK12, CHK2, FANCA, HDAC2, PALB2	ATM, ATR,BRCA,CK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C
HRRm rPFS OS	NR vs NR ; HR-0.5(.3-.7)* NR vs 28.5 HR 0.66(.4-.9)*	16.5 vs 13.7 HR-0.72(.5-.9)* 29.3 vs 32.2 HR-1.01 (.7-1.3)	27.9 vs 16.4 HR-0.46(.30.7)* NR vs 33.7 HR-0.69 (.4-1.0)
Non HRRm rPFS OS	24.1 vs 19 HR-0.76 (.6-.9)* 42.1 vs 38.9 HR 0.89(.7-1.1)	NR vs NR HR-1.09 (.7-1.5)	NR vs 22.5 HR-0.7 (.5-.8)* NR vs 38.7 HR-0.9 (.7-1.1)
BRCA rPFS OS	NR vs 8.4 HR-0.23 (.1-.4) * NR vs 23 HR-0.29 (.1-.5)*	16.6 vs 10.9 HR -0.53 (.3-.7)* 30.4 vs 28.6 HR-0.79 (.5-1.1)	NR vs NR HR- 0.23 (.1-.5)* NR vs NR HR 0.61 (.3-1.2)
Non BRCA rPFS OS	24.1 vs 19 HR-0.76 (.6-.9)* 39.6 vs 38 HR-0.91 (.7-1.1)		NR vs NR HR-0.66 (.3-1.1)
Prior ARPI	0.15%	3	8
Prior Docetaxel	24	19	29
FDA label	BRCA mutated mCRPC	BRCA mutated mCRPC	HRR mutated mCRPC

BRCAAway: DESIGN



Husain GU ASCO 2024; Abstr 19

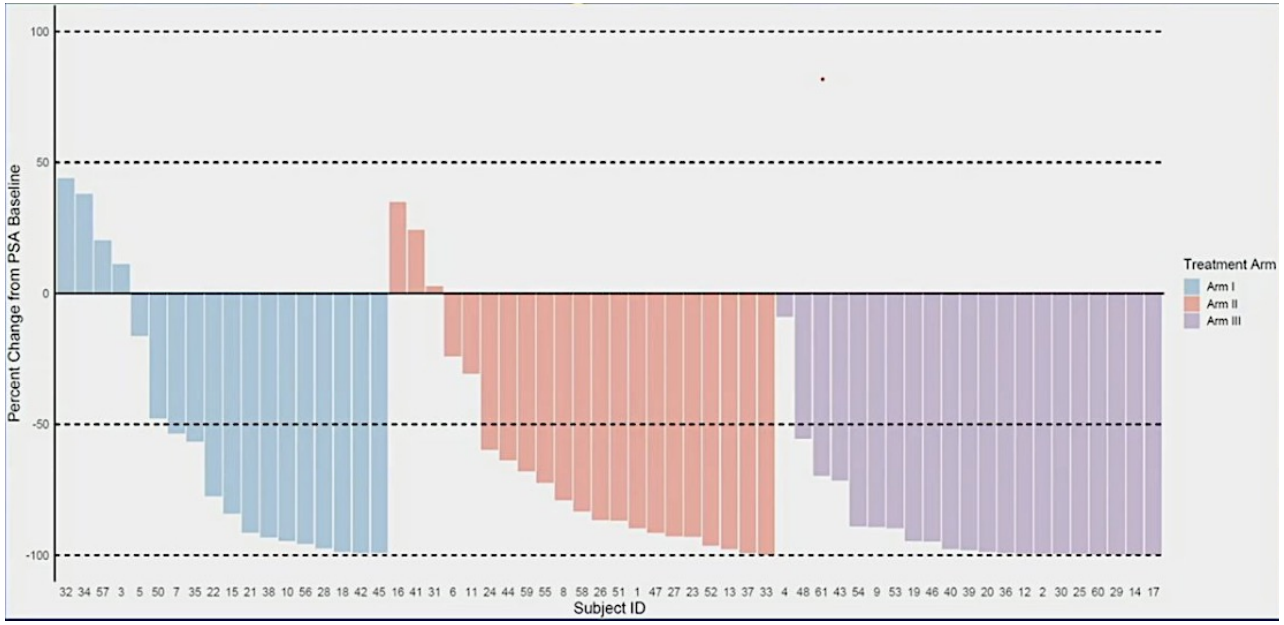
BRCAAway: Results

Abiraterone Olaparib Combination

	Arm I (n = 19)	Arm II (n = 21)	Arm III (n = 21)
Median PFS, months (95% CI)	**8.4 (2.9, 17)**	**14 (8.4, 20)**	**39 (22, NR)**
Objective RR, % (95% CI)	**22** (6.4, 48)	**14** (3, 36)	**33** (15, 57)
PSA RR, % (95% CI)	**61** (36, 83)	**67** (43, 85)	**95** (76, 100)
Undetectable PSA RR, % (95% CI)	**17** (3.6, 41)	**14** (3, 36)	**33** (15, 57)

Crossover

		PFS (mos)	PFS2 (mos)	ORR	PSA50
Abi-Olaparib	8/19	8.3	16	38	50
Olaparib-Abi	8/21	7.2	16	25	63



Husain GU ASCO 2024; Abstr 19

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

No prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn,ooo] (category 1)
  - Docetaxel[fff,ppp] (category 1)
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 1)
  - Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation (category 1)
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,sss] (category 1)
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior novel hormone therapy/no prior docetaxel[mmm,ttt]

- Preferred regimens
  - Docetaxel (category 1)[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation (category 2B)
  - Olaparib for HRRm[uuu] (category 1)
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCA mutation[vvv]
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy] (category 2B)
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Abiraterone[u] + dexamethasone[nnn,www]
  - 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]
  - Niraparib/abiraterone[u,fff,zzz] for BRCA mutation
  - Olaparib/abiraterone[u,fff,nnn,qqq] for BRCA mutation
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,sss]
  - Talazoparib/enzalutamide for HRRm[u,fff,yyy]
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior docetaxel and prior novel hormone therapy[mmm,ttt]

- Useful in certain circumstances
  - Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[xxx] (category 1)

(The following systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[fff,ooo] (category 1)
  - 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[ooo,uuu] (category 1)
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff]
  - Radium-223[rrr] for symptomatic bone metastases[ooo] (category 1)
  - Rucaparib for BRCA mutation[vvv]
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

See Footnotes for Systemic Therapy M1 CRPC (PROS-15A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Data Free Zone

- Patients who have received PARP combinations with Prior ARSI

	PROPEL	MAGNITUDE	TALAPRO-2
Genes	ATM, BRCA, BARD1, BRP1,CDK12,CHK1/2; FANCL, PALB2, RAD51B/C,D/54L	ATM, BRCA, BRP1, CDK12, CHK2, FANCA, HDAC2, PALB2	ATM, ATR,BRCA,CK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C
Prior ARPI (%)	0.15%	3	8
Prior Docetaxel (%)	24	19	29
FDA label	BRCA mutated CRPC	BRCA mutated CRPC	HRR mutated CRPC

No Overall Survival Yet

	PROPEL #	MAGNITUDE	TALAPRO-2
Genes	ATM, BRCA, BARD1, BRP1,CDK12,CHK1/2; FANCL, PALB2, RAD51B/C,D/54L	ATM, BRCA, BRP1, CDK12, CHK2, FANCA, HDAC2, PALB2	ATM, ATR,BRCA,CK2, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51C
HRRm rPFS OS	 NR vs NR ; HR-0.5(.3-.7)* NR vs 28.5 HR 0.66(.4-.9)	 16.5 vs 13.7 HR-0.72(.5-.9)* 29.3 vs 32.2 HR-1.01 (.7-1.3)	 27.9 vs 16.4 HR-0.46(.30.7)* NR vs 33.7 HR-0.69 (.4-1.0)
Non HRRm rPFS OS	 24.1 vs 19 HR-0.76 (.6-.9) 42.1 vs 38.9 HR 0.89(.7-1.1)	 NR vs NR HR-1.09 (.7-1.5)	 NR vs 22.5 HR-0.7 (.5-.8)* NR vs 38.7 HR-0.9 (.7-1.1)

OS in Cohort B in PROfound negative (non BRCA/ATM)
HRRm+=28% ; ITT- NS; BRCA- HR 0.29

Significant Cross Resistance with NHT: Results of the Control Arm

Contemporary trials looking at alternate NHT in the control arm

	PSA50 (%)	rPFS (mos)	OS	Ref
PROfound	8	3.5	19.1 HR-0.69	DeBono NEJM 2020
CONTACT-02	12	4.2	-	Agarwal GU ASCO 2023
IMbassador250	3	4.1	-	Powles Nat Med 2022
PSMAfore	20	5.5	-	Sartor ESMO 2023

Low response of monoRx ARSI
Does a combo with PARPi add to just more toxicity?

TALAPRO-2: Safety

	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. Lancet Oncology 2023.

Ongoing trials in mHSPC

Trial	Estimated #	Control arm	Experimental arm	Estimated completion date
AMPLITUDE NCT04497844	696	ADT/Abi/Pred	ADT/Abi/Pred/ Niraparib	11/2024
TALAPRO-3 NCT04821622	599	ADT/Enza	ADT/Enza/ Talazoparib	9/2025

Conclusions

- Mono Rx PARPi active in BRCA mutations
- Combinations of PARPI/ARPI active in BRCA mutations in mCRPC with no prior exposure to ARPI
- No level 1 evidence to use combination of NHT/PARPi in patients who have had prior NHT
- No survival advantage with the combination of NHT/PARPi yet
- Benefit in non BRCA HRR is less
- Benefit in non HRR does not justify the cost/toxicity of the combo

MODULE 5: Other Novel Therapies for Patients with Metastatic Prostate Cancer — Dr Heath

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Defining PSMA positivity and the role of alpha-emitting therapy in the era of PSMA radioligands

Neil Love, MD

David S Morris, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

David S Morris, MD

How do you define PSMA PET positivity?

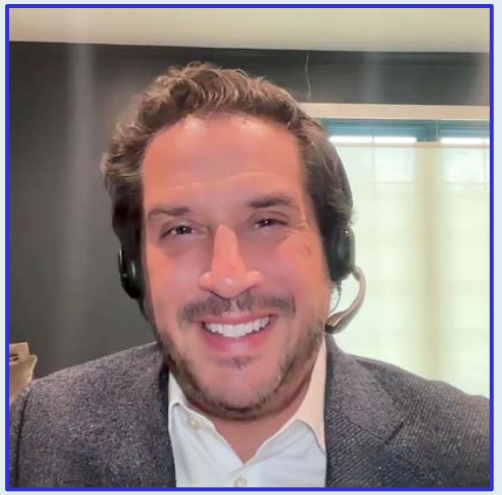
Where do you see alpha-emitting therapy such as radium-223 playing a role in this era of PSMA-directed radioligands?

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Comments

Integrating PSMA PET imaging into the surveillance of patients; recent analyses of lutetium Lu 177 vipivotide tetraxetan survival outcomes in the pretaxane setting

Neil Love, MD



Jason Hafron, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Jason Hafron, MD

Do you use PSMA PET imaging for the surveillance of patients with mCRPC or metastatic hormone-sensitive disease who have stable PSA values?

What is your perspective on recent analyses of lutetium Lu 177 vipivotide tetraxetan therapeutic outcomes in the pretaxane setting that have shown a radiographic progression-free survival benefit but not an overall survival benefit?

RTP
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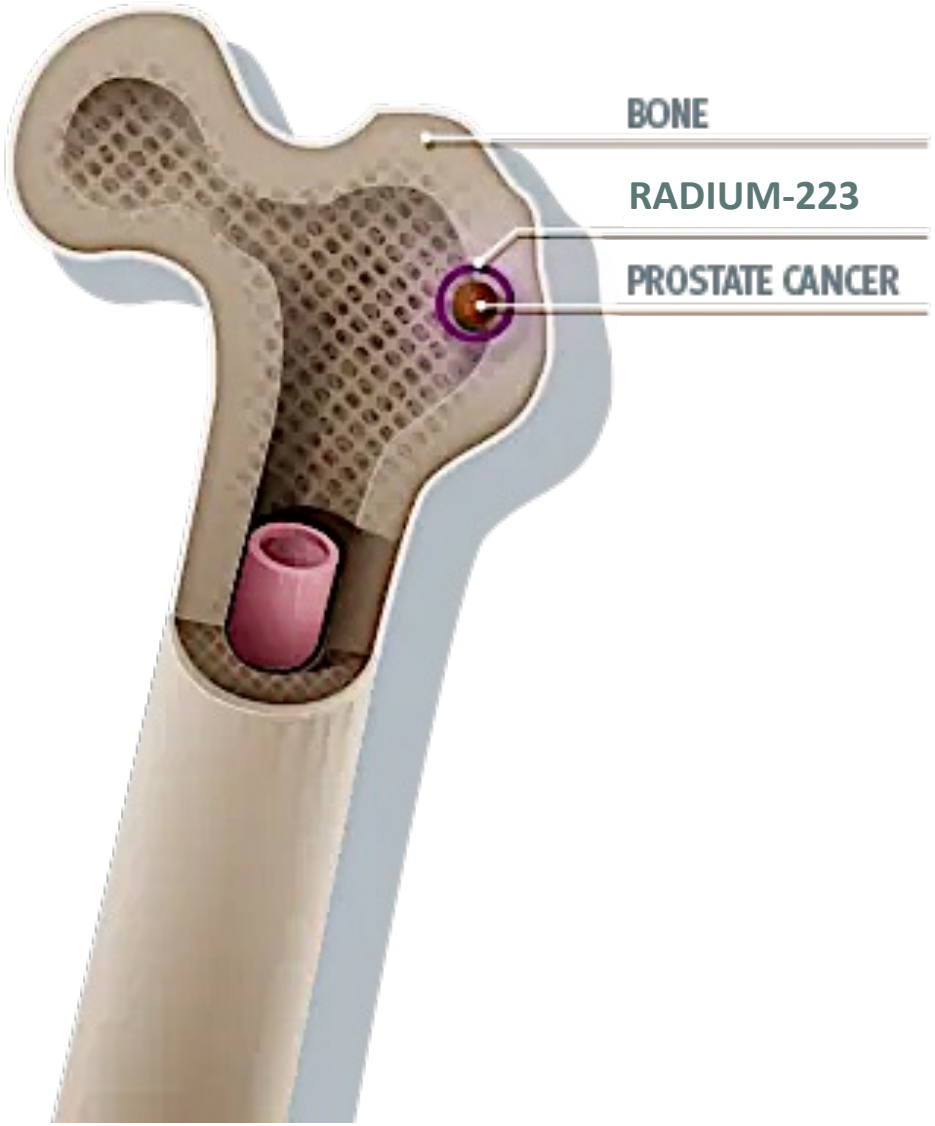
TO PRACTICE

Other Novel Therapies for Patients with Metastatic Prostate Cancer

Elisabeth I. Heath, MD FACP
Professor of Oncology
Associate Center Director, Translational Sciences
Chair, Genitourinary Oncology Multidisciplinary Team
Detroit, MI

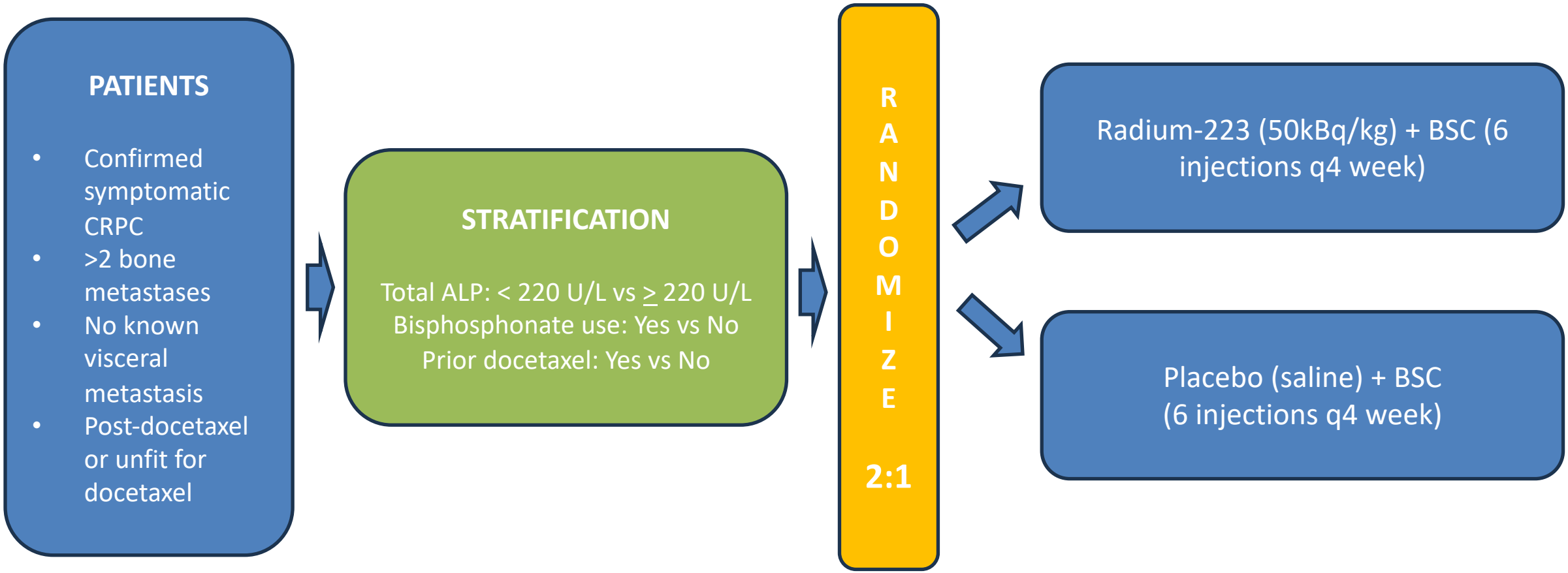
Radium-223

- Radium-223 is radioactive material (alpha emitter) that goes specifically to bone metastasis
- High linear energy transfer of alpha particles leads to high frequency of double strand breaks in nearby cells including cancer cells
- Treatment only for men with symptomatic, bone-only metastatic cancer



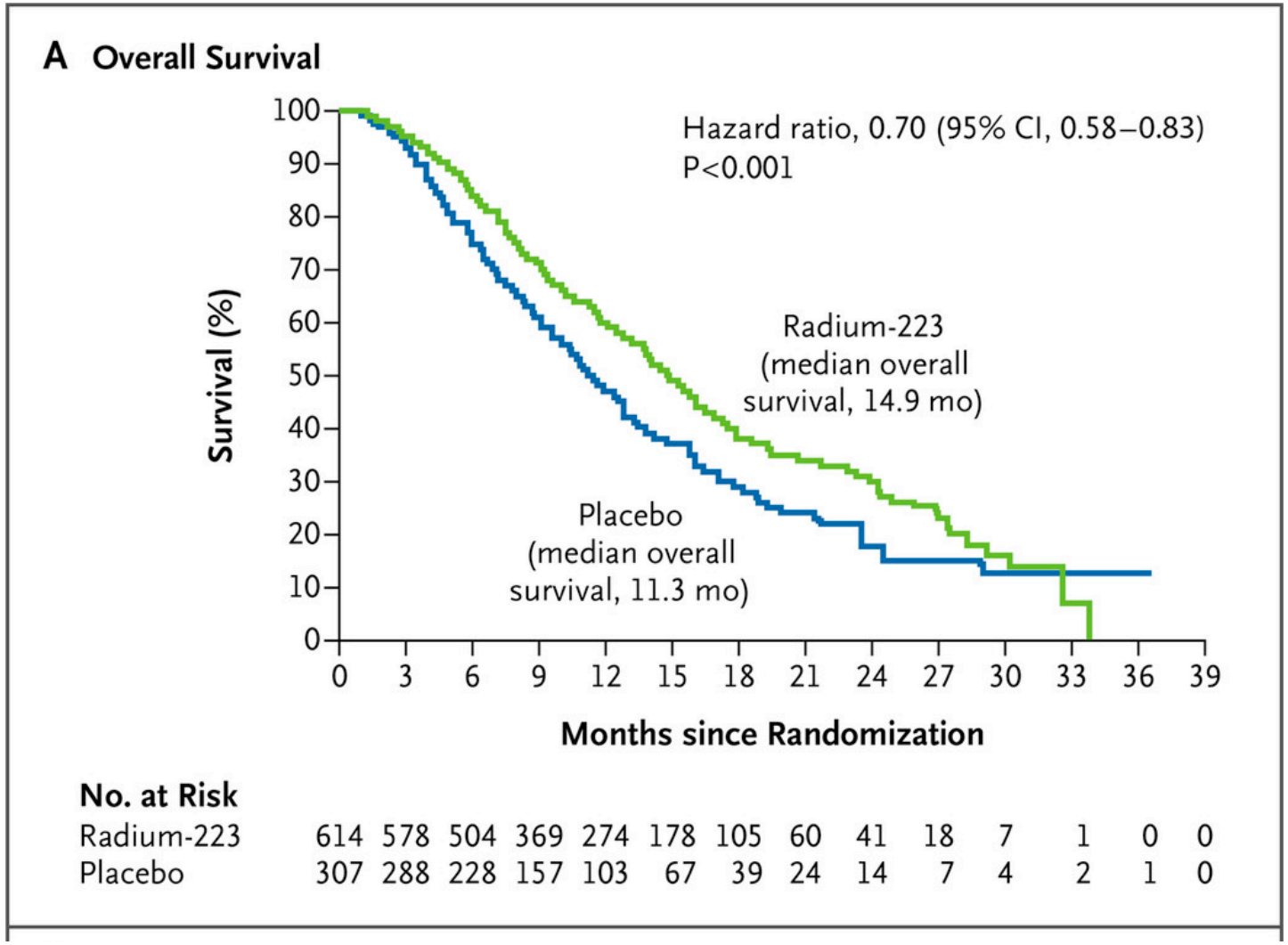
Parker C et al. N Engl J Med 2013;369:213-223.

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase II Study Design



Parker C et al. N Engl J Med 2013;369:213-223.

ALSYMPCA Survival and Follow-Up



Final long-term safety follow-up

- Myelosuppression incidence low
- Long-term follow-up showed no AML, MDS, or new primary bone cancer
- One patient with aplastic anemia after 16 mos post last injection

Parker C et al. N Engl J Med 2013; 369:213-223.
Parker C et al. European Urology 2018; 73:427-435.

Real World Data

- REASSURE: global, prospective, observational study of radium-223 in men with mCRPC
- 1465 patients evaluable
- 12% were treated with subsequent taxane chemotherapy
- 7% of drug-related grade ≥ 3 adverse events in patients who received taxane post radium-223
- Taxane therapy post-radium feasible and tolerable
- Radium-223 plus docetaxel Phase III DORA study enrolling (NCT03574571)

Higano CS et al. Cancer 2024 Feb 10: DOI10.1002/cncr.35221.

Combination Studies

- ERA-223: radium-223 plus abiraterone (NCT02043678)
  - Combination did NOT improve symptomatic skeletal event-free survival and was associated with increased frequency of bone fractures
- PEACE III: radium-223 plus enzalutamide (NCT02194842)
  - Addition of bone protective agent reduced risk of fracture
- Radium-223 plus nivolumab (NCT04109729)
- Radium-223 plus Lu-177 PSMA-I&T (NCT05383079)
- Radium-223 plus niraparib (NCT03076203)

Smith M et al. Lancet Oncol. 2019;20(3):408-419.
Gillessen S et al. ASCO 2021; Abstract 5002.

Phase III VISION Trial

Eligible patients with mCRPC

- Previous treatment with <u>both</u>
  - ≥1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard for care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, ^{223}Ra, investigational drugs
- ECOG performance status 0-2
- Life expectancy >6 mo
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11
- Conventional bone scan or CT positive for metastatic disease

Randomization stratified by

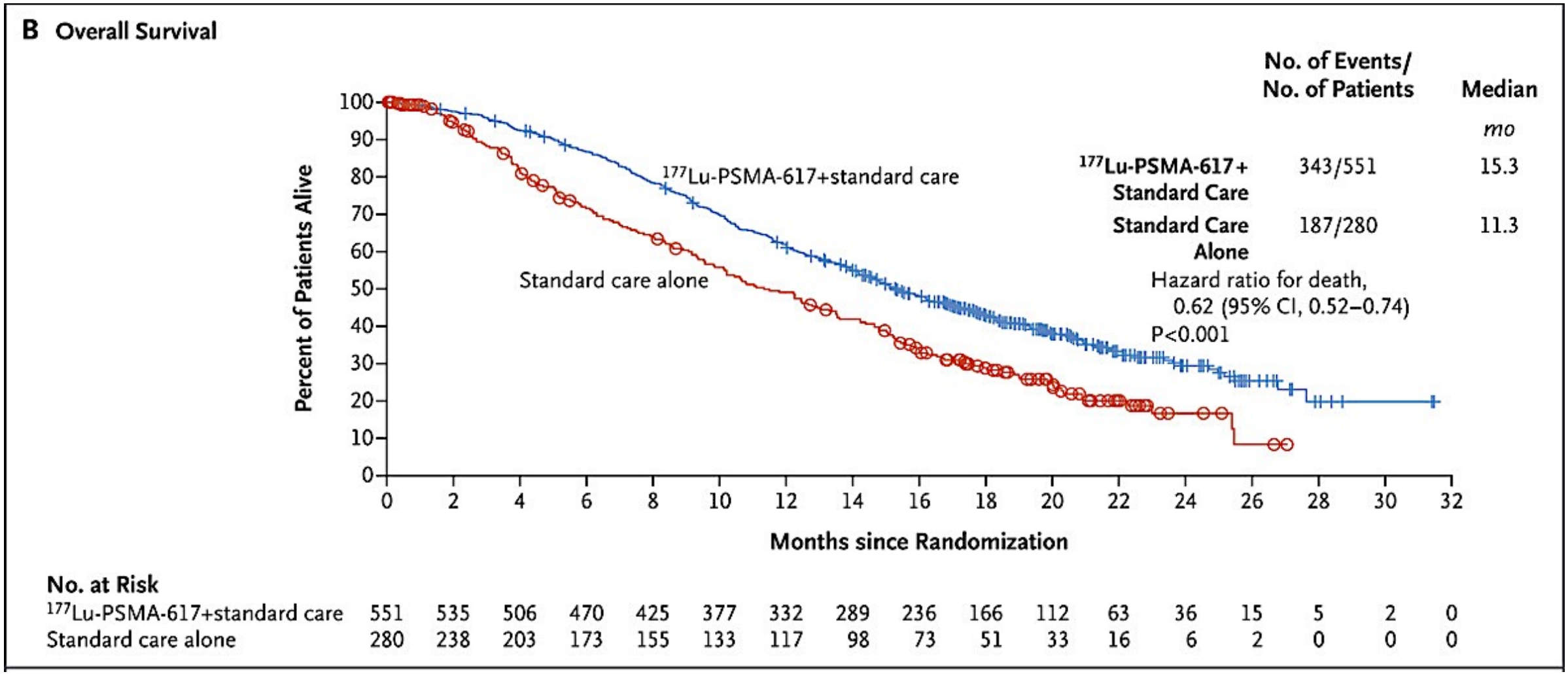
- ECOG status (0-1 or 2)
- LDH (high or low)
- Liver metastases (yes or no)
- Androgen receptor pathway inhibitors in SOC (yes or no)

CT/MRI/bone scans

- Every 8 wk (treatment)
- Every 12 wk (follow-up)
- Blinded independent central review

Sartor O et al. J Nucl Med 2022;63:823-829.
Sartor O et al. N Engl J Med 2021;385:1091-1103.

Phase III VISION Trial



Sartor O et al. N Engl J Med 2021;385:1091-1103.

Phase III VISION Trial

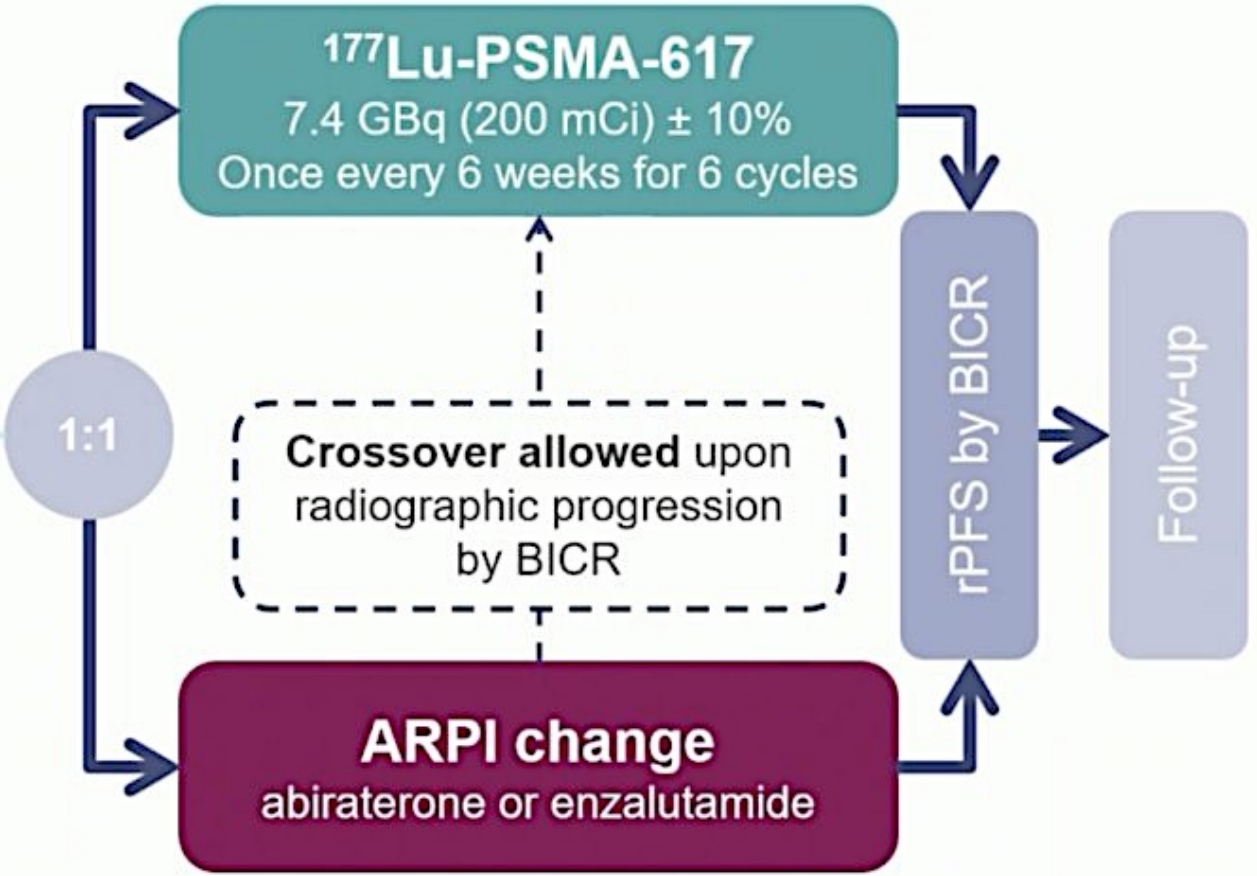
- Lutetium-177 (^{177}Lu)-PSMA-617 plus standard of care (SoC) delayed time to worsening in health-related quality of life and time to skeletal events compared to SoC alone
- Longer exposure to (^{177}Lu)-PSMA-617 plus SoC not associated with higher toxicity risk (no safety concerns with cycles 5-6)

Fizazi K et al. Lancet Oncol 2023;24:597-610.
Chi KN et al. Eur Urol 2024;85:382-391.

Phase III PSMAfore Trial

Eligible adults

- Confirmed progressive mCRPC
- ≥ 1 PSMA-positive metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT and no exclusionary PSMA-negative lesions
- Progressed once on prior second-generation ARPI
  - Candidates for change in ARPI
- Taxane-naive (except [neo]adjuvant > 12 months ago)
  - Not candidates for PARPi
- ECOG performance status 0–1



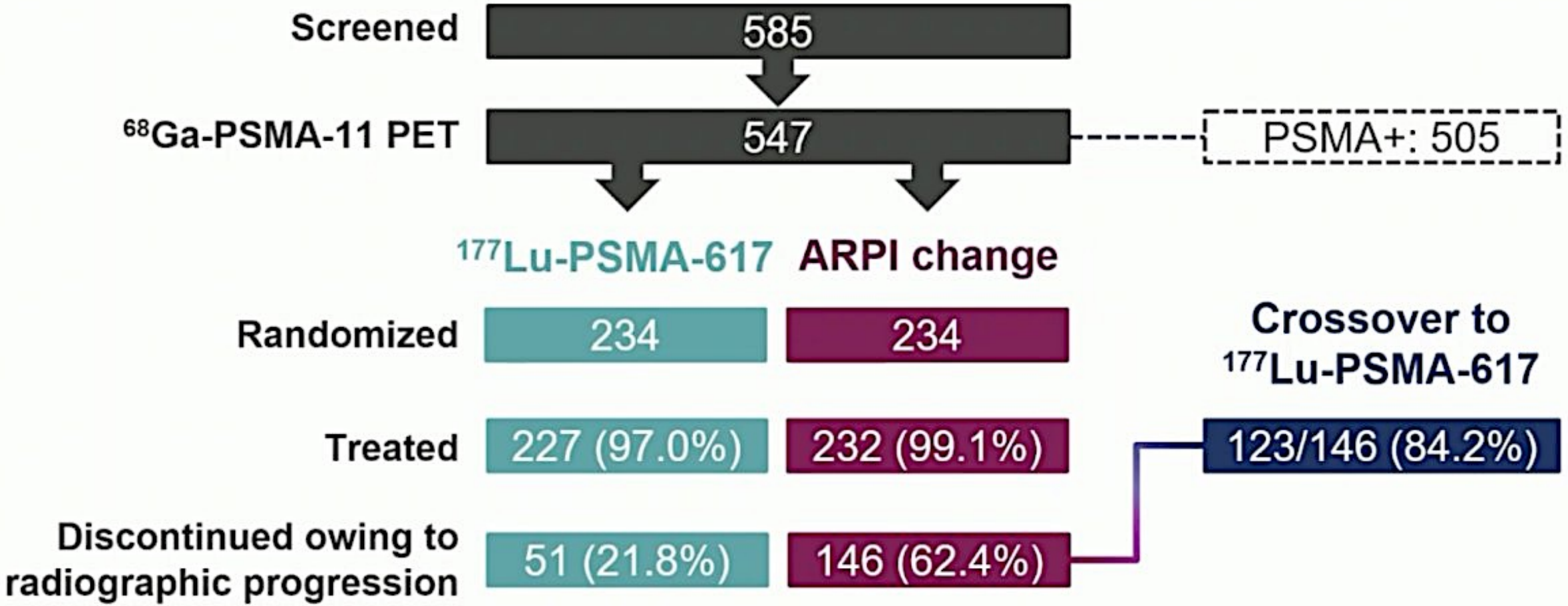
Stratification factors

- Prior ARPI setting (castration-resistant vs hormone-sensitive)
- BPI-SF worst pain intensity score (0–3 vs > 3)

MADRID 2023 ESMO congress

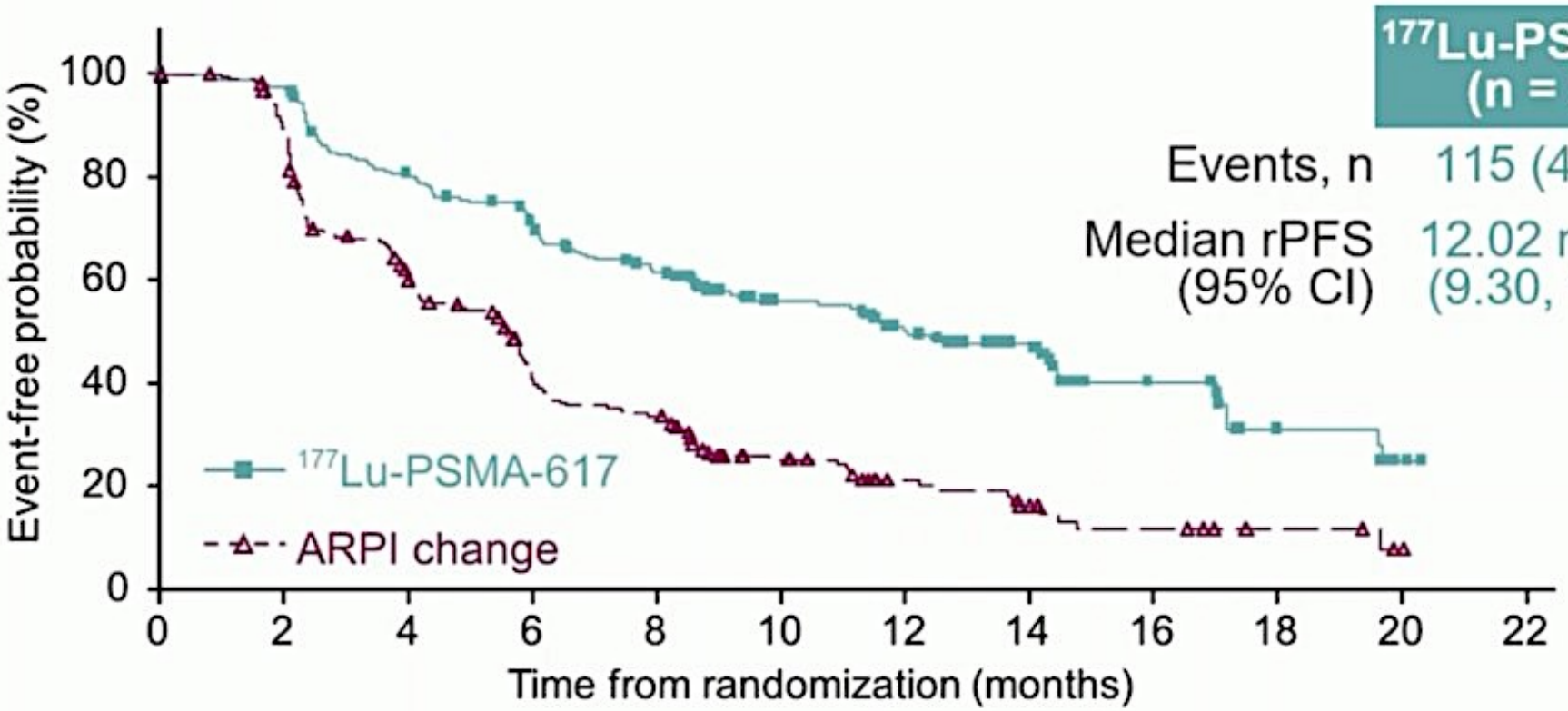
Sartor O et al. 2023 ESMO; Abstract LBA13.

Phase III PSMAfore Trial



Sartor O et al. 2023 ESMO; Abstract LBA13.

Phase III PSMAfore Trial



	177Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

Number of patients still at risk

234	216	174	150	125	82	64	45	20	10	2	0
234	197	126	79	65	36	21	12	8	4	1	0

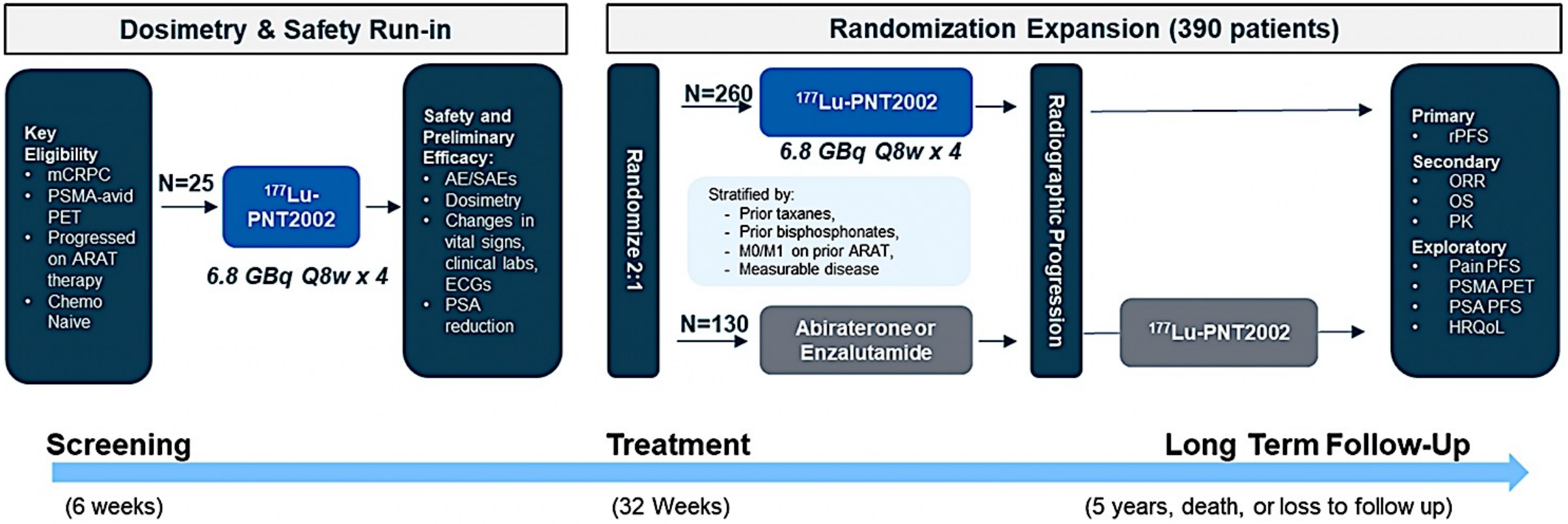
Sartor O et al. 2023 ESMO; Abstract LBA13.

Phase III PSMAfore Trial

- (^{177}Lu)-PSMA-617 prolonged rPFS versus ARPI change in taxane-naïve patients with PSMA+ mCRPC
- Secondary endpoints including PSA response, objective response rate, time to symptomatic skeletal events, time to worsening in health related quality of life and pain favored (^{177}Lu)-PSMA-617
- OS data collection ongoing, trend toward (^{177}Lu)-PSMA-617
- Safety profile manageable and well tolerated

Sartor O et al. 2023 ESMO; Abstract LBA13.

Phase III SPLASH Trial



^{177}Lu-PNT2002 (also known as [Lu-177]-PSMA-I&T)

Chi KN et al. ASCO 2021; Abstract TPS5087.

Topline results

Dec. 18, 2023-- Positive Topline Results Announced from Pivotal SPLASH Trial in Metastatic Castration-Resistant Prostate Cancer.

The SPLASH trial met its primary endpoint, demonstrating a median radiographic progression-free survival (rPFS) per blinded independent central review of 9.5 months for patients treated with ^{177}Lu-PNT2002, compared to 6.0 months for patients treated with ARPI in the control arm, a statistically significant 29% reduction in the risk of radiographic progression or death (hazard ratio [HR] 0.71; p=0.0088). At the time of the analysis, interim overall survival (OS) results were immature (46% of protocol-specified target OS events reached), the HR was 1.11.

https://www.globenewswire.com/news-release/2023/12/18/2797730/0/en/Lantheus-and-POINT-Biopharma-Announce-Positive-Topline-Results-from-Pivotal-SPLASH-Trial-in-Metastatic-Castration-Resistant-Prostate-Cancer.html

Topline results

^{177}Lu-PNT2002 demonstrated a favorable safety profile.

	^{177}Lu-PNT2002 Arm	ARPI Arm
TEAEs of CTCAE Grade ≥3	30.1%	36.9%
Serious TEAEs	17.1%	23.1%
TEAEs Leading to Discontinuation	1.9%	6.2%

https://www.globenewswire.com/news-release/2023/12/18/2797730/0/en/Lantheus-and-POINT-Biopharma-Announce-Positive-Topline-Results-from-Pivotal-SPLASH-Trial-in-Metastatic-Castration-Resistant-Prostate-Cancer.html

CONTACT-02: Scientific Rationale

- Prostate cancer associated with immune-suppressive tumor microenvironment (TME)
  - Tregs and immunosuppressive M2 macrophages recruited to TME, limited CD8+ T cells, and correlated with worse prognosis
  - Promotion of immune-permissive TME is potential therapeutic strategy
- Immune checkpoint inhibitors (ICI) alone have limited activity in prostate cancer
- ICI in combination with receptor tyrosine kinase (RTK) inhibitors against Tyro3, Axl, and Mer (TAM) kinases has increased efficacy in preclinical studies
- Cabozantinib, RTK inhibitor against TAM promotes an immune-permissive environment that consists of decreased Tregs and increased cytokines
- ICI in combination with RTK inhibitor effective in other cancers such as renal cell carcinoma

Lundholm M et al. Sci Rep 2015;5:15651. Kiniwa Y et al. Clin Cancer Res 2007;13(23):6947-6958. Hansen AR et al. Ann Oncol 2018;29(8):1807-1813. Davidsen K et al. Cancer Res 2018;78(suppl.13), Abstract 3774. Axelrod HD et al. Mol Cancer Res 2019;17(2):356-369. Choueri TK et al. N Engl J Med 2015;373(19):1814-1823.

CONTACT-02: Clinical Background Data

- COMET-1
  - Phase III randomized, double-blind study of cabozantinib versus prednisone
  - No OS improvement in overall population (11 vs 9.8 months, HR=0.9, p=0.213)
  - Higher OS rate with cabozantinib with visceral metastasis
- COSMIC-021
  - Phase Ib open-label study of cabozantinib and atezolizumab in multiple solid tumors including renal and prostate cancer
  - Cohort 6 in mCRPC with prior NHT
    - 44 patients in cohort, ORR 32%, 3 patients (CR), 11 patients (PR), 67% with PSA decrease ≥ 50%
    - 36 patients with visceral and/or extra-pelvic lymph node metastasis, ORR 33%

Smith MR et al. J Clin Oncol 2016;34(25):3005-2013. Pal SK et al. J Clin Oncol 2021;39(33):3725-3736. Agarwal N et al. J Clin Oncol 2020; 8(suppl.15), Abstract 5564.

CONTACT-02: Study Design

Patient population

- mCRPC + extrapelvic soft tissue metastasis
- Progression on prior NHT
- Ongoing ADT
- No prior systemic nonhormonal therapies, except for taxane-based chemotherapy for mCSPC
- ECOG 0–1

1:1 randomization

- Cabozantinib 40 mg QD PO + atezolizumab 1200 mg Q3W IV
- Abiraterone 1000 mg QD PO + prednisone 5 mg BID PO -OR- Enzalutamide 160 mg QD PO

Treatment until loss of clinical benefit or intolerable toxicity*

Stratification factors

- Liver involvement (Y vs N)
- Prior docetaxel for advanced CSPC (Y vs N)
- Disease state when first NHT was given (mCRPC vs nmCRPC vs mCSPC)

Endpoints and assessments

- **Primary endpoints:**
  – rPFS and OS
- **Secondary endpoint:**
  – ORR
- **Additional endpoints:**
  – Safety, PK, Biomarkers
- **Assessments:**
  - Tumor, bone scans, PROs – every 9 weeks (RECIST 1.1) by BIRC†
  - Safety, PK, biomarker – every 3 weeks‡
  - Survival – every 8 weeks§

Agarwal N et al. Future Oncol 2022;18(10);1185-1198.

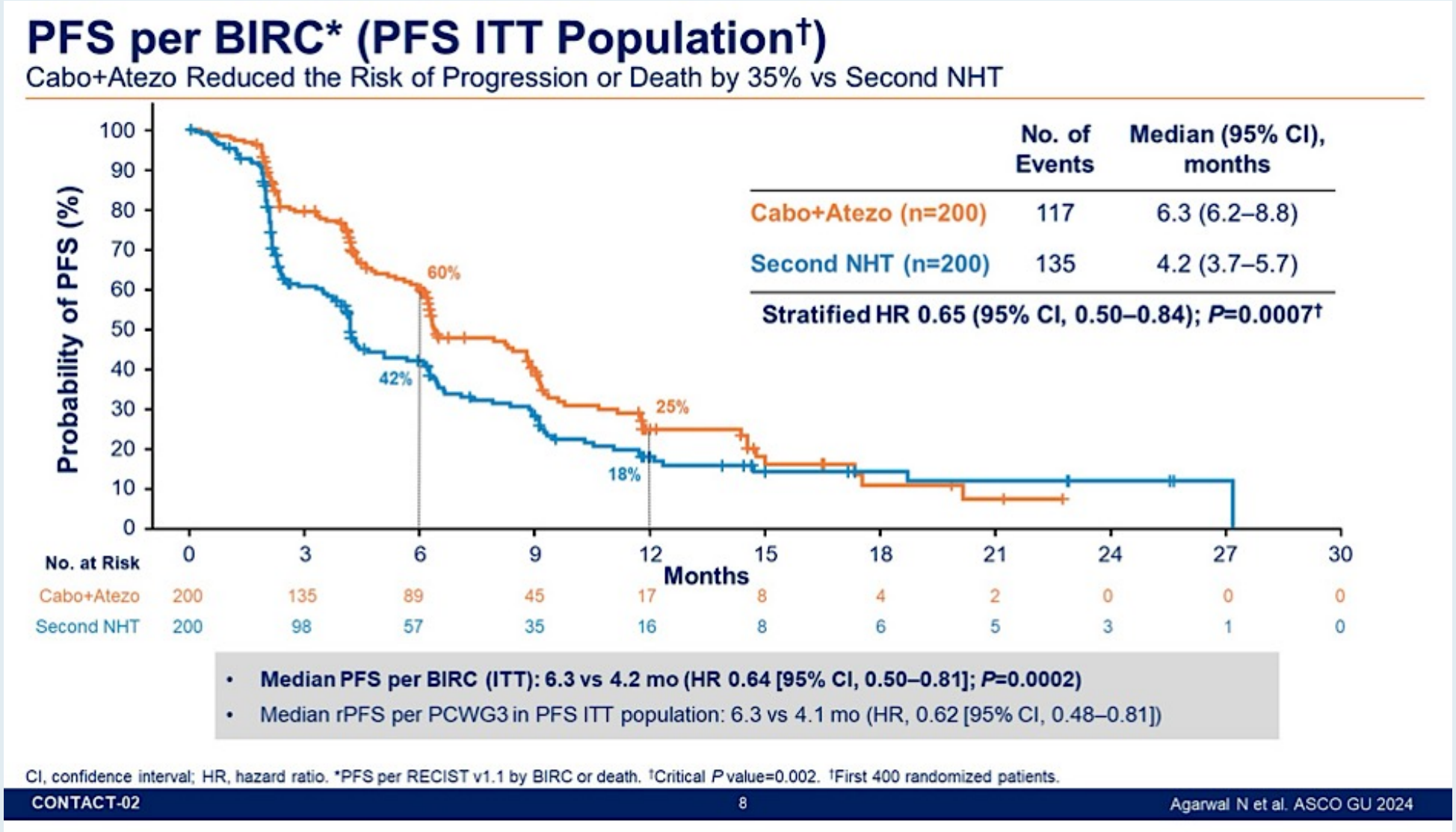
Topline results

Aug. 21, 2023-- The global phase 3 CONTACT-02 pivotal trial met one of two primary endpoints, demonstrating a statistically significant improvement in progression-free survival (PFS) at the primary analysis.

At a prespecified interim analysis for the primary endpoint of overall survival (OS) that occurred at the same time as the primary analysis of PFS, a trend toward improvement of OS was observed; however, the data were immature and did not meet the threshold for statistical significance. Therefore, the trial will continue to the next analysis of OS as planned.

https://ir.exelixis.com/news-releases/news-release-details/exelixis-and-ipsen-announce-positive-results-phase-3-contact-02

CONTACT-02 Primary Analysis: PFS with Cabozantinib and Atezolizumab for mCRPC

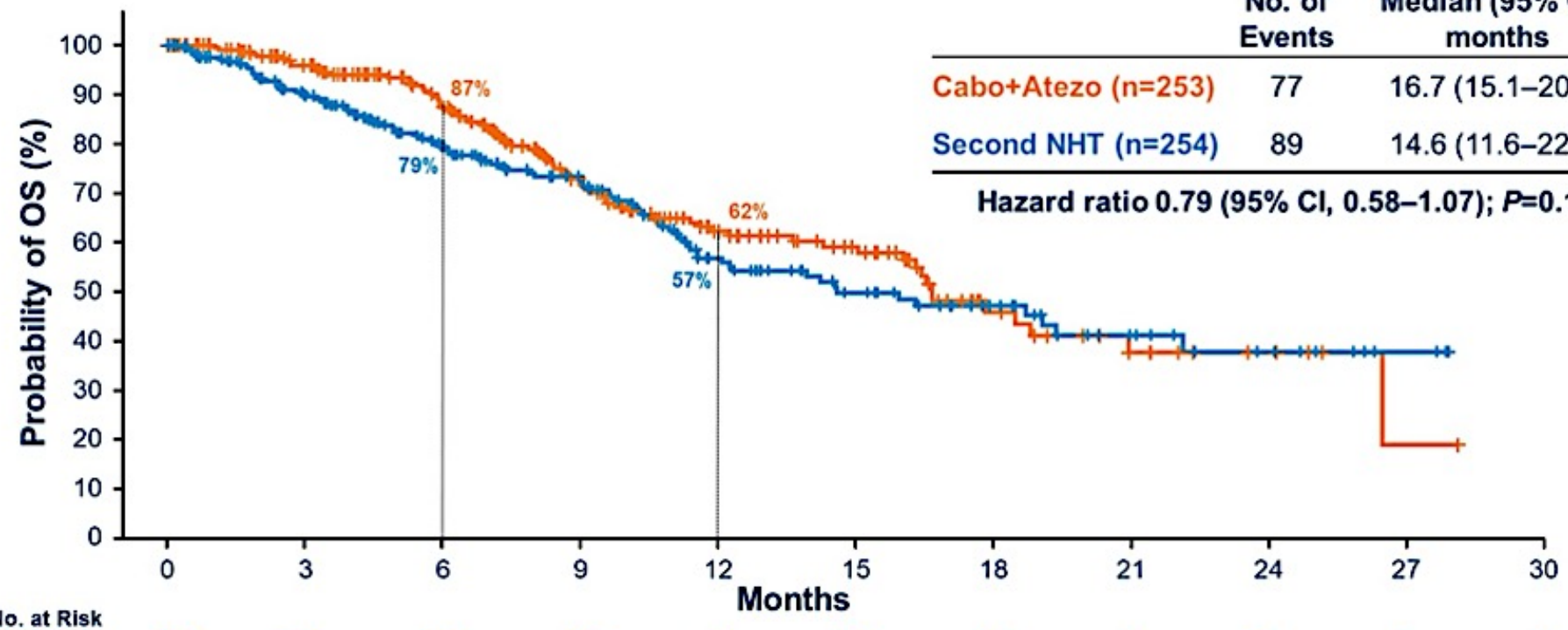


Agarwal N et al. Genitourinary Cancers Symposium 2024;Abstract 18.

CONTACT-02: Interim OS Analysis with Cabozantinib and Atezolizumab for mCRPC

Interim OS (ITT Population)

49% of Target Number of Events



	No. of Events	Median (95% CI), months
Cabo+Atezo (n=253)	77	16.7 (15.1–20.9)
Second NHT (n=254)	89	14.6 (11.6–22.1)

Hazard ratio 0.79 (95% CI, 0.58–1.07); *P*=0.13

No. at Risk											
Cabo+Atezo	253	204	155	104	68	48	20	10	5	1	0
Second NHT	254	198	141	107	66	43	28	15	9	3	0

Critical *P* value for OS is 0.002675 at this interim analysis using a prespecified Lan-DeMets O'Brien-Fleming (LD-OF) alpha-spending function.

CONTACT-02 11 Agarwal N et al. ASCO GU 2024

Agarwal N et al. Genitourinary Cancers Symposium 2024;Abstract 18.

Novel Targets in Clinical Trials

- Chimeric antigen receptor (CAR) T cells, based on genetic engineering of the patient's own T cells for targeted tumor cell lysis
- Bromodomain (BET) inhibitors
- Androgen receptor (AR) degraders (PROTACs)
- Bicyclic peptides or drug conjugates (synthetic short peptides that are chemically bonded to form a two-loop structure, resembling a bicycle)
- **904 interventional and accruing clinical trials for patients with prostate cancer**

Clinicaltrials.gov accessed 04/20/2024

Second Opinion: Urologic Oncology Investigators Discuss How They Apply Clinical Research in the Care of Patients with Prostate Cancer

A CME Satellite Symposium Held in Conjunction with the American Urological Association Annual Meeting 2024 (AUA2024)

Friday, May 3, 2024

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Rahul Aggarwal, MD
Adam S Kibel, MD
Laurence Klotz, CM, MD
Sandy Srinivas, MD

Moderator

Elisabeth I Heath, MD

RTP
RESEARCH TO PRACTICE

Second Opinion: Urologic Oncology Investigators Discuss How They Apply Clinical Research in the Care of Patients with Urothelial Bladder Cancer

A CME-Accredited Virtual Event

Monday, May 6, 2024
5:00 PM – 6:00 PM ET

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS

Moderator

Neil Love, MD

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Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.

Online/Zoom attendees: The CME credit link is posted in the chat room.

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