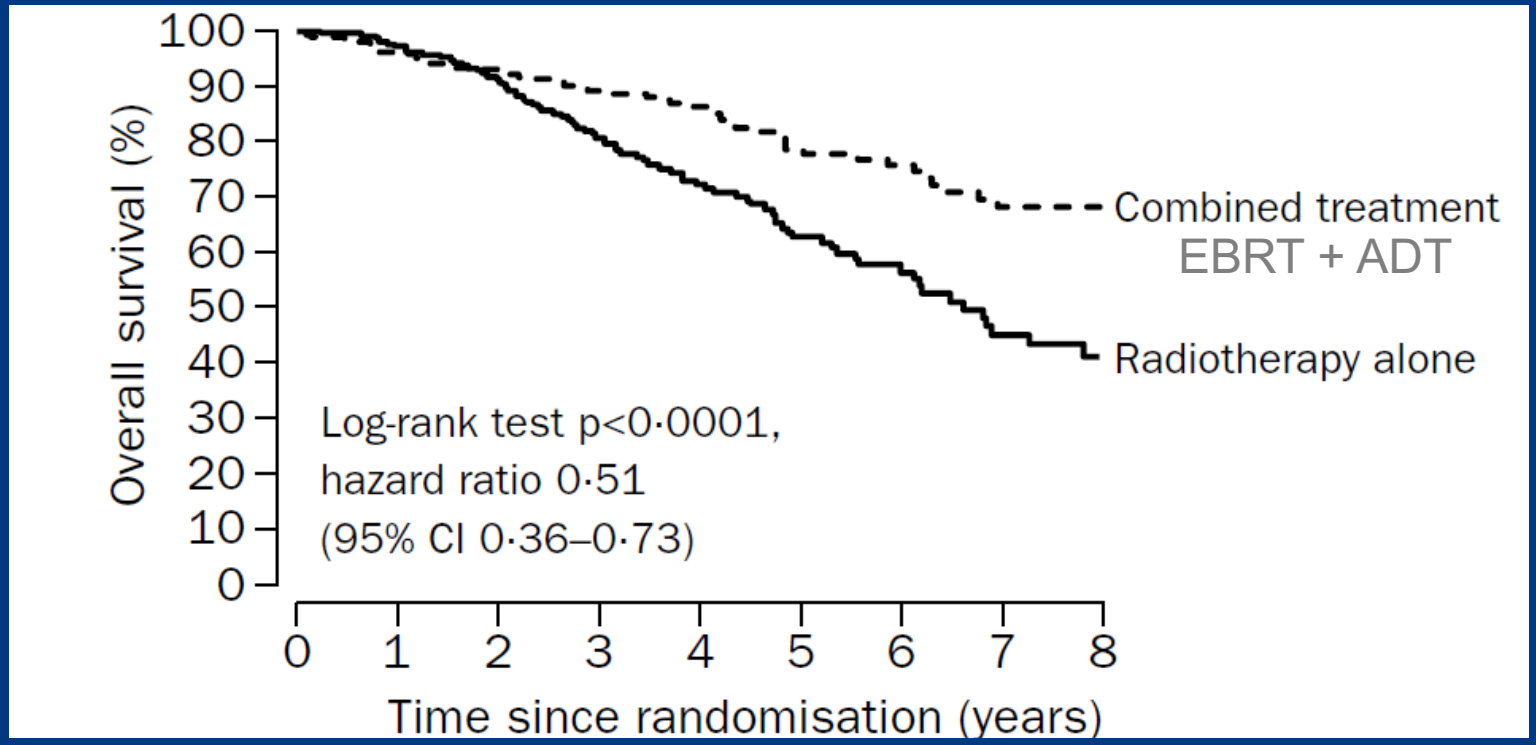
Treatment Intensification for Locally Advanced and BCR Prostate Cancer Patients

Neal Shore, MD, FACS

ADT Is a Key Component of Treatment for High-Risk Prostate Cancer

Androgen deprivation therapy improves survival for men with high-risk prostate cancer when added to EBRT

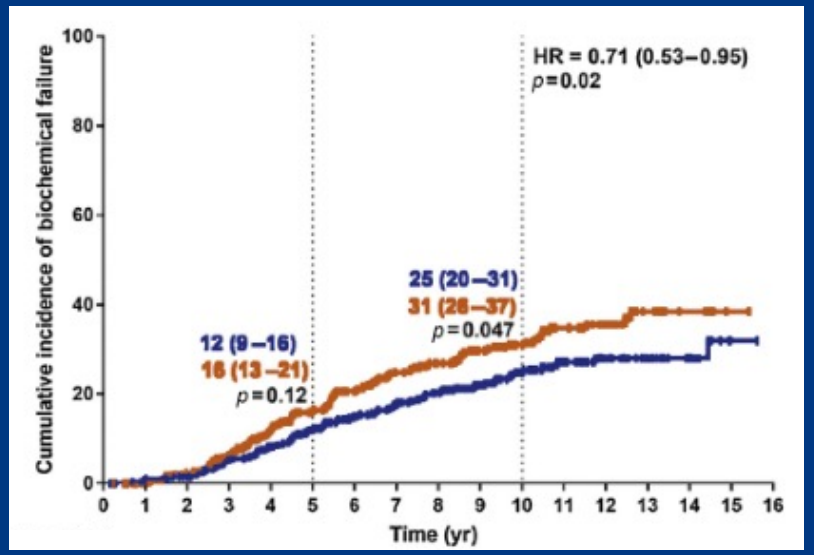


ADT Potentiates Radiation Damage by Blocking DNA Damage Repair

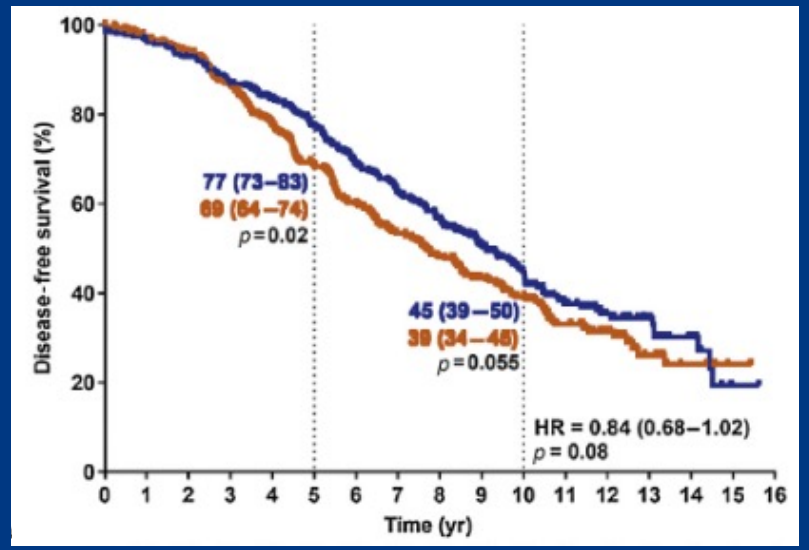
Bolla Lancet 2002. Goodwin JF Polkinghorn WR Cancer Discovery 2013.

18 months ADT Provides Better Quality of Life than 36 months of ADT

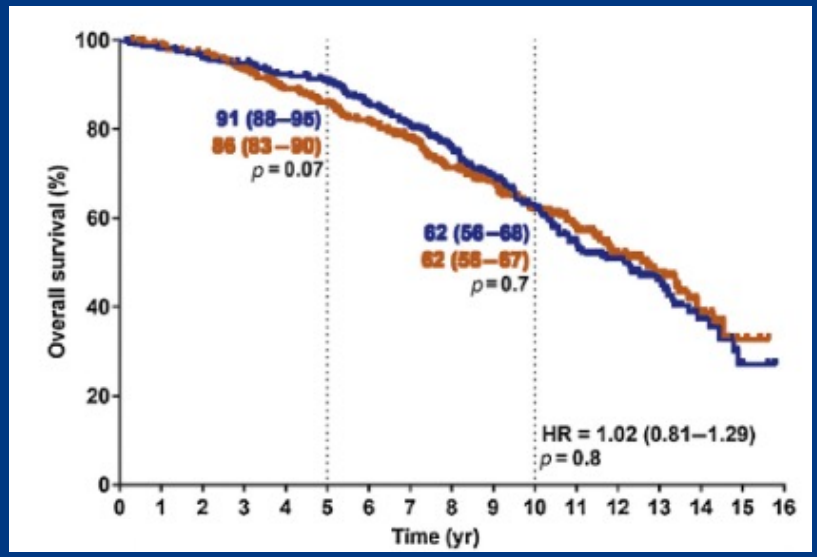
PCS IV, 2000-2008



More Frequent Biochemical Failure



No Difference Disease-specific survival

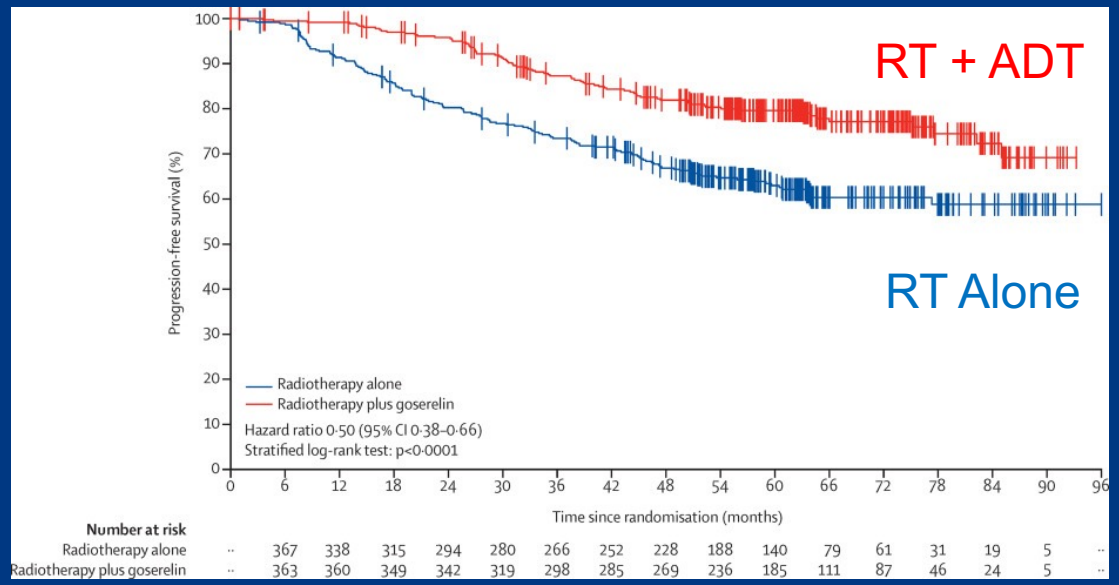


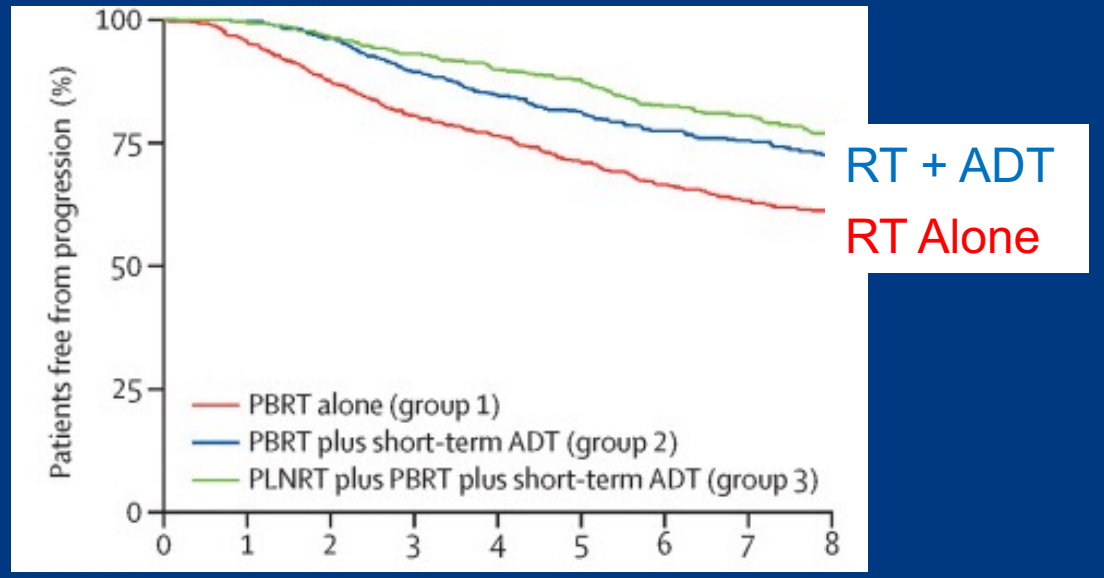
No Difference in OS BUT not a non-inferiority trial

Nabid A European Urology 2018; 74:432.

We Don’t Know The Optimal Choice

ADT is not required for all patients & may not be enough for some patients





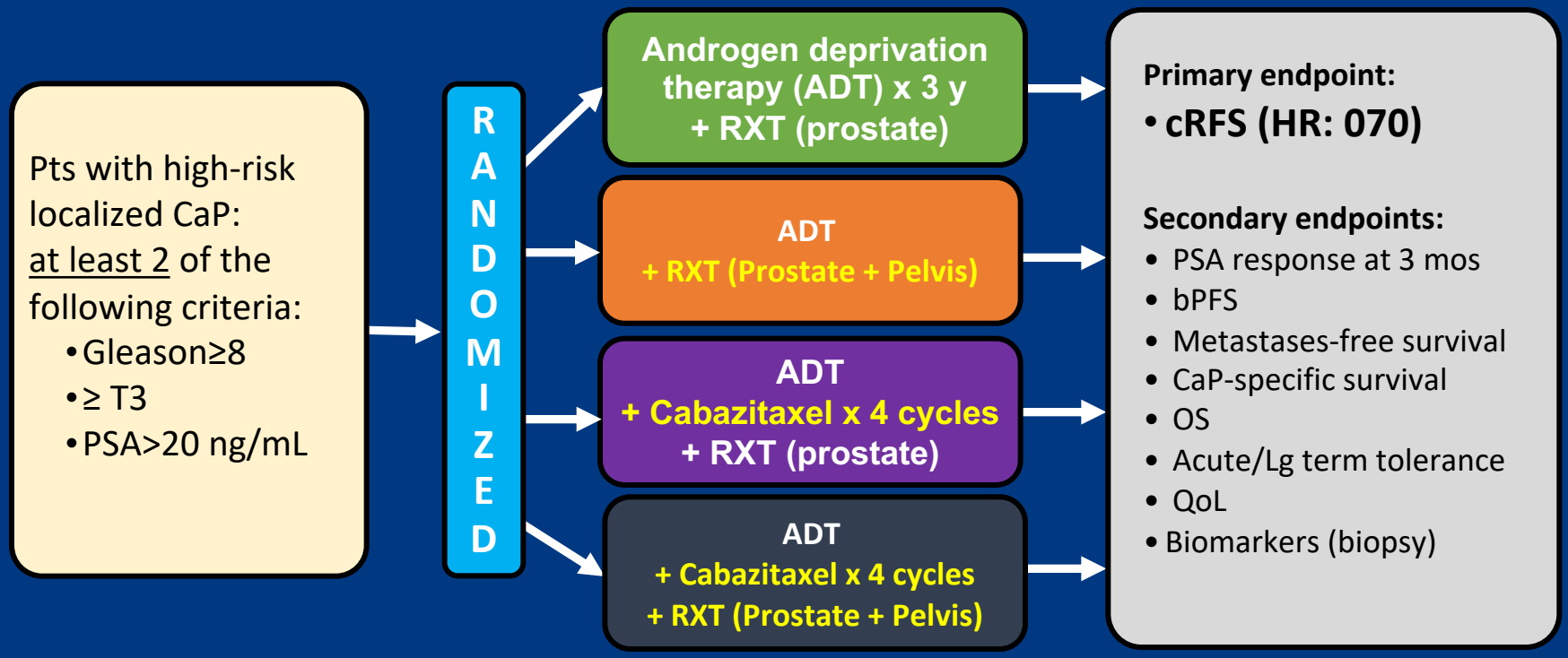
GETUG 16

- 6 mo ADT improved freedom from progression
- **50% no recurrence** @10yrs w/ RT alone
- **29% recurred** @ 10 yrs w/ RT + ADT

SPPORT

- 4-6 mo ADT improved freedom from progression
- 70% no recurrence @5yrs w/ RT alone
- **20% recurred** @ 5 yrs w/ prostate bed RT + ADT

PEACE-2: Phase III Trial of Cabazitaxel and Pelvic Irradiation in Patients With High-risk Localized Prostate Cancer



n= 750 pts (completed)

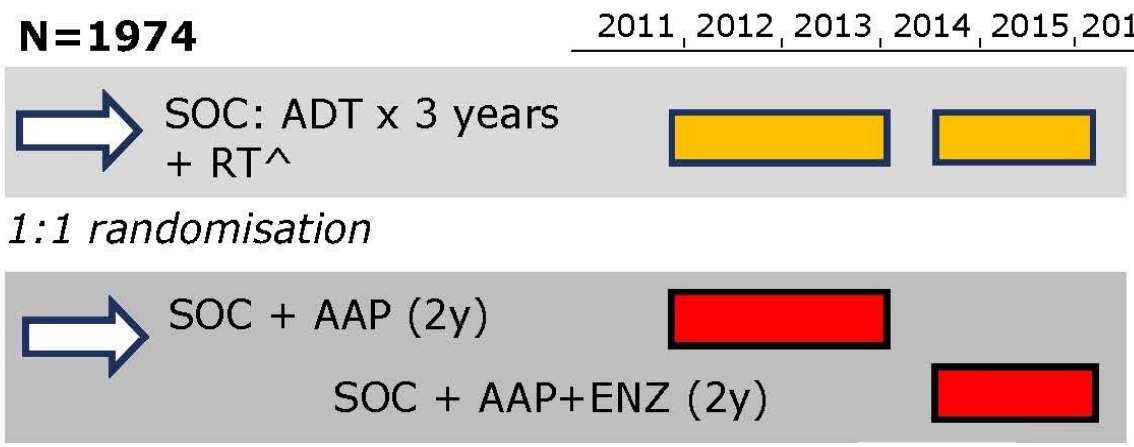
Study sponsor: Unicancer

NCT01952223

STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC

Study design

- M0 pts in AAP comparison: continued FU with **no further** efficacy inspections
- 2019 - amended the reporting plan* to split M1 & M0, power the 1^{ary} end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



- No overlapping controls
- Same protocol & eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC [1]

Attard, et al. Lancet, 2022

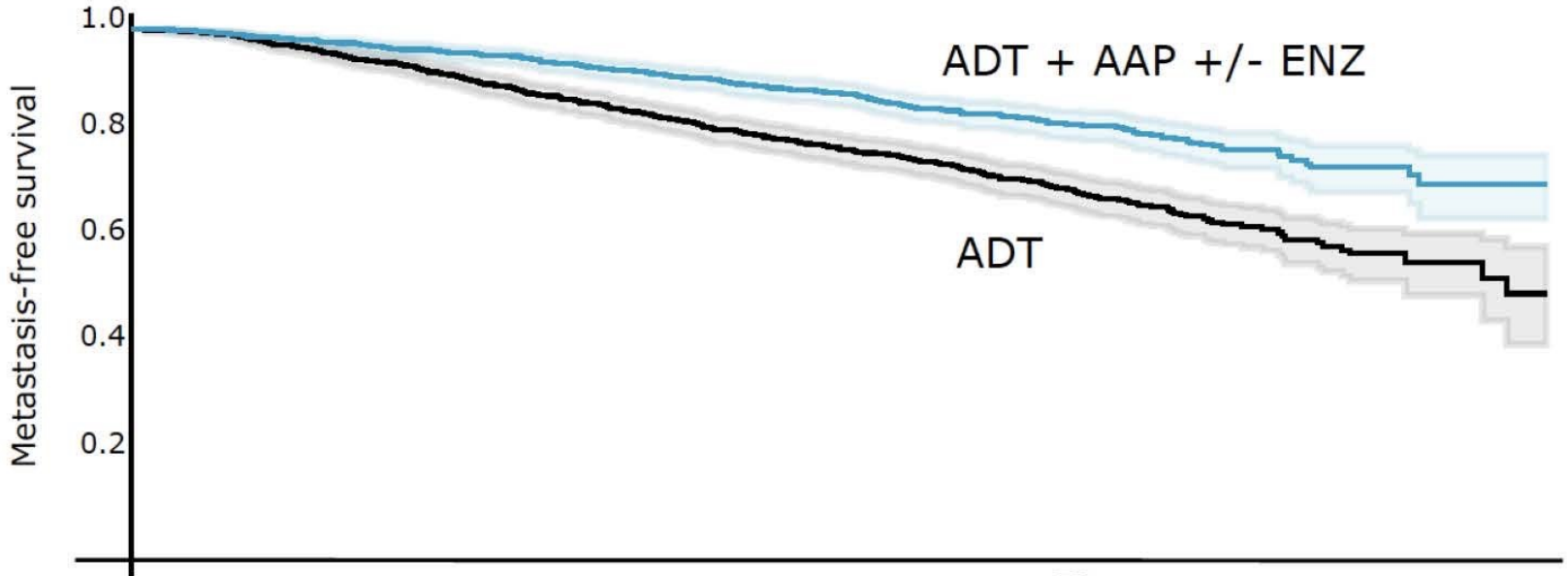
STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC

- Baseline characteristics well balanced
- Median age = 68
- Median PSA = 34
- 39% N1
- 79% Gleason 8-10
- 97% patients newly diagnosed
  - **85% receiving radiation**
  - **15% receiving primary ADT**
- Median follow-up = 72 months
- No benefit to abi + enza vs. abi alone
  - **arms combined**

Attard, et al. Lancet, 2022

STAMPEDE: Abiraterone ± Enzalutamide in nmCSPC

Metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Events
180 ADT+ AAP +/- ENZ
306 ADT

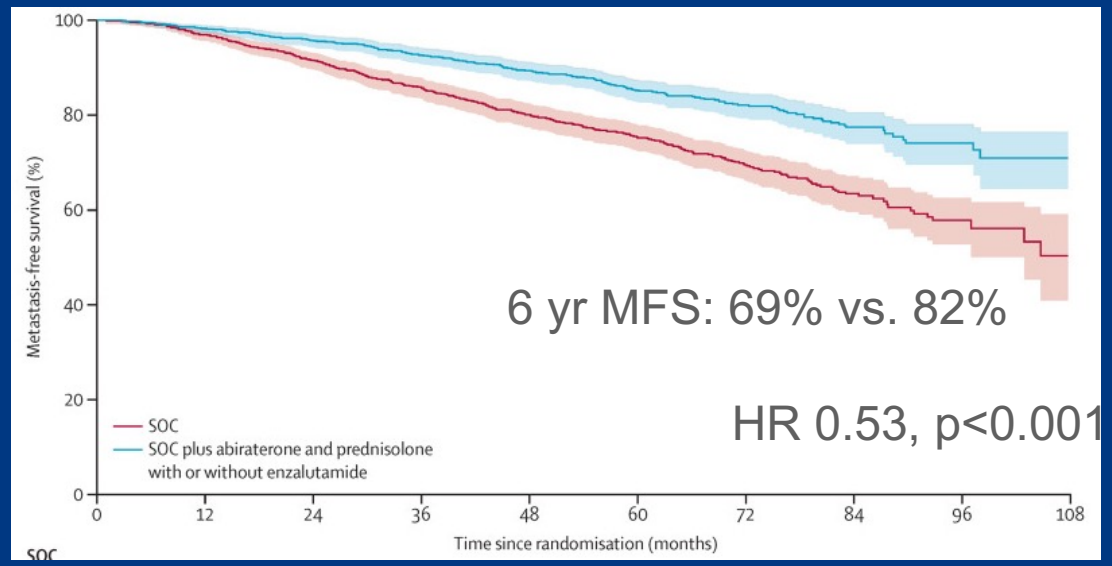
HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

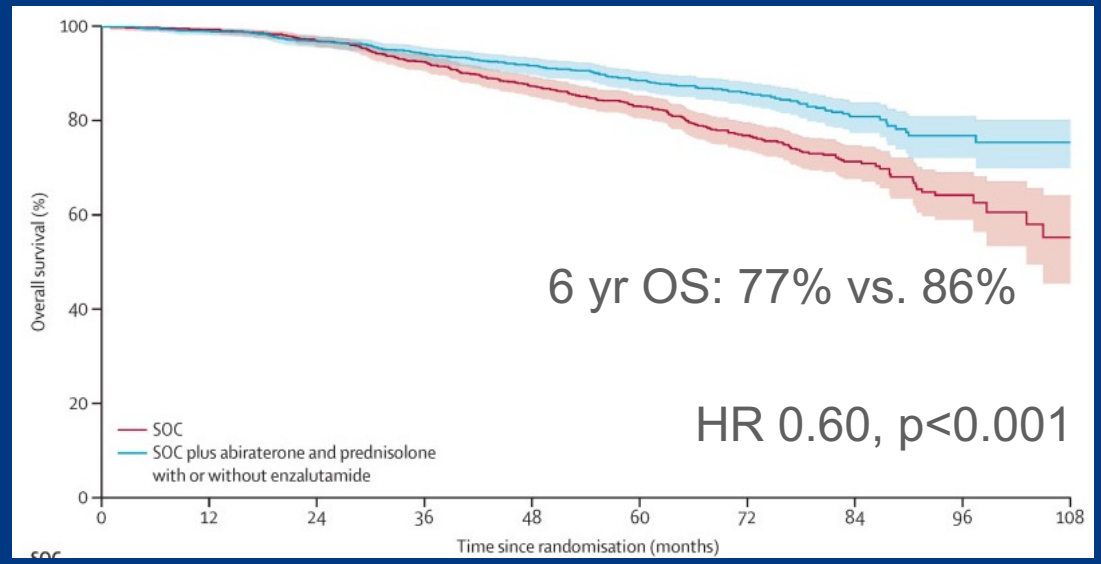
6-year MFS improved from 69% to 82%

Attard, et al. Lancet, 2022

Improvement in PFS, MFS, and OS with the Addition of Abiraterone and Prednisone to ADT – Very High Risk

- STAMPEDE 1,974 PTS. Median 6-year follow up.
  - Node positive or 2 of the following: T3/4, Gleason 8-10, PSA >40, high-risk relapse





Metastasis-free survival	Overall survival

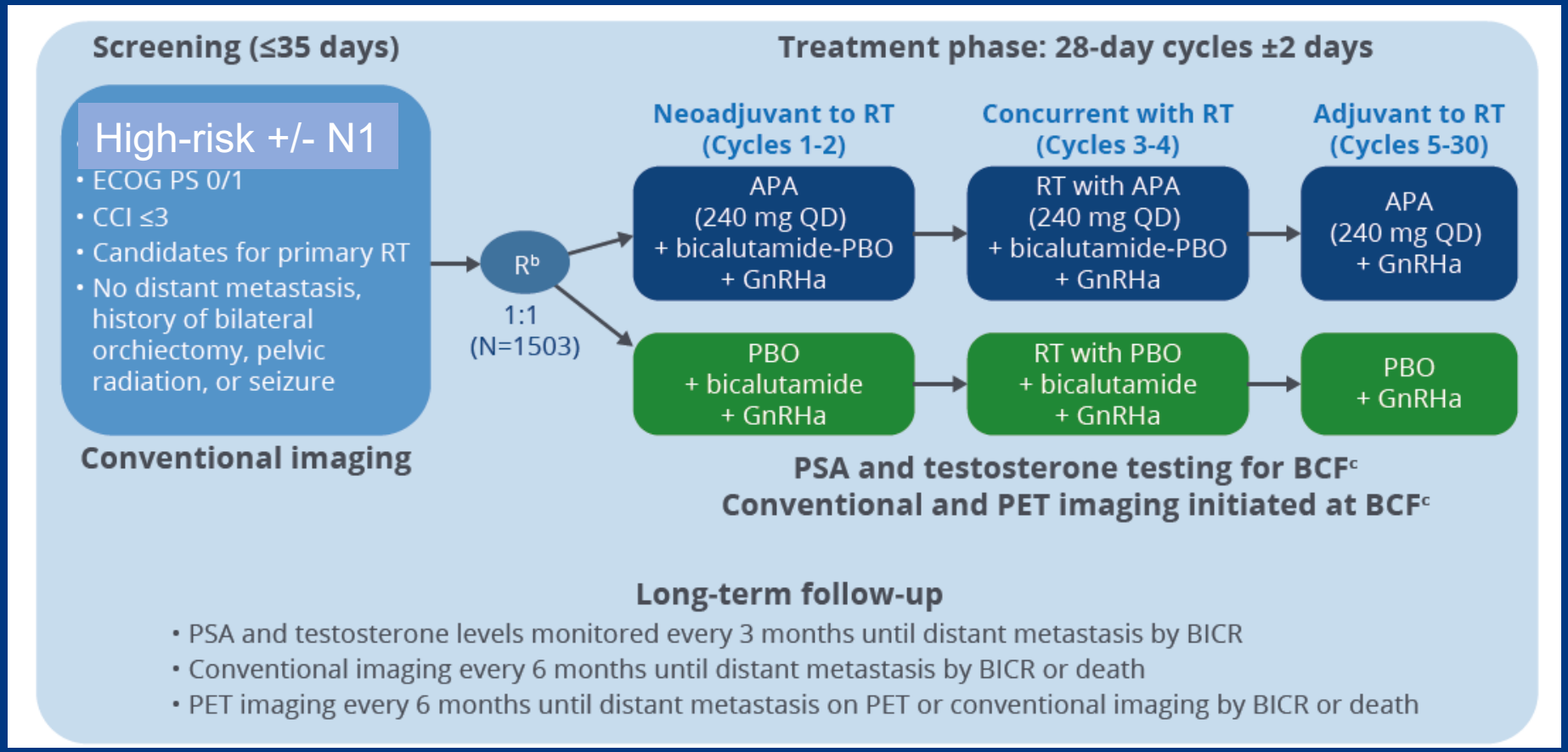
Median age 68. 73% T3/4. 79% GI8-10. Median PSA 34. 39% Node-positive

No additional benefit to enzalutamide in addition to abiraterone.

Attard G Lancet 2021; 399:447.

ATLAS trial design

N1=13%



MFS

ENZARAD (ANZUP 1303) STUDY SCHEMA

Study Chairs:
Scott Williams & Paul Nguyen

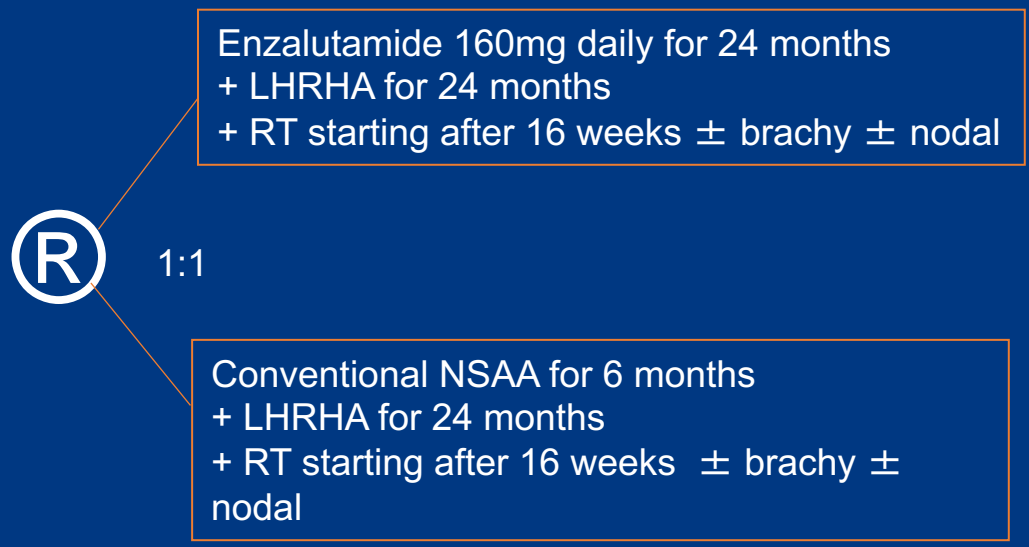
n= 802 participants

Eligibility

Localized prostate cancer
High risk of recurrence
Suitable for EBRT

Stratification

Gleason score 8-10
T3-4 disease
N1 disease
PSA ≥20 ng/mL
Brachytherapy boost
Pelvic nodal RT
Study Site

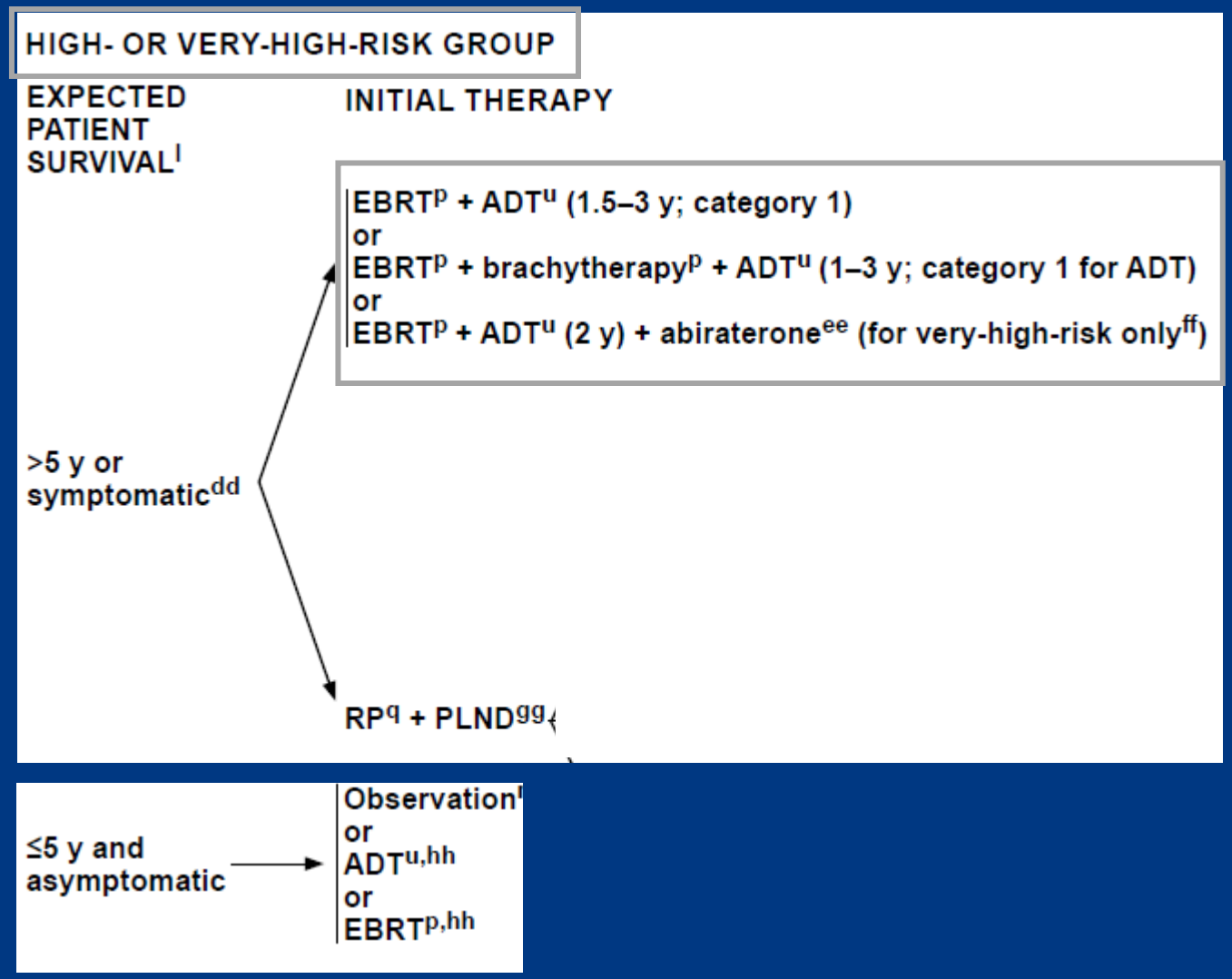


Endpoints

Metastasis-free survival (primary)
Overall survival
Cause specific survival
PSA progression free survival
Clinical progression free survival
Castration-resistance
Health related quality of life
Adverse events
Incremental cost-effectiveness

*Conventional Non-Steroidal Anti-Androgens: bicalutamide 50mg daily, nilutamide 150mg daily, or flutamide 250mg tid

Treatment Options For High-Risk Prostate Cancer



High-Risk

No very high-risk features and exactly one high-risk feature:

- cT3a OR
- Grade Group 4 or 5 OR
- PSA > 20 ng/ml

Very High-Risk

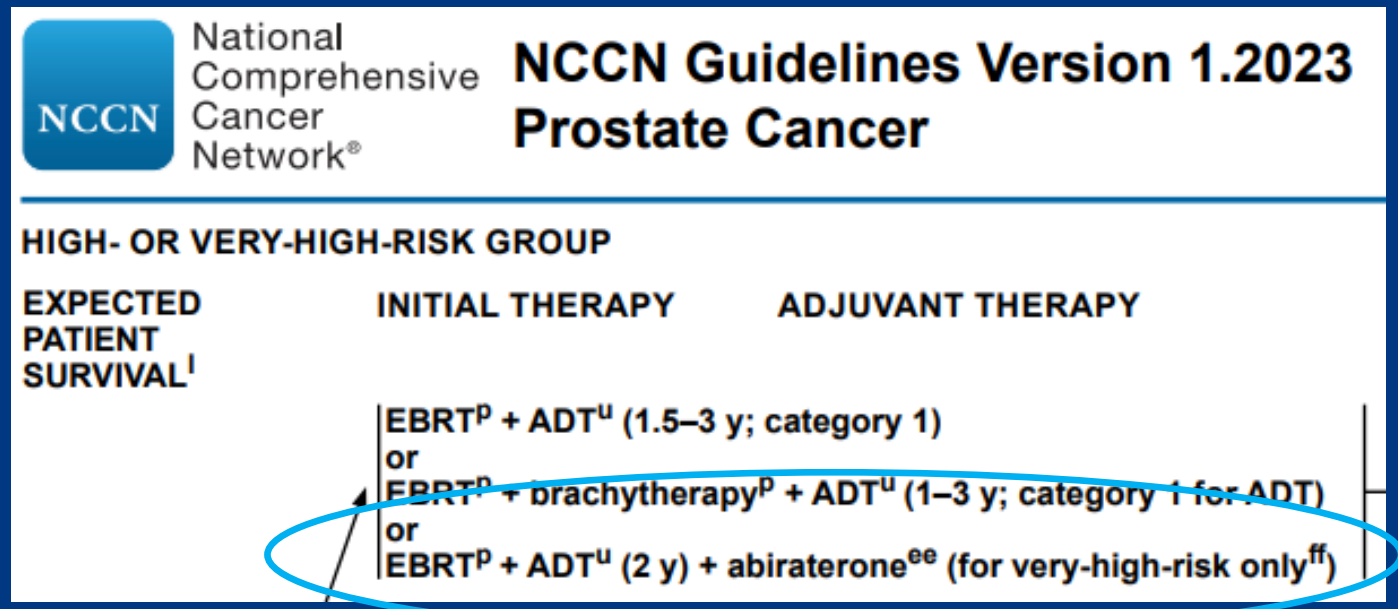
Has at least one of the following:

- cT3b to T4 OR
- Primary pattern 5 OR
- 2 to 3 high-risk feature
- >4 cores with Grade Group 4 or 5

NCCN National Comprehensive Cancer Network®
NCCN Guidelines Version 1.2023
Prostate Cancer

ADT with External Beam Radiation For Very High-Risk Prostate Cancer

- 24 months of ADT with abiraterone



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

HIGH- OR VERY-HIGH-RISK GROUP

EXPECTED PATIENT SURVIVAL[l]	INITIAL THERAPY	ADJUVANT THERAPY
	EBRT[p] + ADT[u] (1.5–3 y; category 1)	
	or	
	EBRT[p] + brachytherapy[p] + ADT[u] (1–3 y; category 1 for ADT)	
	or	
	EBRT[p] + ADT[u] (2 y) + abiraterone[ee] (for very-high-risk only[ff])	

Very High-Risk
Has at least one of the following:

- cT3b to T4 OR
- Primary pattern 5 OR
- 2 to 3 high-risk feature
- >4 cores with Grade Group 4 or 5

Clinical case(Scenario 1)

- 65 years old with rising PSA 3.2 to 6.1 over 2 years. Testosterone 320 ng/dL. Normal DRE.
- MRI prostate: 26 mL prostate. Extracapsular extension and seminal vesicle invasion. PIRADS 5
- Biopsy demonstrated Gleason 4+3=7 in 6 of 12 cores

Case(Scenario 2)

- MRI shows 1.4 cm left pelvic sidewall lymph node.
- CT abd/pelvis with left sided hydronephrosis from bladder thickening at left ureteral junction. Left pelvic lymphadenopathy. Bone scan negative. PSMA PET confirms cT4N1 disease.
- DRE cT4
- No significant comorbidities.

Which therapy would you recommend with EBRT?

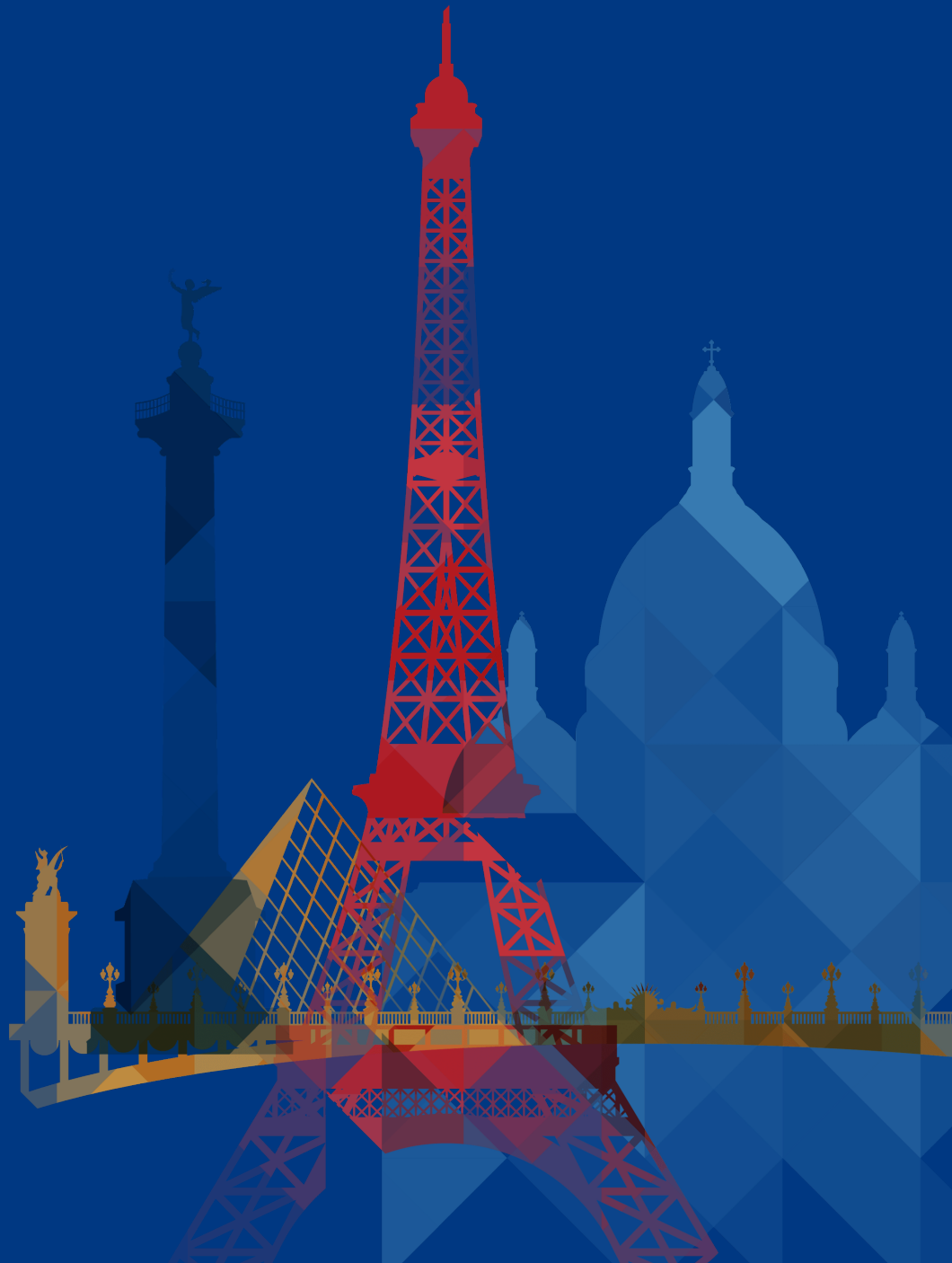
1. ADT alone
2. ADT with bicalutamide
3. ADT with abiraterone/prednisone

PARIS 2022 ESMO congress

PRESTO: A Phase 3 Open-Label Study of Androgen Annihilation in Patients with High-Risk Biochemically Relapsed Prostate Cancer (AFT-19)

Rahul Aggarwal, on behalf of the Alliance AFT-19 Study Investigators

Paris, France
11 SEP 2022

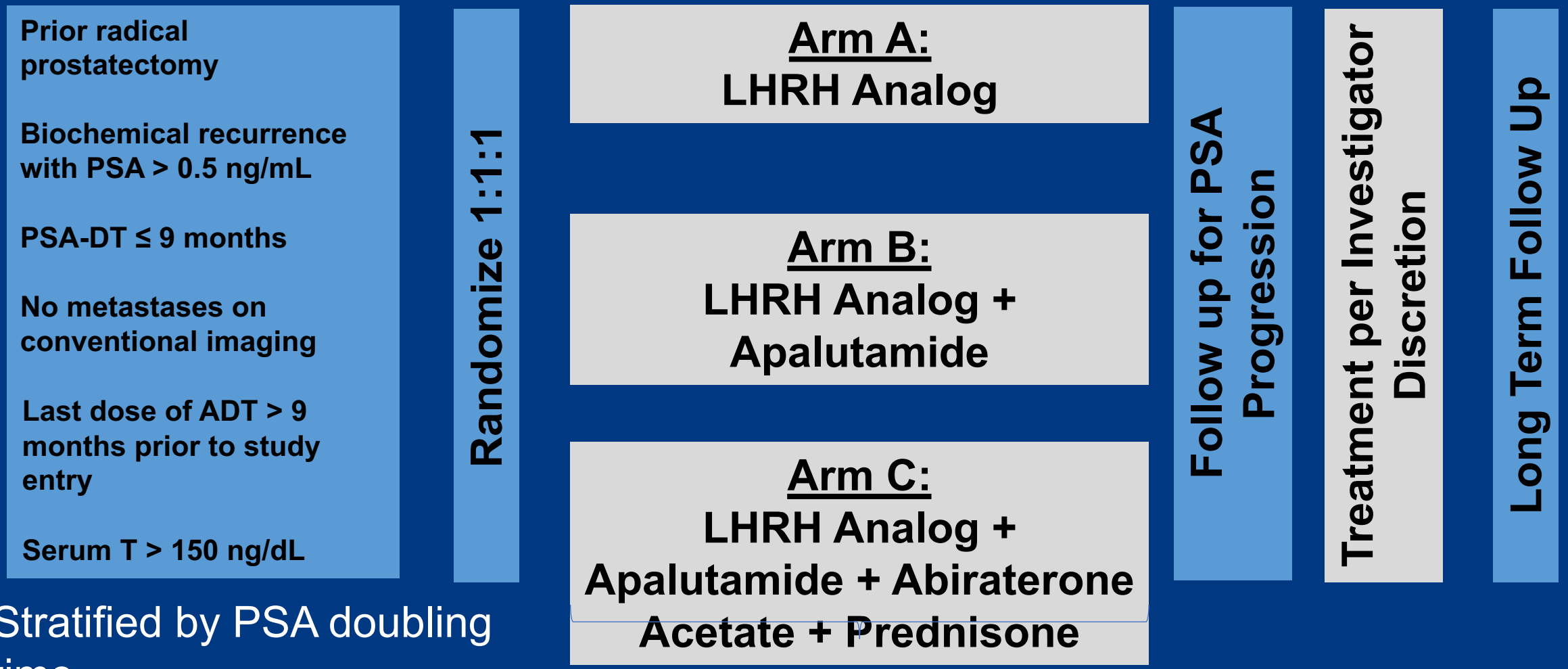


Biochemically recurrent prostate cancer

- Men with biochemically recurrent prostate cancer following radical prostatectomy and a short PSA doubling time are at high risk for the development of distant metastases and prostate cancer related mortality[1]
- Intermittent androgen deprivation therapy (ADT) is a standard treatment approach for biochemically recurrent prostate cancer[2]
- A prior phase 3 study demonstrated non-inferiority of intermittent versus continuous ADT with respect to overall survival, with improvement in several key QOL parameters[3]

1. Pound CR, et al. JAMA 1999; 2. NCCN Guidelines version 4.2022; 3. Crook JM, et al. NEJM 2012

Study Schema



Stratified by PSA doubling time
(< 3 months vs. 3 – 9 months)

52 Weeks

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Study Objectives

To compare each experimental arm versus control with respect to:

- Primary Objective: PSA progression-free survival, with PSA progression defined as **nadir + 2 ng/mL during treatment** or **> 0.2 ng/mL following treatment confirmed by repeat measurement (> 2 wks)**

- Secondary Objectives:
  - PSA progression-free survival in testosterone-evaluable population (T > 50 ng/dL)
  - Time to recovery of serum testosterone (T > 50 ng/dL)
  - Safety profile
  - 36-month PSA progression-free survival rate
  - Metastasis-free survival
  - Time to castration resistance
  - Short- and long-term patient reported quality of life

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Baseline Characteristics

	Arm A (N = 166)	Arm B (N = 168)	Arm C (N = 169)	Overall Study Cohort (N =503)
Median Age (Q1, Q3)	67.0 (60.3, 71.1)	66.0 (60.7, 70.3)	67.3 (62.4, 71.3)	66.7 (61.2, 70.9)
Race (%)				
American Indian/Alaska Native	1 (0.6)	0 (0.0)	2 (1.2)	3 (0.6)
Asian	3 (1.8)	0 (0.0)	10 (5.9)	13 (2.6)
Black or African-American	7 (4.2)	13 (7.7)	12 (7.1)	32 (6.4)
Native Hawaiian/Pacific Islander	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
Other	2 (1.2)	1 (0.6)	2 (1.2)	5 (1.0)
White	142 (85.5)	144 (85.7)	135 (79.9)	421 (83.7)
Unknown/Not Reported/Missing	10 (6.0)	10 (6.0)	7 (4.1)	27 (5.4)
Ethnicity (%)				
Hispanic	10 (6.0)	10 (6.0)	7 (4.1)	27 (5.4)
Non-Hispanic	151 (91.0)	152 (90.5)	155 (91.7)	458 (91.1)
Unknown/Not Reported/Missing	5 (3.0)	6 (3.6)	7 (4.1)	18 (3.6)

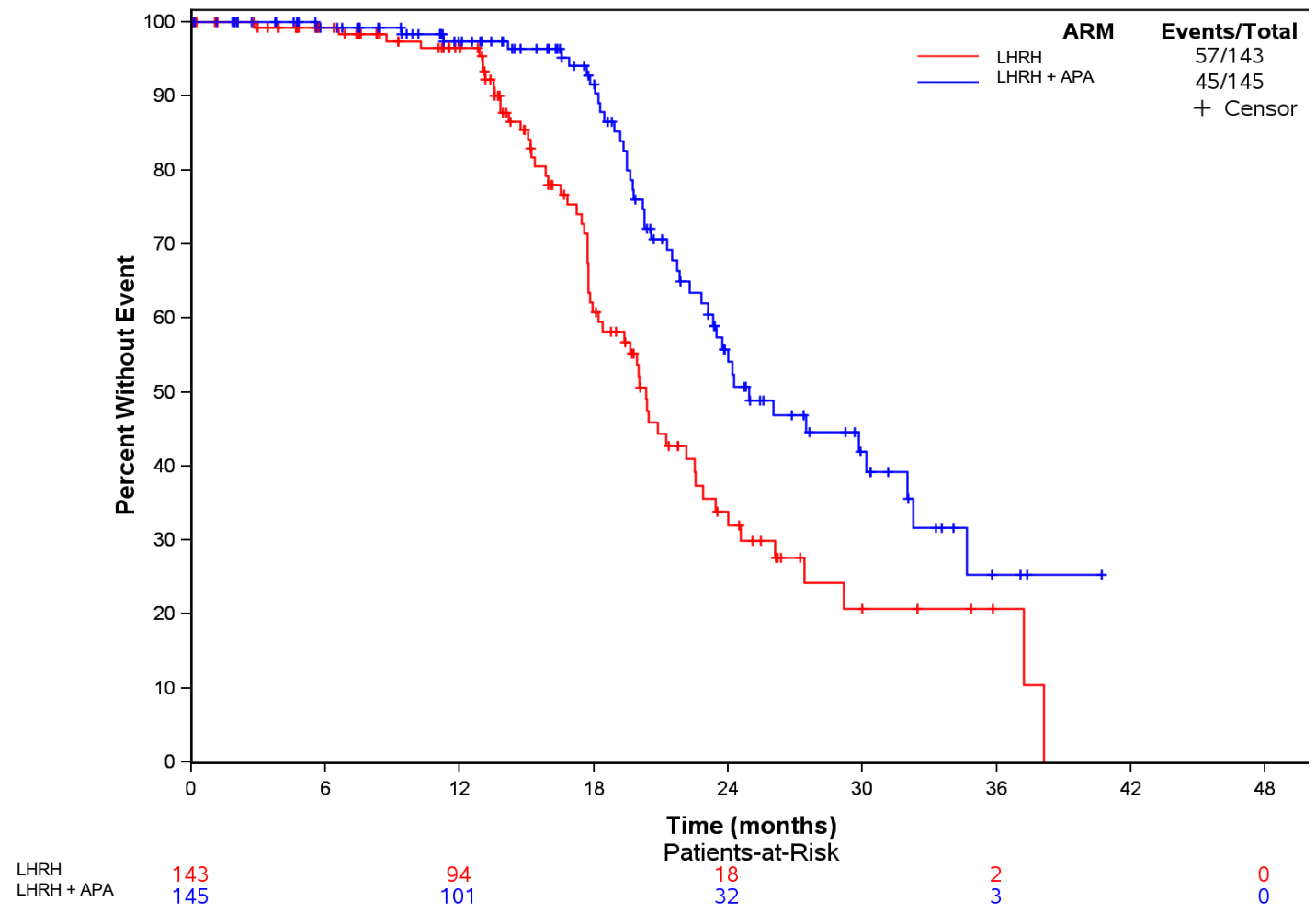
Aggarwal R et al. ESMO 2022;Abstract LBA63.

Baseline Characteristics, cont.

	Arm A (n = 166)	Arm B (n = 168)	Arm C (n = 169)	Overall Study Cohort (N = 503)
Median PSA at study entry, ng/mL (Q1, Q3)	1.73 (1.01, 3.20)	1.80 (0.97, 3.58)	1.77 (0.95, 4.21)	1.77 (0.97,3.57)
PSA doubling time strata (%)				
< 3 months	43 (25.9)	43 (25.6)	44 (26.0)	130 (25.8)
3 – 9 months	123 (74.1)	125 (74.4)	125 (74.0)	373 (74.2)
Median time interval between radical prostatectomy and study entry, years (Q1, Q3)	4.6 (2.8, 7.3)	4.7 (2.8, 6.5)	4.0 (2.8, 6.8)	4.4 (2.8, 6.8)
Prior radiation, N (%)	147 (88.6)	142 (84.5)	137 (81.1)	426 (84.7)
Prior androgen deprivation therapy, N (%)	71 (42.8)	75 (44.6)	67 (39.6)	213 (42.35)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

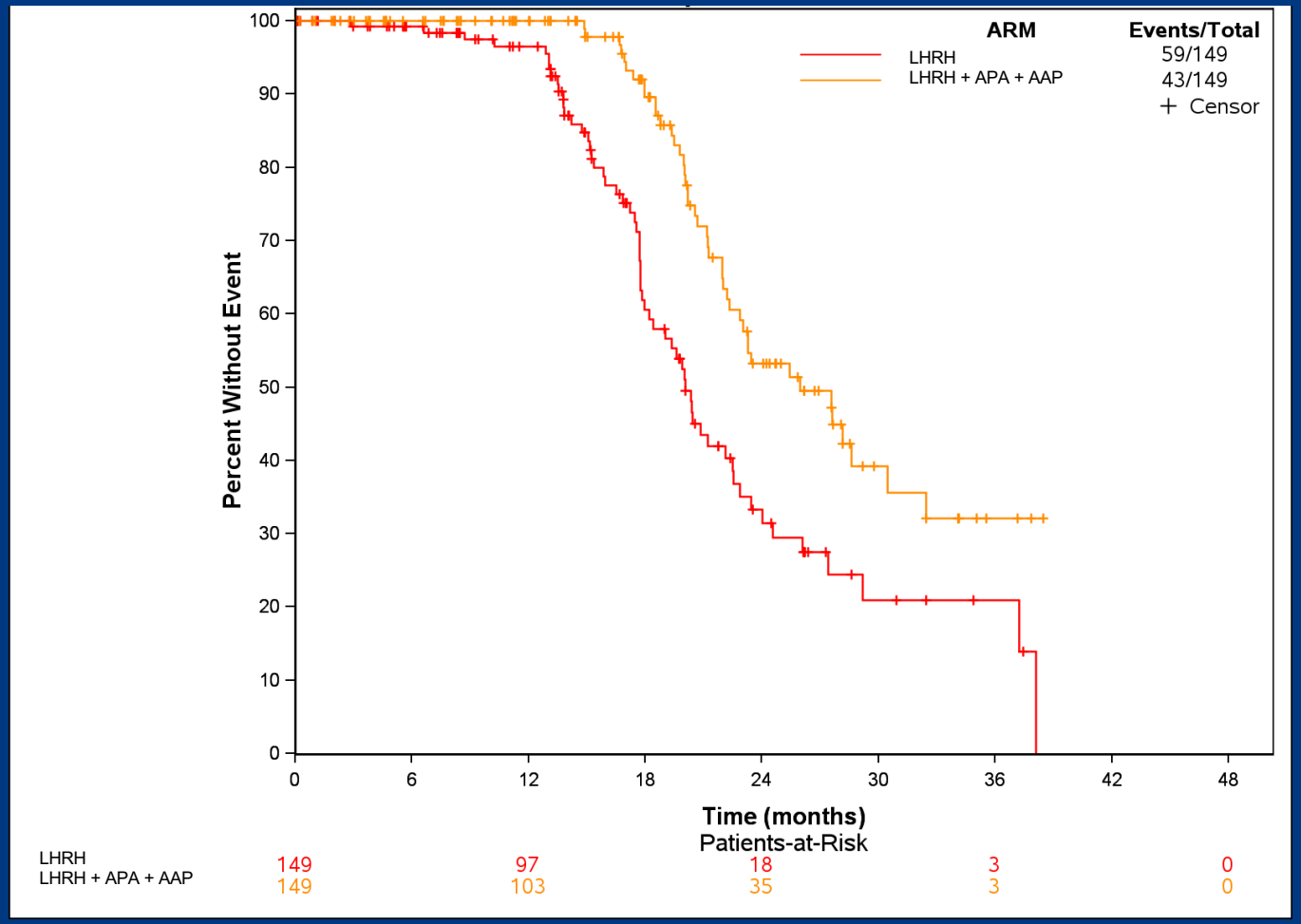
Arm B: ADT + Apalutamide vs. ADT monotherapy



- Median follow up 21.5 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA = 24.9 months (95% CI: 23.3 – 32.3)
  - ADT alone = 20.3 months (95% CI: 18.2 – 22.9)
  - **Hazard ratio 0.52 (95% CI: 0.35 – 0.77)**
  - One-sided p-value = 0.00047)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

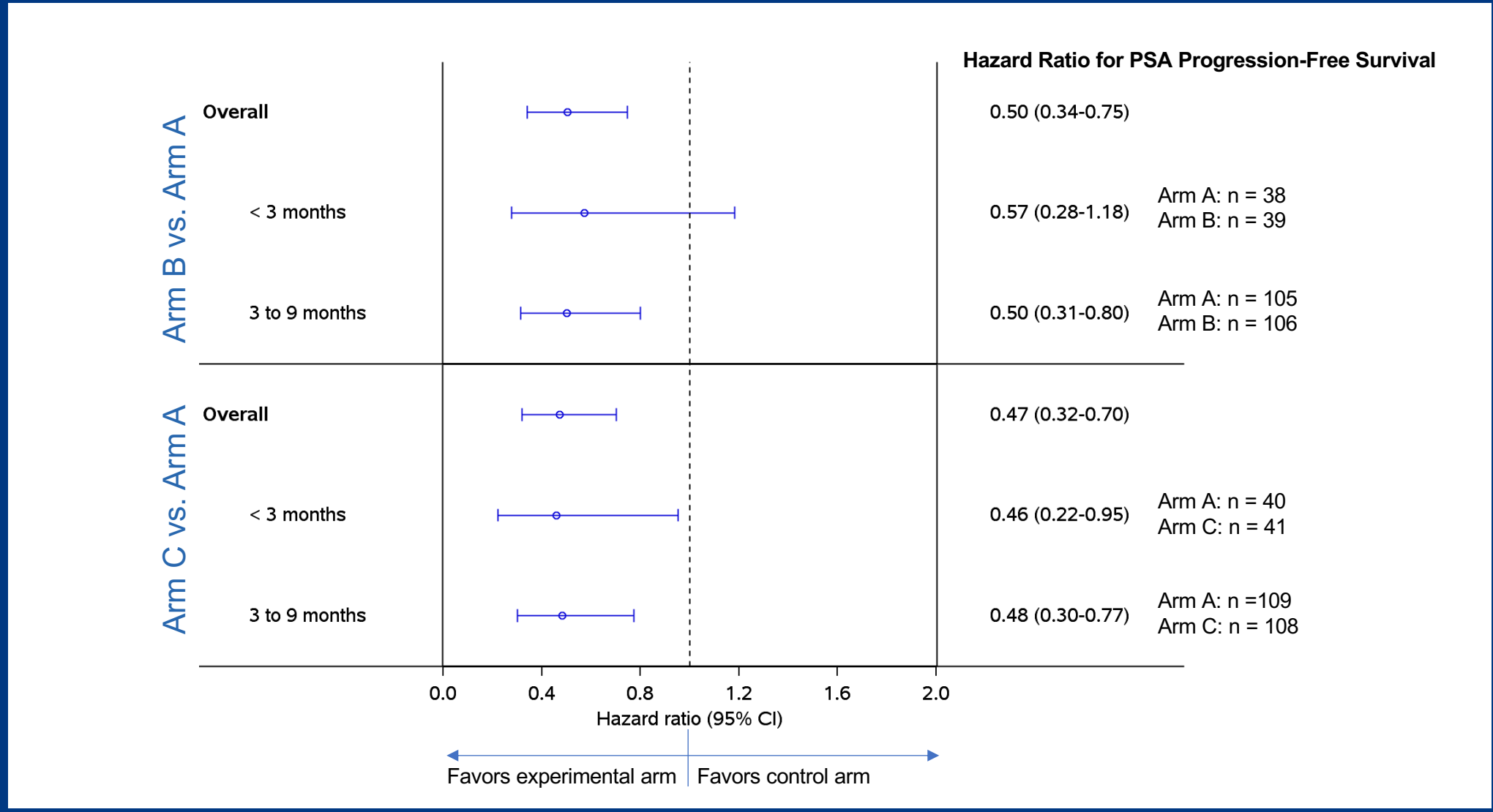
Arm C: ADT + apalutamide + abiraterone acetate + prednisone vs. ADT monotherapy



- Median follow up 21.3 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA + AAP = 26.0 months (95% CI: 22.9 – 32.5)
  - ADT alone = 20.0 months (95% CI: 18.2 – 22.5)
  - **Hazard ratio = 0.48 (95% CI: 0.32 – 0.71)**
  - One-sided p-value = 0.00008

Aggarwal R et al. ESMO 2022;Abstract LBA63.

PSA Progression-Free Survival by PSA doubling time



Aggarwal R et al. ESMO 2022;Abstract LBA63.

Most Common Grade ≥ 2 Adverse Events (N = 484)

	Arm A (n = 160)		Arm B (n = 163)		Arm C (n = 161)	
Adverse Events (AE)	Grade 2	Grade ≥ 3	Grade 2	Grade ≥ 3	Grade 2	Grade ≥ 3
	n (%)		n (%)		n (%)	
Hypertension	19 (12)	12 (8)	25 (15)	12 (7)	18 (11)	31 (19)
Hot flashes	19 (12)	1 (1)	8 (5)	0	23 (14)	0
Fatigue	14 (9)	0	8 (5)	3 (2)	16 (10)	2 (1)
Injection site reaction	9 (6)	0	10 (6)	0	11 (7)	0
Insomnia	9 (6)	0	5 (3)	0	8 (5)	0
Hyperglycemia	0	3 (2)	6 (4)	2 (1)	6 (4)	5 (3)
Rash	2 (1)	1 (1)	7 (4)	3 (2)	3 (2)	5 (3)
Erectile dysfunction	10 (6)	1 (1)	6 (4)	1 (1)	2 (1)	0
Arthralgia	4 (3)	1 (1)	6 (4)	1 (1)	3 (2)	2 (1)
Elevated ALT	1 (1)	0	1 (1)	0	2 (1)	0

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Summary of Adverse Events (N = 484)

	Arm A (n=160)	Arm B (n=163)	Arm C (n=161)
Adverse Events (AE)	n (%)	n (%)	n (%)
Any AE	145 (90.6)	148 (90.8)	155 (96.3)
Grade 3 or 4 AE	30 (18.8)	41 (25.2)	61 (37.9)
Any Serious AE	13 (8.1)	14 (8.6)	28 (17.4)
AE leading to treatment discontinuation	0 (0.0)	3 (1.8)	5 (3.1)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Limitations

- PSA-based rather than metastasis-free survival primary endpoint
  - Follow up is ongoing to estimate median metastasis-free survival in each study arm

- Metabolic imaging (e.g. fluciclovine or PSMA PET) not required at screening
  - Truly M0 biochemically recurrent CSPC population shrinking with stage migration
  - Role of metastasis-directed therapy in oligometastatic CSPC in conjunction with ADT remains to be defined

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Conclusions

- PRESTO is the first phase 3 study to report results of ADT plus AR pathway inhibition in biochemically recurrent, non-metastatic, castration-sensitive prostate cancer

- The addition of apalutamide to androgen deprivation for a finite duration of treatment leads to a statistically significant prolongation of PSA progression-free survival
  - No adverse impact on time to testosterone recovery
  - Safety profile consistent with prior studies

- There does not appear to be further benefit with addition of abiraterone acetate + prednisone to apalutamide

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Conclusions (continued)

- Follow up is ongoing to estimate the impact of ADT plus AR pathway inhibition on patient-reported outcomes, time to subsequent therapy, and metastasis-free survival

- Given that treatment decisions in biochemically recurrent prostate cancer are often predicated on PSA kinetics alone, ADT plus apalutamide for a finite treatment period could be considered for high-risk patients with a short PSA doubling time

AUA 2023

CHICAGO ★ APR 28-MAY 1

EMBARK: A Phase 3 Randomized Study of Enzalutamide or Placebo Plus Leuprolide Acetate and Enzalutamide Monotherapy in High-Risk Biochemically Recurrent Prostate Cancer

Neal D. Shore,[1] Murilo de Almeida Luz,[2] Ugo De Giorgi,[3] Martin Gleave,[4] Geoffrey T. Gotto,[5] Gabriel P. Haas,[6] Miguel Ramirez-Backhaus,[7] Antti Rannikko,[8] Jamal Tarazi,[9] Swetha Sridharan,[10] Jennifer Sugg,[6] Yiyun Tang,[11] Ronald F. Tutrone, Jr.,[12] Balaji Venugopal,[13] Arnauld Villers,[14] Henry H. Woo,[15] Fabian Zohren,[16] Stephen J. Freedland[17]

[1]Carolina Urologic Research Center/GenesisCare US, Myrtle Beach, SC, USA; [2]Erasto Gaertner Hospital, Curitiba, Brazil; [3]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [4]University of British Columbia, Vancouver, BC, Canada; [5]University of Calgary, Calgary, AB, Canada; [6]Astellas Pharma Inc., Northbrook, IL, USA; [7]Servicio de Urología, Fundación Instituto Valenciano de Oncología, Valencia, Spain; [8]University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [9]Pfizer Inc., Collegeville, PA, USA; [10]Calvary Mater, Newcastle, NSW, Australia; [11]Pfizer Inc., San Francisco, CA, USA; [12]Chesapeake Urology Research Associates, Towson, MD, USA; [13]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [14]University of Lille, Department of Urology, Claude Huriez Hospital, CHU LILLE, Lille, France; [15]Sydney Adventist Hospital, Sydney, NSW, Australia; [16]Pfizer Inc., Cambridge, MA, USA; [17]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Introduction

- Within 10 years following definitive therapy, between 20–50% of patients experience disease recurrence characterized by rising PSA levels.[1-3]
- Limited level 1 clinical data exist for the treatment of patients with BCR.
- Patients with high-risk BCR are at increased risk of prostate cancer-specific mortality.[3-5]
- Evidence from phase 3 clinical trials demonstrates that treatment intensification with ARSI, such as enzalutamide, consistently improves patient outcomes across the prostate cancer continuum.[6-10]

The objective of EMBARK was to evaluate enzalutamide in combination with leuprolide acetate and enzalutamide monotherapy in patients with high-risk BCR.

1. Kupelian PA, et al. *Cancer.* 2002;95:2302–7. 2. Kupelian PA et al. *Urology*. 2006;68;593–8. 3. Freedland SJ et al. *JAMA*. 2005;294:433–9. 4. Freedland SJ, et al. *J Clin Oncol.* 2007; 25:1765–71. 5. Markowski MC, et al. *Clin Genitourin Cancer.* 2019;17:470–1. 6. Scher HI, et al. *N Engl J Med.* 2012;367:1187–97. 7. Beer TM, et al. *N Engl J Med.* 2014;371:424–33. 8. Hussain M, et al. *N Engl J Med*. 2018;378:2465–74. 9. Armstrong AJ, et al. *J Clin Oncol.* 2019;37:2974–86. 10. Davis ID, et al. *N Engl J Med.* 2019;381:121–31. ARSI, androgen receptor signaling inhibitor; BCR, biochemical recurrence; PSA, prostate-specific antigen.

AUA 2023
CHICAGO ✶ APR 28-MAY 1

EMBARK study design

Patient population:

- Screening PSA ≥1 ng/mL after RP and at least 2 ng/mL above the nadir for primary EBRT
- PSADT ≤9 mo
- No metastases on bone scan or CT/MRI per central read
- Testosterone ≥150 ng/dL
- Prior hormonal therapy ≥9 mo prior to R (neoadjuvant/adjuvant for ≤36 mo OR ≤6 mo for rising PSA)

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)

R
1:1:1

N = 1068

Enzalutamide (160 mg oral qd) + leuprolide acetate (22.5 mg IM/q12w)
n = 355
Blinded

Placebo + leuprolide acetate (22.5 mg IM/q12w)
n = 358
Blinded

Enzalutamide monotherapy (160 mg oral qd)
n = 355
Unblinded

PSA <0.2 ng/mL at week 36

Yes → Suspend treatment at week 37 Monitor PSA (reinitiate if PSA rises)[a]

No → Remain on treatment

Primary endpoint[b]:
MFS by BICR, enzalutamide + leuprolide acetate vs. leuprolide acetate alone

Key secondary endpoints[b,c]:

- MFS by BICR, enzalutamide monotherapy vs. leuprolide acetate alone
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- OS[c]

Other secondary endpoints:

- Safety[d]

[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]Intent-to-treat 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. BICR, blinded independent central review; CT, computed tomography; d, day; EBRT, external beam radiotherapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

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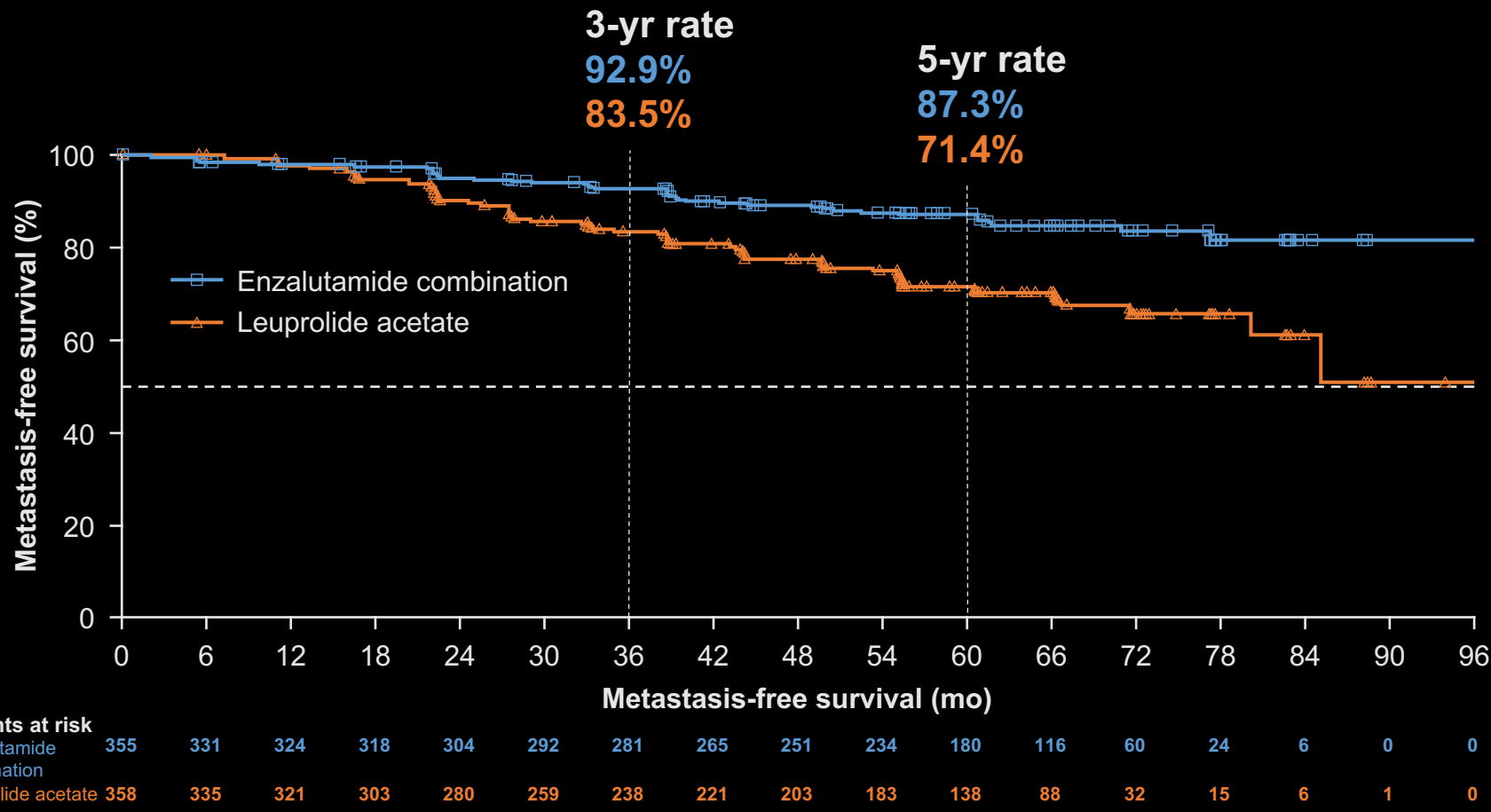
Demographics

Characteristic	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)	Enzalutamide monotherapy (n = 355)
Age, median (range), yr	69 (51–87)	70 (50–92)	69 (49–93)
Race, n (%)[a]			
White	293 (82.5)	301 (84.1)	295 (83.1)
Asian	26 (7.3)	26 (7.3)	26 (7.3)
Black	16 (4.5)	16 (4.5)	15 (4.2)
Other[b]	10 (2.8)	10 (2.8)	5 (1.4)
PSADT, n (%)[c]			
≤3 mo	69 (19.4)	80 (22.3)	76 (21.4)
>3 to ≤9 mo	285 (80.3)	277 (77.4)	278 (78.3)
PSADT, median, mo	4.6	5.0	5.0
Serum PSA, median, n (%), ng/mL[d]	5.0	5.5	5.3
≤10	278 (78.3)	273 (76.3)	272 (76.6)
>10	77 (21.7)	83 (23.2)	82 (23.1)
Prior hormonal therapy, n (%)	107 (30.1)	113 (31.6)	112 (31.5)
RP alone, n (%)	90 (25.4)	75 (20.9)	99 (27.9)
RT alone, n (%)	86 (24.2)	104 (29.1)	90 (25.4)
RP and RT, n (%)	179 (50.4)	179 (50.0)	166 (46.8)

[a]Not reported included: enzalutamide combination, n = 10 (2.8%); leuprolide acetate, n = 5 (1.4%); enzalutamide monotherapy, n = 14 (3.9%). [b]Includes patients who identified as multiple races (enzalutamide combination, n = 5; leuprolide acetate, n = 9; enzalutamide monotherapy, n = 5), American Indian or Alaskan Native (enzalutamide combination, n = 4; leuprolide acetate, n = 1; enzalutamide monotherapy, n = 0), Native Hawaiian or other Pacific Islander (enzalutamide combination, n = 1; leuprolide acetate and enzalutamide monotherapy, n = 0). [c]Missing included n = 1 (0.3%) for each treatment group. [d]Missing included: leuprolide acetate, n = 2; enzalutamide monotherapy, n = 1. RT, radiation therapy; yr, year.

Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	45 (13)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.42 (0.31–0.61); *P*<0.0001[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); *P*<0.0001

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value was based on a stratified log-rank. CI, confidence interval; HR, hazard ratio; IWRS, interactive web response system; NR, not reached.

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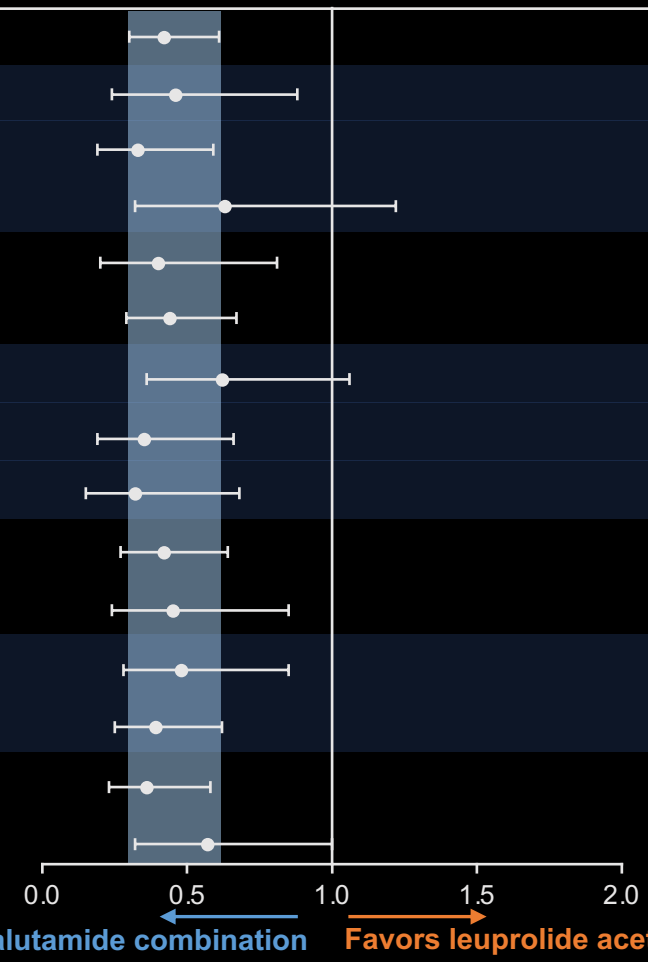
Subgroup analysis of MFS for enzalutamide combination vs. leuprolide acetate

Subgroup		Enzalutamide combination	Leuprolide acetate	MFS HR (95% CI)
		Events, n /patients, n		
All patients		45/355	92/358	0.42 (0.30–0.61)
PSADT	≤3 mo	14/69	30/80	0.46 (0.24–0.88)
	>3 to ≤6 mo	18/187	35/142	0.33 (0.19–0.59)
	>6 to ≤9 mo	13/98	27/135	0.63 (0.32–1.22)
Baseline age	≤65 years	11/81	28/91	0.40 (0.20–0.81)
	≥65 years	34/274	64/267	0.44 (0.29–0.67)
Geographic region	North America	22/144	32/137	0.62 (0.36–1.06)
	Europe	14/130	33/128	0.35 (0.19–0.66)
	ROW	9/81	27/93	0.32 (0.15–0.68)
Baseline PSA	≤10 ng/mL	31/278	64/273	0.42 (0.27–0.64)
	>10 ng/mL	14/77	28/83	0.45 (0.24–0.85)
Prior hormonal therapy	Yes	19/107	34/113	0.48 (0.28–0.85)
	No	26/248	58/245	0.39 (0.25–0.62)
Prior RP	Yes	26/269	61/254	0.36 (0.23–0.58)
	No	19/86	31/104	0.57 (0.32–1.00)



Data cutoff: January 31, 2023. For all patients, HR and 95% CI are based on stratified Cox regression model stratified by randomization stratification factors; for subgroups, HR and 95% CI are based on unstratified Cox regression model.

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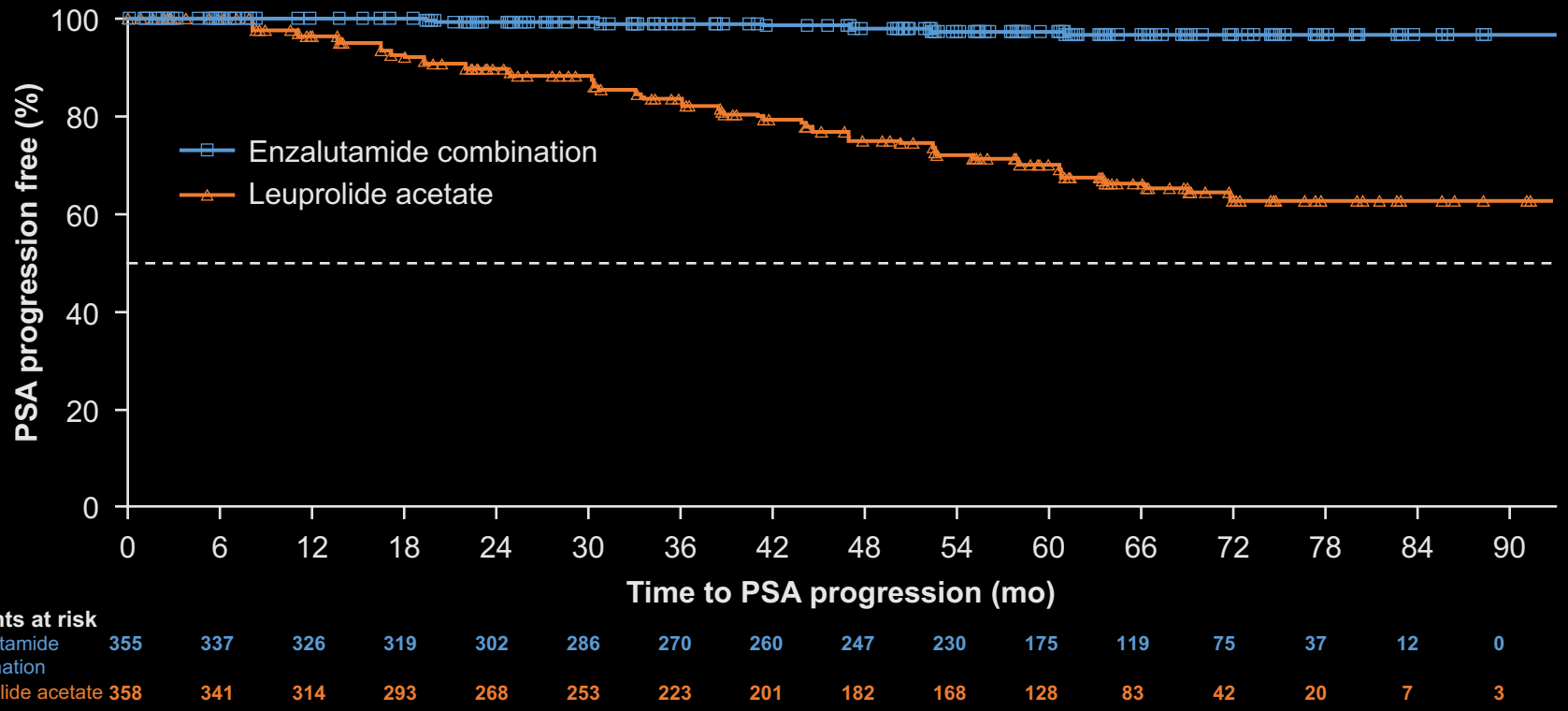
Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	337	326	319	302	286	270	260	247	230	175	119	75	37	12	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	8 (2)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.07 (0.03–0.14); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

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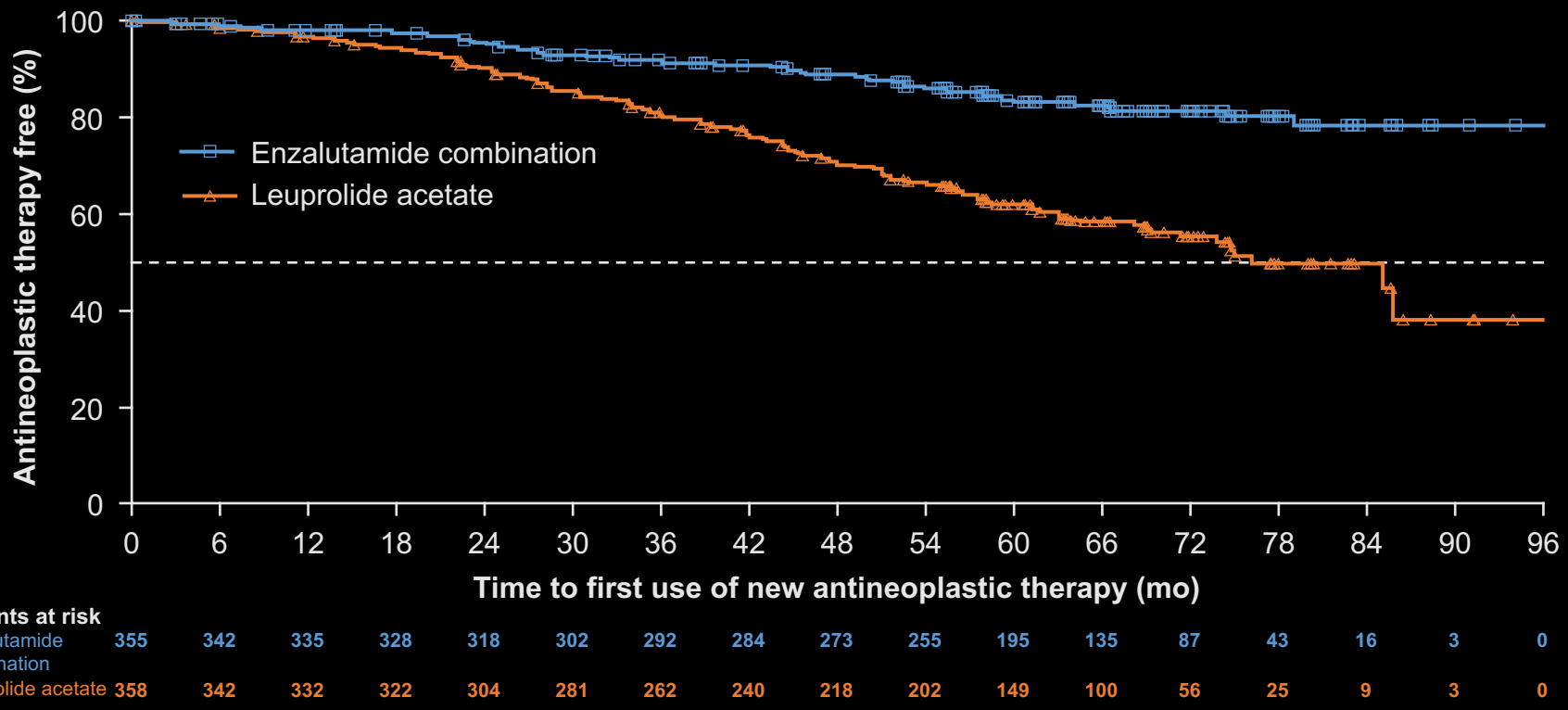
Key secondary endpoint — Time to first use of new antineoplastic therapy for enzalutamide combination vs. leuprolide acetate



Patients at risk

Enzalutamide combination	355	342	335	328	318	302	292	284	273	255	195	135	87	43	16	3	0
Leuprolide acetate	358	342	332	322	304	281	262	240	218	202	149	100	56	25	9	3	0

	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	58 (16)	140 (39)
Median time to first use of new antineoplastic therapy (95% CI), mo	NR (NR)	76.2 (71.3–NR)

HR (95% CI): 0.36 (0.26–0.49); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the two-sided *P*-value is based on a stratified log-rank test.

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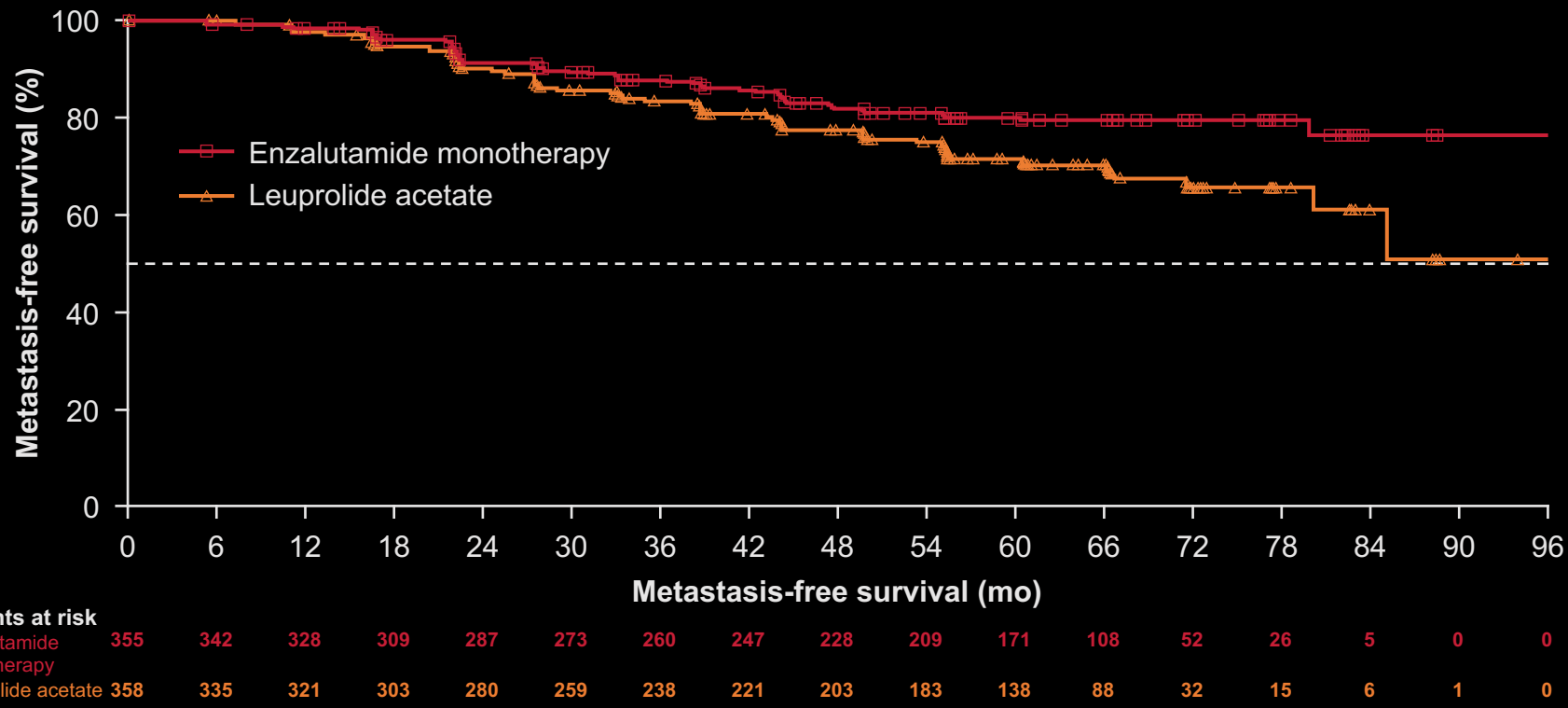
Key secondary endpoint — MFS for enzalutamide monotherapy vs. leuprolide acetate



	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.63 (0.46–0.87); *P*=0.0049[a]

A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.56 (0.40–0.78); *P*=0.0006

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy; the two-sided *P*-value was based on a stratified log-rank test.

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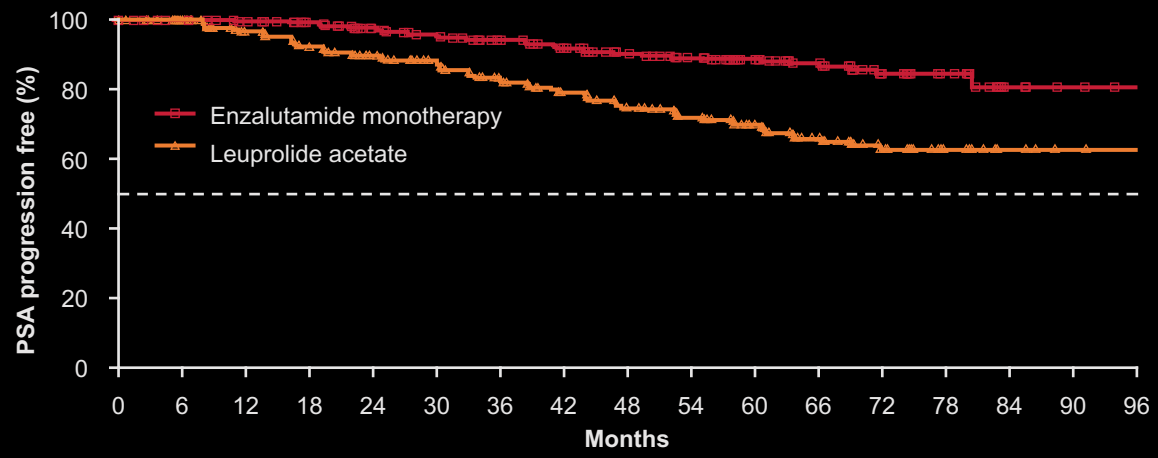
Key secondary endpoints — Enzalutamide monotherapy vs. leuprolide acetate

Time to PSA progression



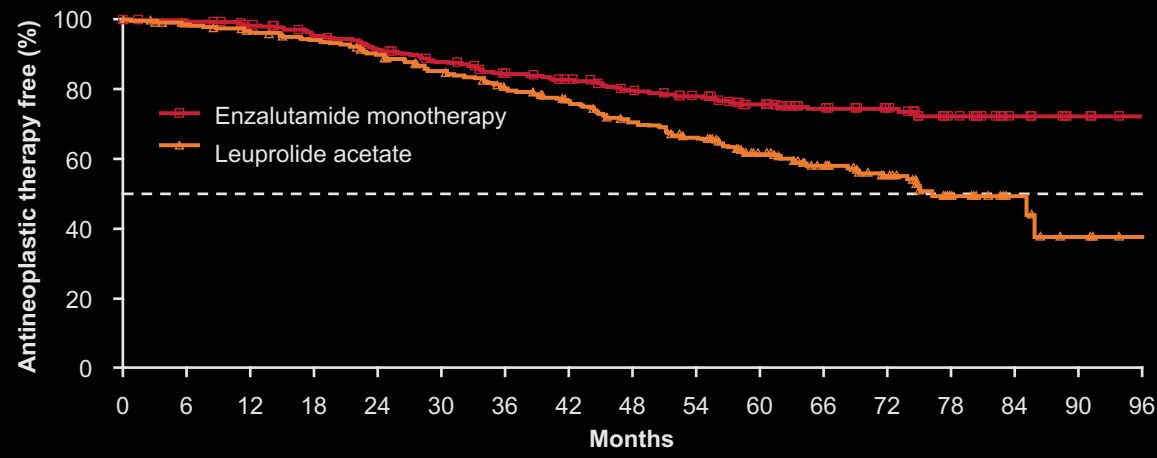
Patients at risk

Enzalutamide monotherapy	355	346	328	311	291	279	262	246	228	213	168	108	63	37	8	3	0
Leuprolide acetate	358	341	314	293	268	253	223	201	182	168	128	83	42	20	7	3	0

	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	37 (10)	93 (26)
Median time to PSA progression (95% CI), mo	NR (NR)	NR (NR)

HR (95% CI): 0.33 (0.23–0.49); *P*<0.0001[a]

Time to first use of new antineoplastic therapy



Patients at risk

Enzalutamide monotherapy	355	352	341	327	312	297	279	268	252	240	192	124	80	40	12	3	0
Leuprolide acetate	358	342	332	322	304	281	262	240	218	202	149	100	56	25	9	3	0

	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Events, n (%)	84 (24)	140 (39)
Median time to first use of new antineoplastic therapy (95% CI), mo	NR (NR)	76.2 (71.3–NR)

HR (95% CI): 0.54 (0.41–0.71); *P*<0.0001[a]

Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy; the two-sided *P*-value was based on a stratified log-rank test.

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Safety profile

Event, n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	343 (97.2)	164 (46.5)	345 (97.5)	151 (42.7)	347 (98.0)	177 (50.0)
Treatment-related AE	305 (86.4)	62 (17.6)	283 (79.9)	31 (8.8)	312 (88.1)	57 (16.1)
Serious AE	123 (34.8)	110 (31.2)	112 (31.6)	100 (28.2)	131 (37.0)	116 (32.8)
Treatment-related serious AE	26 (7.4)	22 (6.2)	8 (2.3)	7 (2.0)	17 (4.8)	17 (4.8)
AE leading to dose reduction	25 (7.1)	11 (3.1)	16 (4.5)	5 (1.4)	56 (15.8)	14 (4.0)
AE leading to permanent discontinuation	73 (20.7)	31 (8.8)	36 (10.2)	19 (5.4)	63 (17.8)	34 (9.6)
AE leading to death	6 (1.7)[b]	–	3 (0.8)[b]	–	8 (2.3)[b]	–

- Median treatment duration excluding treatment suspension was 32.4 mo (range, 0.1–83.4 mo) for enzalutamide combination, 35.4 mo (range, 0.7–85.7 mo) for leuprolide acetate, and 45.9 mo (0.4–88.9 mo) for enzalutamide monotherapy.
- The most common AE leading to study drug discontinuation was fatigue (enzalutamide combination, 3.4% [n = 12]; leuprolide acetate, 1.1% [n = 4]; enzalutamide monotherapy, 2.3% [n = 8]).

Data cutoff: January 31, 2023. [a]Percentages may not total 100 because of rounding. Shown are AE that occurred from the time of first dose of study treatment through 30 days after permanent discontinuation. AE were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. [b]Grade 5 AE; none were considered treatment-related. AE, adverse event.

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Most common TEAEs

Most common TEAEs (>15% of patients), n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
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)
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0

- The most common AEs (>15% of patients) for all treatment cohorts were hot flash, fatigue; plus gynecomastia in the enzalutamide monotherapy cohort; most were grade <3.

Data cutoff: January 31, 2023. [a]Percentages may not total 100 because of rounding. Shown are AEs that occurred from the time of first dose of study treatment through 30 days after permanent discontinuation. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. TEAE, treatment-emergent AE.

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Selected TEAEs of special interest

Clustered TEAEs of special interest, n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue[b]	178 (50.4)[c]	14 (4.0)	134 (37.9)[c]	6 (1.7)	191 (54.0)[c]	17 (4.8)
Musculoskeletal events[d]	163 (46.2)[c]	13 (3.7)	148 (41.8)[c]	4 (1.1)	158 (44.6)[c]	6 (1.7)
Hypertension	89 (25.2)[c]	27 (7.6)	74 (20.9)	21 (5.9)	77 (21.8)[c]	20 (5.6)
Fall	74 (21.0)	4 (1.1)	51 (14.4)	4 (1.1)	56 (15.8)	7 (2.0)
Fracture[e]	65 (18.4)	14 (4.0)	48 (13.6)	9 (2.5)	39 (11.0)	7 (2.0)
Cognitive and memory impairment	53 (15.0)[c]	2 (0.6)	23 (6.5)	2 (0.6)	50 (14.1)[c]	0
Loss of consciousness[f]	20 (5.7)	17 (4.8)	12 (3.4)	6 (1.7)	12 (3.4)	8 (2.3)
Ischemic heart disease	19 (5.4)	14 (4.0)	20 (5.6)	11 (3.1)	32 (9.0)	21 (5.9)
Other selected CV events[g]	18 (5.1)	13 (3.7)	17 (4.8)	10 (2.8)	13 (3.7)	8 (2.3)
Convulsion (seizure)	4 (1.1)	2 (0.6)	0	0	3 (0.8)	2 (0.6)

- The most common AEs of special interest for all treatment cohorts (≥10% of patients) were fatigue, fall, fracture, hypertension, and musculoskeletal events.

Data cutoff: January 31, 2023. [a]Percentages may not total 100 because of rounding. Shown are AEs that occurred from the time of first dose of study treatment through 30 days after permanent discontinuation. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. [b]Fatigue events included asthenia. [c]The most common (≥10% of patients) TEAEs. [d]Musculoskeletal events included back pain, arthralgia, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal stiffness, muscular weakness, and muscle spasms. [e]Fractures excluded tooth fracture and fracture of the penis. [f]Loss of consciousness included syncope and presyncope. [g]Other selected CV events included hemorrhagic central nervous system vascular conditions, ischemic central nervous system vascular conditions, and cardiac failure. CV, cardiovascular.

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EMBARK: Conclusions

- In patients with high-risk BCR, compared with leuprolide acetate, **enzalutamide combination** demonstrated a statistically significant and clinically meaningful improvement in MFS (HR 0.42; 95% CI, 0.30–0.61; *P*<0.0001).
  - A consistent treatment effect in pre-specified subgroups
  - Significant delays in time to PSA progression and time to first new antineoplastic therapy
  - A trend toward improved survival in interim analysis (HR 0.59; 95% CI, 0.38–0.90; *P*=0.0142); study ongoing for final analysis
- **Enzalutamide monotherapy** also demonstrated statistically significant and clinically meaningful improvements in MFS (HR 0.63; 95% CI 0.46–0.87; *P*=0.0049), time to PSA progression, and time to first new antineoplastic therapy.
  - A trend toward improved survival in interim analysis
- No new safety signals observed to date with enzalutamide treatment

Enzalutamide in combination with ADT, if approved in this setting, has the potential to become a new standard of care for patients with high-risk BCR.

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Clinical Case: BCR

- 70 yo WM 18 months post RP
- PSA 5.0,PSADT 6 month
- Conventional Imaging (CT/BS) negative
- MedHx: ECOG 0; +HTN/elevated lipids
- Genomic profiling not done

Clinical Case: BCR, continued

Initiate therapy:

a. ADT alone
b. ADT + APA
c. ADT + Enza
d. Monotx Enza
e. Wait till conventional imaging positive

Clinical Case : BCR, continued

Questions:

1: Role genomic molecular markers((Decipher,Prolaris, OncotypeDx)

2: Role genetic alteration testing (germline,somatic)

3: Role PSMA PET

4: Role Metastasis Directed Therapy (RT vs Excision) ,+/- T suppression

THANK YOU