

Biyokimyasal Rekürens ve PSA Persistansı

Dr. Deniz Tural

**Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji**

Ders Planı

☐ Giriş

☐ Tanım

☐ PSMA PET/CT prognostik ve prediktif

☐ Salvage RT

☐ Salvage RT+LHRH

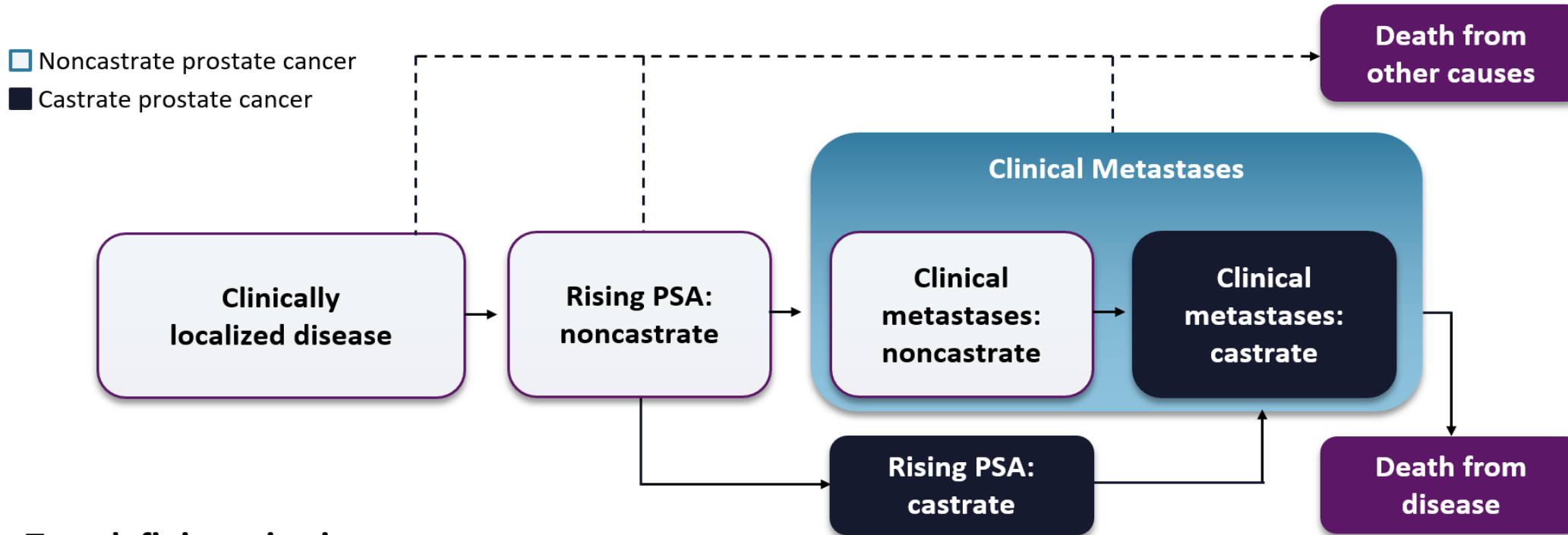
☐ ADT süresi ne olmalı

☐ Yoğunlaştırılmış tedavi ihtiyacı var mı

☐ Sonuç

Prostat kanserinin seyri

Clinical Disease States Model of Prostate Cancer¹



Two defining criteria

- Rising PSA in the setting of castrate testosterone levels (<50 ng/dL)
- No radiographically identifiable metastasis

Biyokimyasal Rekürens ve PSA Persistansı

Tanım

PSA persistansı; Prostatektomi yapılan hastalarda 4-8 hafta sonrası ≥ 0.1 ng/ml olması

- ❑ Genel olarak, >T3a, gleason skoru ≥ 8 , cerrahi sınır+, pelvik lenf nodu+ ve kötü prognoz ile ilişkili
- ❑ %5-20 oranında görülür
- ❑ PSMA PET/CT nüksü belirlemede sensitivitesi yüksek, özellikle PSA ≥ 0.2 ng/ml olan hastalarda
- ❑ PSA persistansın olan hastaların %74 PSA artışı devam eder ve metastaz riski bu grup için yüksek

PSA Persistansı sağkalım sonuçları

Table 4 – Multivariable Cox regression models predicting metastasis, death, and cancer-specific death in the subgroup with postoperative persistent PSA (≥ 0.1 ng/ml at 6 wk after RP)

	Predicting metastasis			Predicting death			Predicting cancer-specific death		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Year of surgery	1.23	1.17–1.30	<0.001	0.96	0.91–1.02	0.2	0.91	0.85–0.98	<0.01
Age	0.97	0.95–0.99	0.02	1.03	0.99–1.07	0.2	1.03	0.98–1.10	0.3
Preoperative PSA	1.01	0.99–1.01	0.4	0.98	0.97–1.01	0.1	0.99	0.97–1.01	0.3
Pathologic stage $\leq T2c$ (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic stage T3a	1.59	0.95–2.66	0.1	1.77	0.70–4.49	0.2	1.95	0.38–10.03	0.4
Pathologic stage T3b	2.01	1.21–3.35	<0.01	2.92	1.16–7.33	0.02	4.48	0.93–21.72	0.1
Pathologic GG1–2 (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic GG3–5	3.17	1.92–5.24	<0.001	2.49	1.30–4.77	<0.01	5.05	1.76–14.46	<0.01
Negative surgical margin (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Positive surgical margin	0.93	0.67–1.27	0.6	1.60	0.98–2.62	0.1	1.50	0.77–2.93	0.2
Pathologic lymph node status N0 (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic lymph node status N1	1.32	0.96–1.83	0.1	1.49	0.87–2.54	0.1	1.46	0.71–2.99	0.3
Pathologic lymph node status Nx	0.68	0.35–1.30	0.2	0.79	0.39–1.63	0.5	1.09	0.41–2.86	0.9
CCI 0	1.00	–	–	1.00	–	–	1.00	–	–
CCI ≥ 1	0.89	0.63–1.25	0.5	1.82	1.07–3.13	0.03	1.06	0.51–2.21	0.9

CCI = Charlson Comorbidity Index; CI = confidence interval; GG = Gleason grade group; HR = hazard ratio; PSA = prostate-specific antigen.

PSA persistansı, pT3 $\geq$, Gleason skoru>, cerrahi sınır+, lenf nodu+ olanlarda kötü sonuç ile ilişkili

PSA Persistansı sağkalım sonuçları

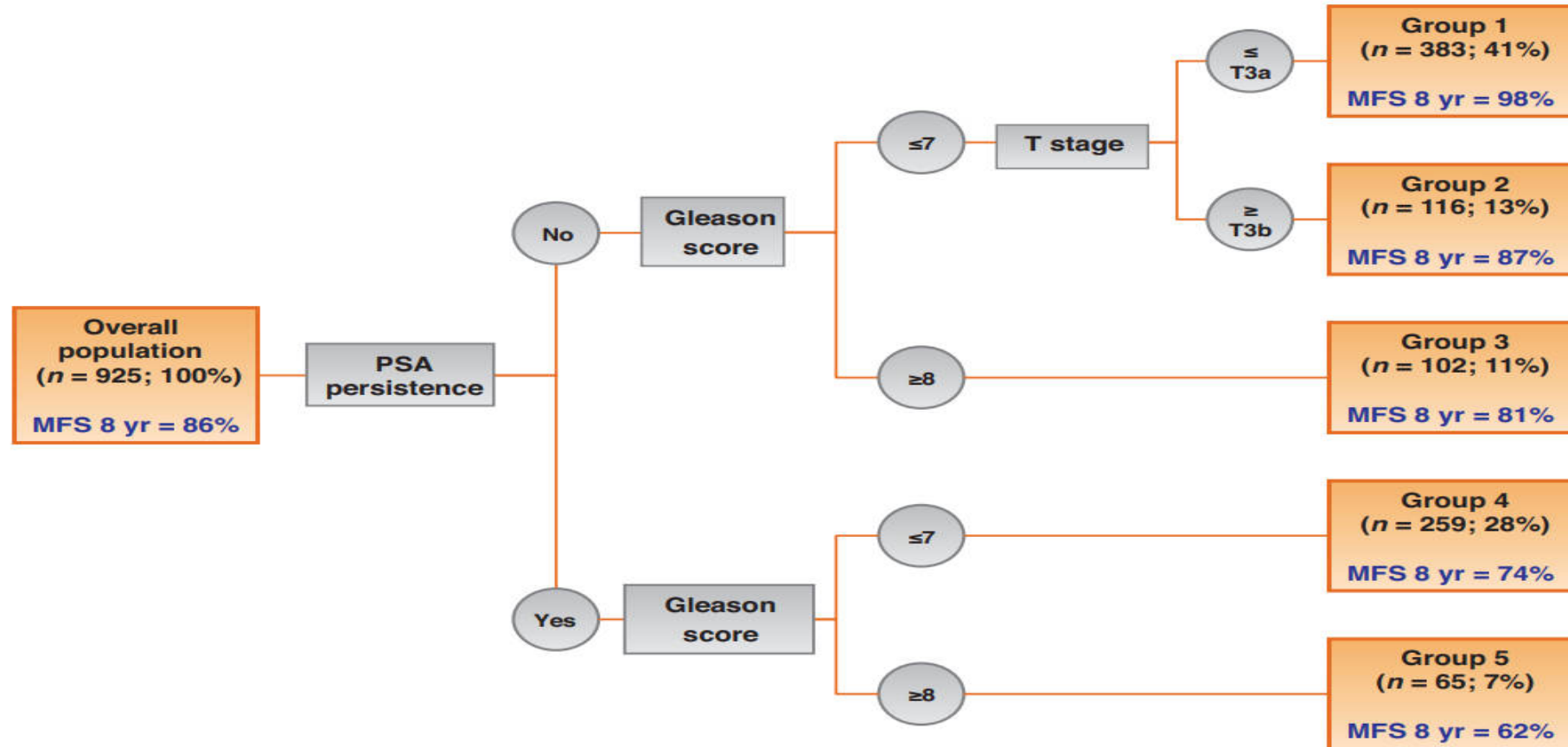


Fig. 1 – A risk stratification tree assessing metastasis-free survival (MFS), based on 925 patients treated with salvage radiation therapy for prostate-specific antigen (PSA) rise after radical prostatectomy.

Biyokimyasal Rekürens

Tanım

- ❑ ① Biyokimyasal Rekürens ; Daha önceleri EUA tanımlaması, Prostatektomi sonrası PSA değeri nadir düzeye düşen hastalarda PSA değerinin artarak ≥ 0.2 ng/ml olarak ölçülmesi ve bunun birkaç ölçümle doğrulanması
- ❑ ② NCCN tanımlaması; Prostatektomi sonrası PSA değeri nadir düzeye düşen hastalarda PSA değerinin artarak ≥ 0.1 ng/ml olarak ölçülmesi ve bunun birkaç ölçümle doğrulanması
- ❑ ② Primer tedavi olarak radyoterapi alan hastalarda PSA değerinin ≥ 2 ng/ml olarak ölçülmesi
- ❑ Biyokimyasal Rekürens, Prostatektomi ve Radyoterapi sonrası risk grubuna göre 27–53%.
- ❑ Biyokimyasal Rekürens olan hastaların hepsinde metastaz görülmez. Bu nedenle risk skorlamasına göre yüksek grupta olanlar erken ya da salvage tedavi almalıdır.

① Van den Broeck T, et al. Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations. Eur Urol Focus 2019)

② Schaeffer E, Srinivas S, Antonarakis ES, et al. NCCN guidelines: prostate cancer, version 3.2023

Biyokimyasal Rekürens Öngörme

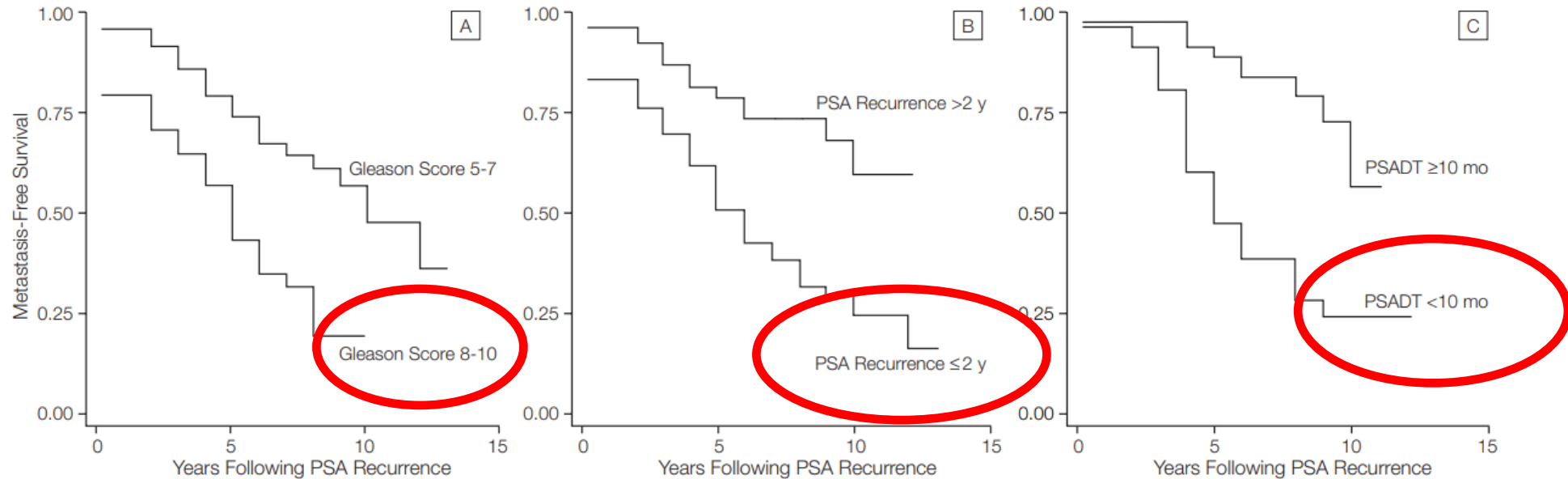
Table 1 – EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer.

Definition			
Low risk	Intermediate risk		High risk
PSA < 10 ng/mL and ISUP grade 1 (GS < 7) and cT1-2a	PSA 10–20 ng/ml or ISUP grade 2/3 (GS 7) or cT2b	PSA > 20 ng/mL or ISUP grade 4/5 (GS > 7) or cT2c	Any PSA, any GS (any ISUP grade), cT3–4, or cN+
Localised			Locally advanced
GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.			

**EAU-EANM-ESTRO-ESUR-SIOG Guidelines on ProstateCancer—2020 Update.
Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent**

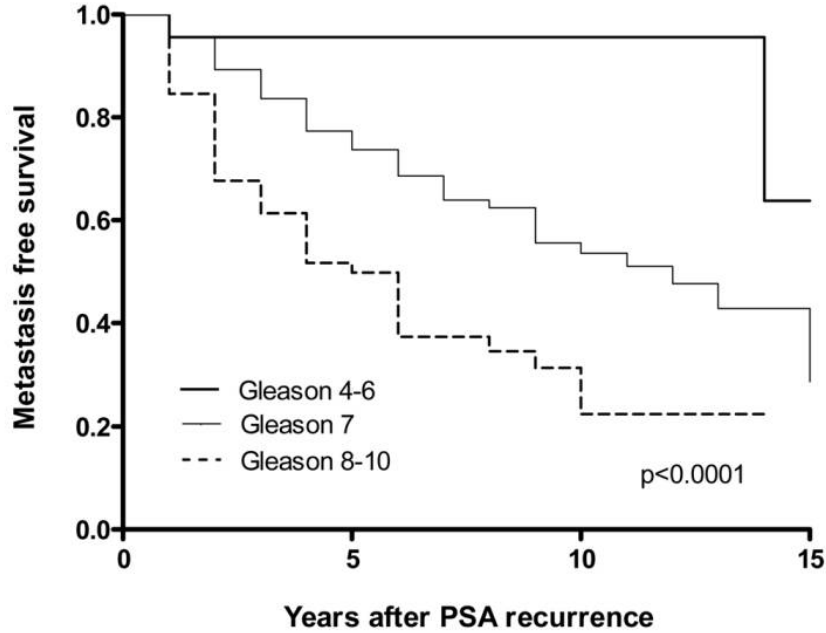
Biyokimyasal Rekürens ve PSA Persistansı Metastaz riski

Figure 3. Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific (PSA) Antigen Elevation After Radical Prostatectomy

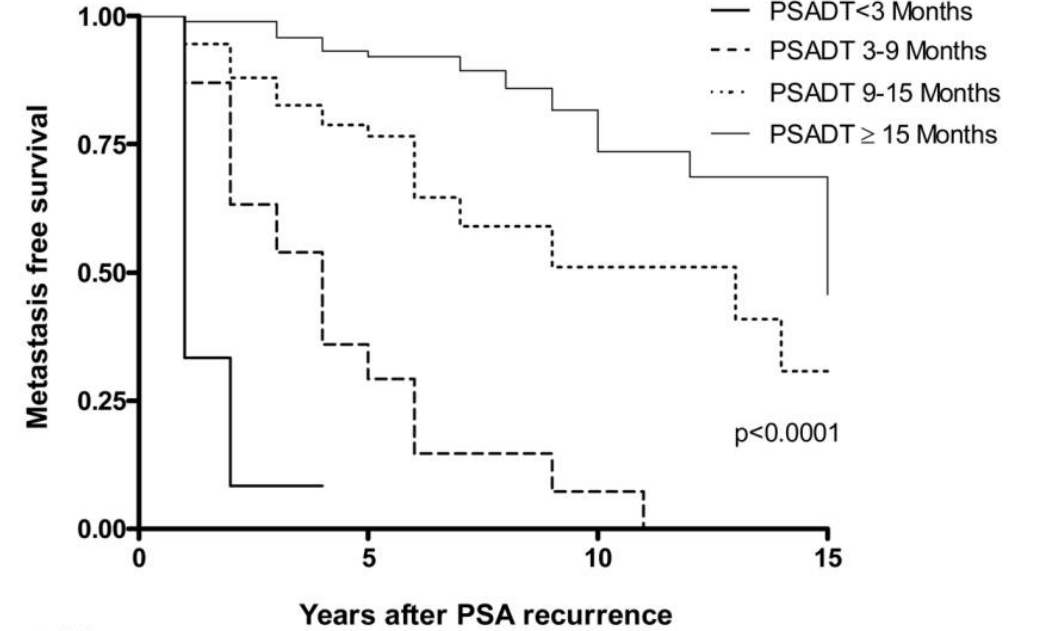


A, Based on Gleason scores in the radical prostatectomy specimen ($P < .001$). B, Based on years until initial biochemical recurrence ($P < .001$). C, Based on prostate-specific antigen doubling time (PSADT) ($P < .001$).

Biyokimyasal Rekürens Metastaz riski



Number at risk					
Gleason score 4-6	88	26	6	1	
Gleason score 7	239	85	29	3	
Gleason score 8-10	123	28	7	0	



Number at risk					
PSADT < 3 Month	46	0	0	0	
PSADT 3-9 Month	106	16	2	0	
PSADT 9-15 Month	86	37	11	1	
PSADT ≥ 15 Month	212	86	30	3	

Cerrahi sonrası mediyen 8 yıl takip süresinde, 450 biyokimyasal nüks gelişen ve herhangi bir salvage tedavi almayan hastanın 134’de metastaz görüldü(%29.8).

Biyokimyasal Rekürens Metastaz riski

Preoperative PSA, ng/mL (continuous)	1.00 (0.99–1.01)	0.567	0.99 (0.98–1.01)	0.424
Pathological Gleason sum				
4–6	1 [reference]		1 [reference]	
7	4.3 (1.7–10.7)	0.002	2.4 (0.9–6.2)	0.067
8–10	10.9 (4.4–27.1)	<0.001	4.5 (1.7–11.9)	0.002
Pathological stage				
Organ-confined disease	1 [reference]		1 [reference]	
Extraprostatic extension	1.2 (0.6–2.3)	0.658	0.6 (0.3–1.3)	0.240
Seminal vesicle invasion	3.0 (1.5–6.0)	0.002	1.3 (0.6–2.8)	0.434
Lymph node involvement	3.1 (1.6–6.0)	0.001	1.1 (0.5–2.2)	0.811
Surgical margin status				
Negative	1 [reference]		1 [reference]	
Positive	0.8 (0.6–1.1)	0.198	0.9 (0.6–1.4)	0.829
Time to PSA recurrence				
≤ 3 years	1 [reference]		1 [reference]	
> 3 years	0.4 (0.3–0.6)	<0.001	1.0 (0.6–1.5)	0.964
PSA doubling time				
≥ 15 months	1 [reference]		1 [reference]	
9.0–14.9 months	2.7 (1.6–4.8)	0.005	2.5 (1.4–4.5)	0.002
3.0–8.9 months	11.6 (7.0–19.3)	<0.001	8.0 (4.5–14.1)	<0.001
< 3.0 months	47.4 (25.2–89.0)	<0.001	33.3 (16.4–67.4)	<0.001

☐ PSA double time

☐ Gleason skoru ≥ 8

☐ Gleason skoru 7?

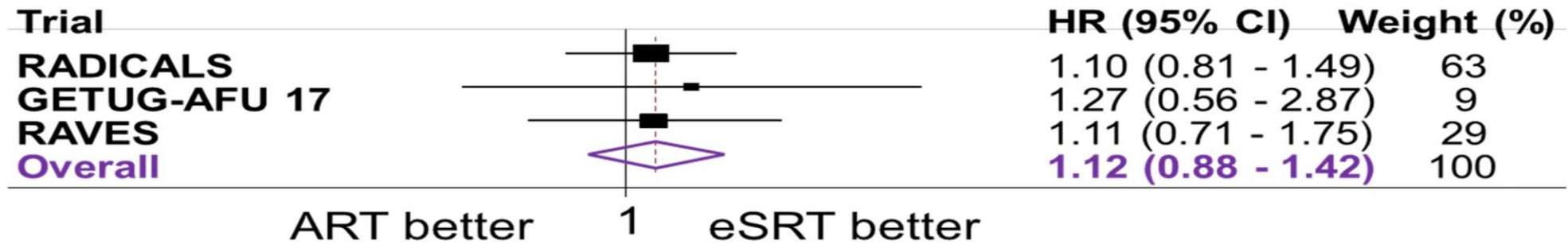
metastaz arasında
güçlü ilişki mevcut

	Pathological Gleason score 8–10 (n = 123)	Pathological Gleason score 7 (n = 239)	Pathological Gleason score 4–6 (n = 88)	PSADT <3 months (n = 46)	PSADT 3–9 months (n = 106)	PSADT 9–15 months (n = 86)	PSADT ≥15 months (n = 212)
Median MFS, years (95% CI)	4 (2, 6)	11 (9, >17)	>15 (14, >15)	1 (0, 1)	4 (2, 4)	13 (6, >15)	15 (15, >17)
Metastasis-free rate at 5 years, % (95% CI)	43 (32, 54)	71 (63, 78)	94 (86, 98)	5 (1, 21) ^a	27 (16, 39)	77 (63, 86)	91 (85, 95)
Metastasis-free rate at 10 years, % (95% CI)	19 (9, 33)	52 (41, 62)	94 (86, 98)	N/A	7 (1, 22)	51 (34, 66)	72 (59, 83)

Radikal Prostatektomi sonrası Adjuvan RT vs Salvage RT

Three Randomized Trials Suggest *Most* Patients Should Get Salvage Radiation, Not Adjuvant

ARTISTIC Meta-Analysis (Vale CL, Lancet Oncology 2020)



Radikal Prostatektomi sonrası Adjuvan RT vs Salvage RT

**BUT, These Three Trials Had Fewer Patients With the *Worst* Prognostic Factors
15% GI 8-10, 19% SVI**

50

	RADICALS-RT ⁵		GETUG-AFU 17 ⁶		RAVES ⁷	
	Adjuvant radiotherapy	Early salvage radiotherapy	Adjuvant radiotherapy	Early salvage radiotherapy	Adjuvant radiotherapy	Early salvage radiotherapy
Patients randomised	697	699	212	212	166	167
Gleason score						
≤6	48 (7%)	48 (7%)	21 (10%)	22 (10%)	8 (5%)	8 (5%)
7	537 (77%)	528 (76%)	173 (82%)	167 (78%)	132 (80%)	134 (80%)
≥8	112 (16%)	123 (17%)	17 (8%)	23 (11%)	26 (16%)	25 (15%)
Positive margins	439 (63%)	443 (63%)	211 (100%)	210 (100%)	110 (66%)	113 (68%)
Seminal vesicle involvement						
Yes	129 (19%)	132 (19%)	44 (21%)	46 (22%)	31 (19%)	33 (20%)
No	568 (81%)	567 (81%)	167 (79%)	165 (78%)	135 (81%)	134 (80%)
Unknown	0	0	1 (<1%)	1 (<1%)	0	0

Radikal Prostatektomi sonrası Adjuvan RT > Salvage RT

- 1. Practical/Gut Feeling: He has over a 90% chance of needing salvage RT so we're not overtreating; if there is any benefit to adjuvant, it will be for younger pts
- 2. Retrospective data: Tilki/D'Amico JCO 2021 – pN0 pts who had both Gleason 8-10 and pT3/4 had lower all-cause mortality w/adjuvant RT than early salvage (aHR=0.33 [0.13-0.85])
- 3. Genomics? – Analysis from Den, et al JCO 2015

Radikal Prostatektomi sonrası Adjuvan RT > Salvage RT

Den, JCO 2015: Decipher May Identify Men Who Benefit Most from Adjuvant RT

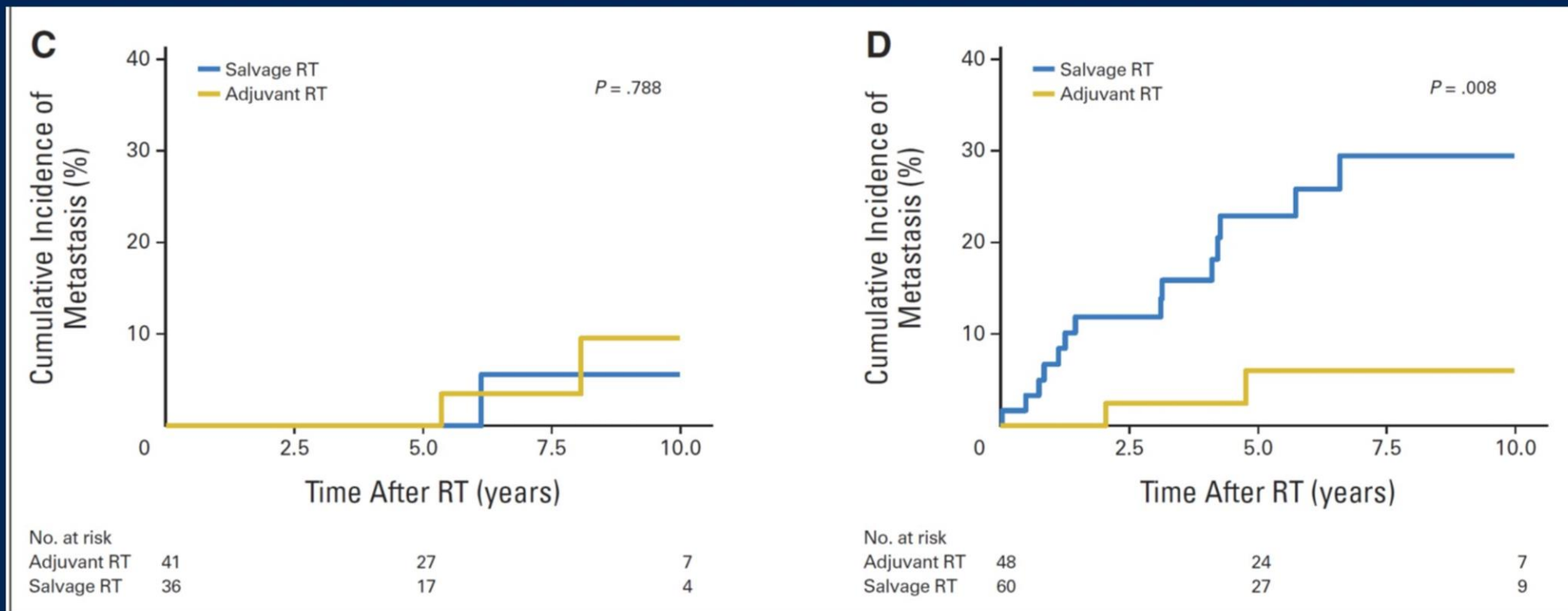
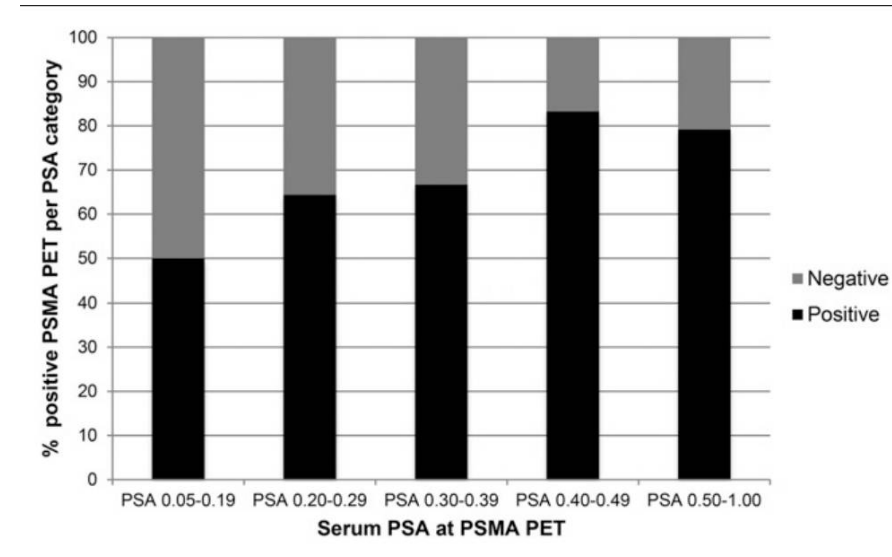


Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (C and D) genomic classifier (GC).

PSMA PET CT pozitifliği prognostik faktör

Characteristic	Number
Median age (y)	65 (range, 57–67)
Median PSA at PSMA PET	0.23 (range, 0.14–0.35)
Tumor stage	
T2	43 (24.8)
T3a	78 (44.4)
T3b	29 (16.6)
Missing	14 (14.2)
Positive surgical margins	55 (32.5)
Gleason score	
6–7	118 (84)
8–10	46 (26)
Months since RP	48 ± 43
PSMA PET result	
Negative	62/164 (38)
Fossa recurrence only	38/164 (23)
Lymph node positive	41/164 (25)
Distant disease	23/164 (14)

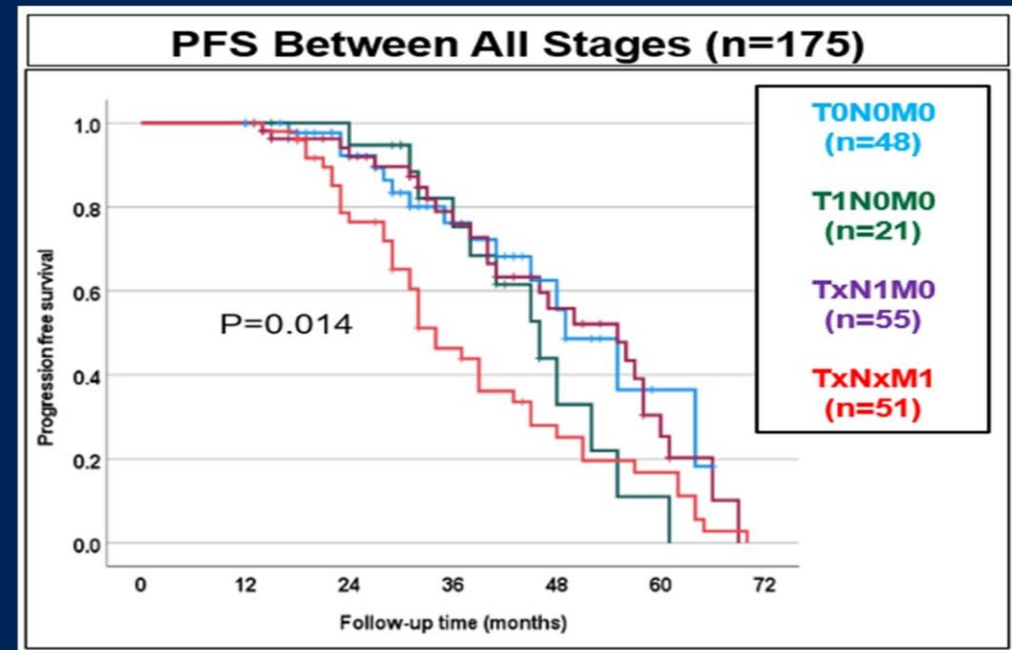
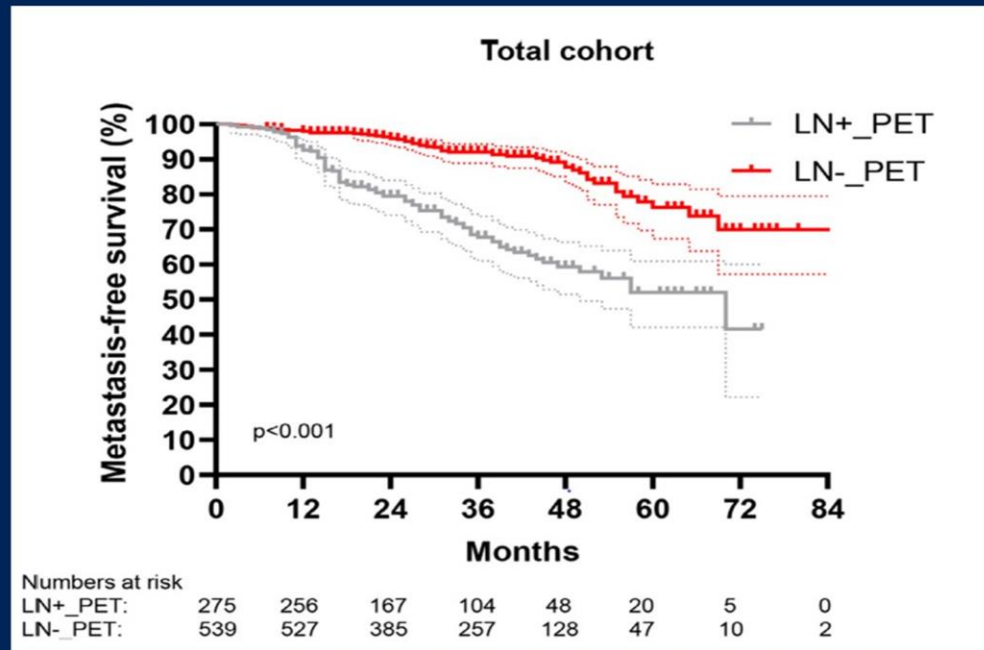


Variable	Odds ratio	Significance (<i>P</i>)
PSMA PET: negative/local, lymph nodes, distant disease	0.15	0.001
PSA at PSMA PET	0.026	0.02
pT stage	0.98	0.98
Gleason score	0.91	0.91
Surgical margins	0.80	0.80

PSMA PET negatif olması salvage RT için prediktif değeri var

PSMA PET CT pozitifliği prognostik faktör

PSMA PET Guided Salvage Radiotherapy Among Prostate Cancer Patients in the Post- Prostatectomy Setting: A Single Center Post-Hoc Analysis



Zamboglou et al. Int J Radiat Oncol Biol Phys. 2022 Aug 1; 113(5): 1015-1024

PSMA PET/CT sağkalım sonucunu etkiler

	Conventional imaging-guided (n=82)	¹⁸ F-fluciclovine- PET/CT-guided (n=83)
Age, years	61 (55–68)	61 (57–68)
Race		
White	52 (63%)	52 (63%)
African-American	29 (35%)	30 (36%)
Other	1 (1%)	1 (1%)
PSA before radiotherapy, ng/mL	0.34 (0.82)	0.34 (0.92)
Extracapsular extension	43 (52%)	39 (47%)
Seminal vesicle invasion	22 (27%)	24 (29%)
Margin-positive	41 (50%)	37 (45%)
Node-positive	14 (17%)	16 (19%)
Gleason score ≥8	29 (35%)	23 (28%)
Androgen deprivation therapy— any use	28 (35%)	30 (38%)
Androgen deprivation therapy— long-term use (18–24 months)	8 (10%)	9 (11%)

Data are median (IQR) or n (%), unless otherwise specified. PSA=prostate-specific antigen.

Table 1: Baseline characteristics of patients enrolled in the study

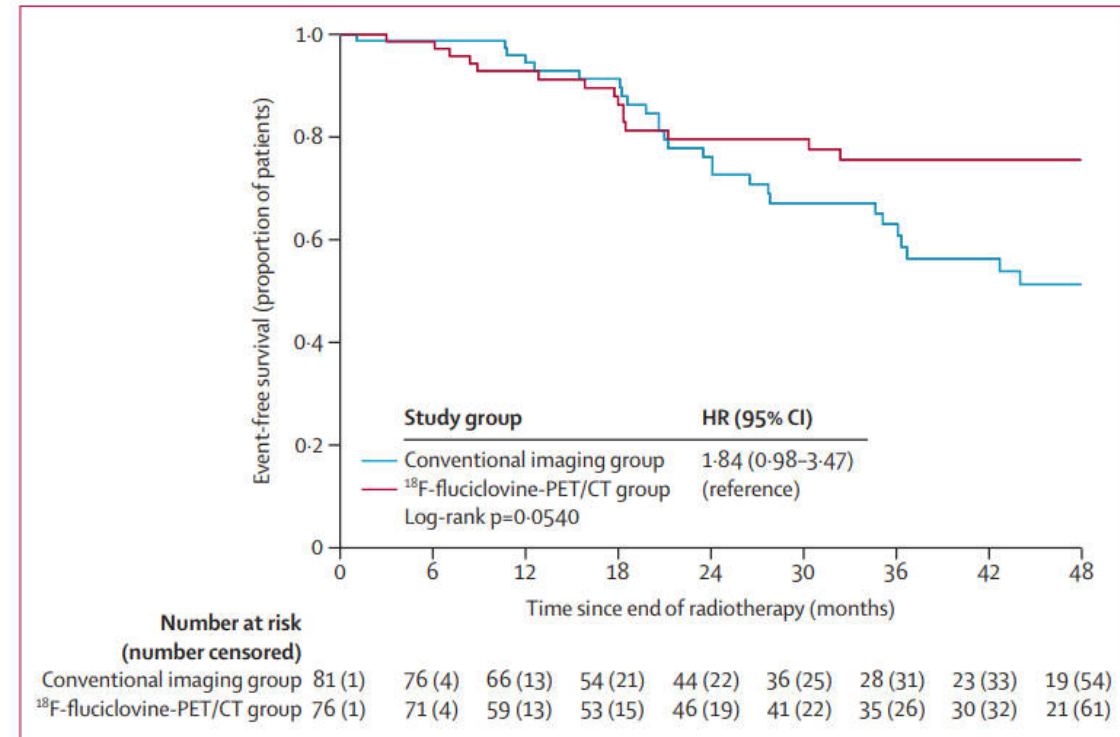


Figure 2: 3 year event-free survival

Figure shows Kaplan-Meier curves for event-free survival among the modified intention-to-treat population, consisting of all patients assigned to a study group who received radiotherapy.

¹⁸F-fluciclovine-PET/CT imaging resulted in a change of radiotherapy choice for 28 (35%) patients(4 metastases)

İdeal Evreleme Nasıl Yapılmalı

	Intermediate Risk T2b and GS7 and/or PSA 10-20	High Risk (or greater) ≥T2c or GS 9-10 or PSA>20	Biochemical Relapse / Progression
NCCN (ver 1.2023)	PSMA PET (unfavorable)	PSMA PET	PSMA PET
ESMO PAN-ASIAN ESMO	CT/MRI + Bone Scan or PSMA PET	CT/MRI + Bone Scan or PSMA PET	PSMA PET
EUA	CT/MRI + Bone Scan	PSMA PET or whole body MRI	PSMA PET

Unfavorable = ≥2 intermediate risk factors (cT2b-cT2c, GG 1 or 2, PSA 10-20) or GG3 or ≥ 50% biopsy cores positive

Lokalize Yüksek Riskli Prostat Kanseri

Regression tree
risk stratification

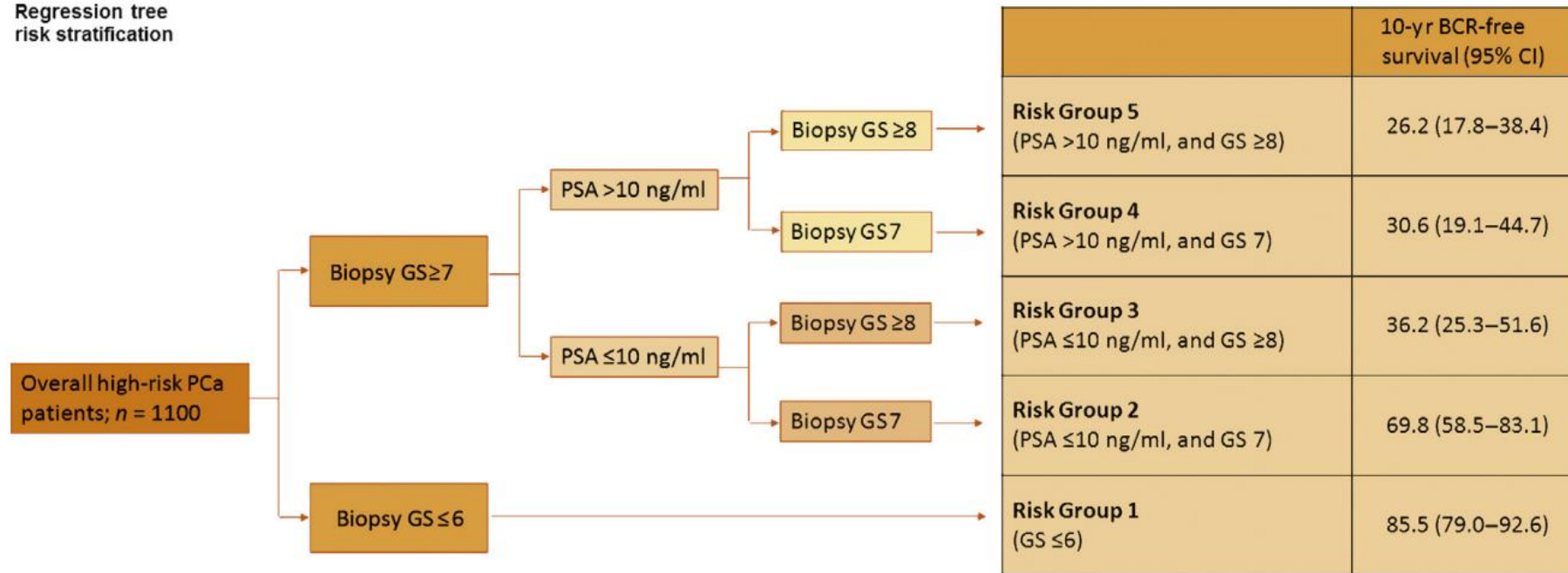


Fig. 1 – A novel biochemical recurrence risk stratification regression tree, based on the data of 1100 D’Amico high-risk prostate cancer patients treated with robot-assisted radical prostatectomy with and without lymph node dissection between 2002 and 2013 at three tertiary care centers.

BCR = biochemical recurrence; CI = confidence interval; GS = Gleason score; PCa = prostate cancer; PSA = prostate-specific antigen.

Lokalizasyon Yüksek Riskli Prostat Kanseri

(B) CR-free survival: Stratified according to novel risk-groups

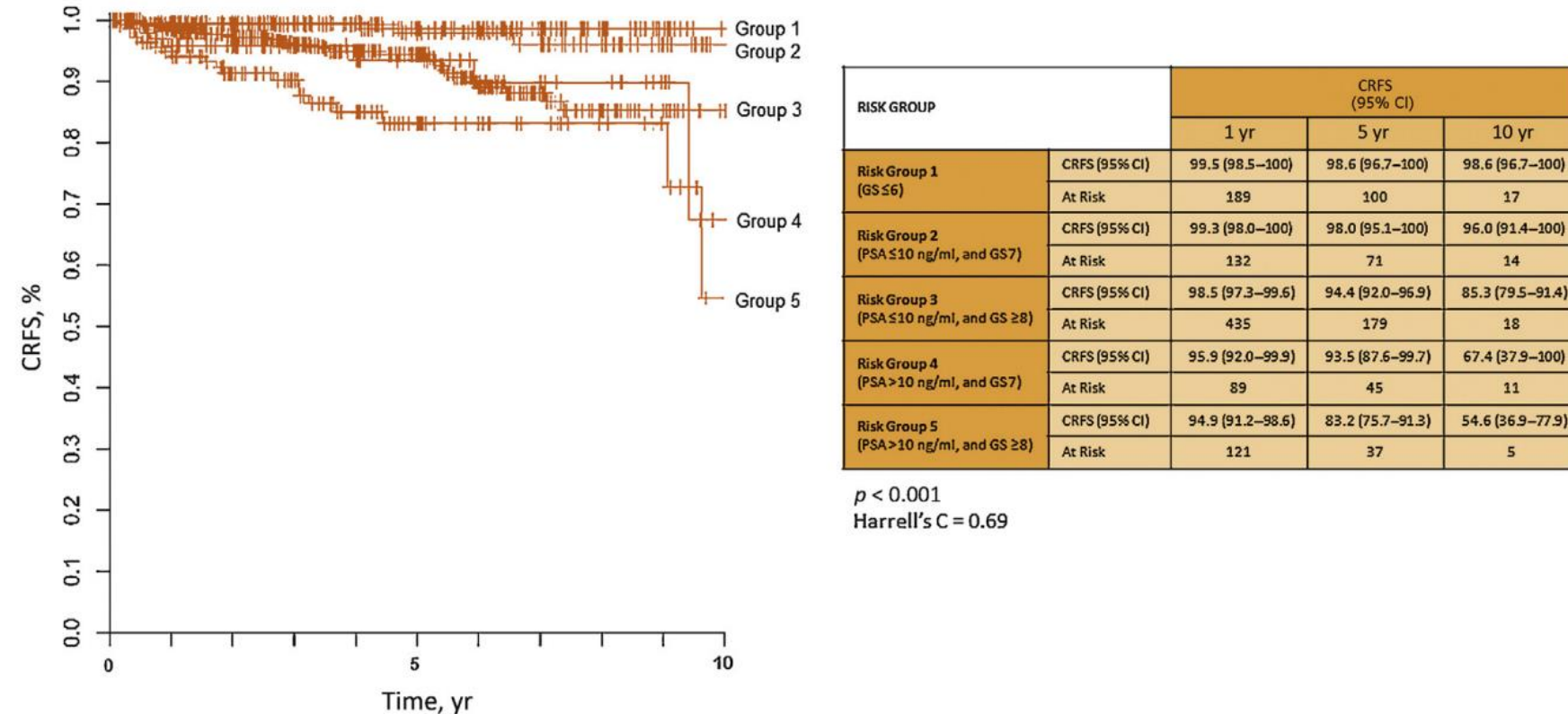


Fig. 3 – Kaplan-Meier curve for clinical recurrence-free survival in (A) the overall cohort and (B) after stratification according to the novel regression tree model.

CI = confidence interval; CRFS = clinical recurrence-free survival; GS = Gleason score; PSA = prostate-specific antigen.

Lokalize Yüksek Riskli Prostat Kanserinde Doz Yoğun Tedavi Gerekli

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

N=1974

2011, 2012, 2013, 2014, 2015, 2016



SOC: ADT x 3 years
+ RT[^]



1:1 randomisation



SOC + AAP (2y)



SOC + AAP+ENZ (2y)



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

Lokalize Yüksek Riskli Prostat Kanserinde Doz Yoğun Tedavi Gerekli

Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol



M0

No evidence of metastases on bone and CT scan of pelvis, abdo, chest
(pre-defined stratification criterion)

Newly-diagnosed

Any of:

- Node-Positive
- ≥ 2 of: Stage T3 or T4
PSA ≥ 40 ng/ml
Gleason 8, 9 or 10

Relapsing after previous RP or RT

Any of:

- Node-positive
- PSA ≥ 4 ng/ml, rising & doubling time < 6 m
- PSA ≥ 20 ng/ml

All patients

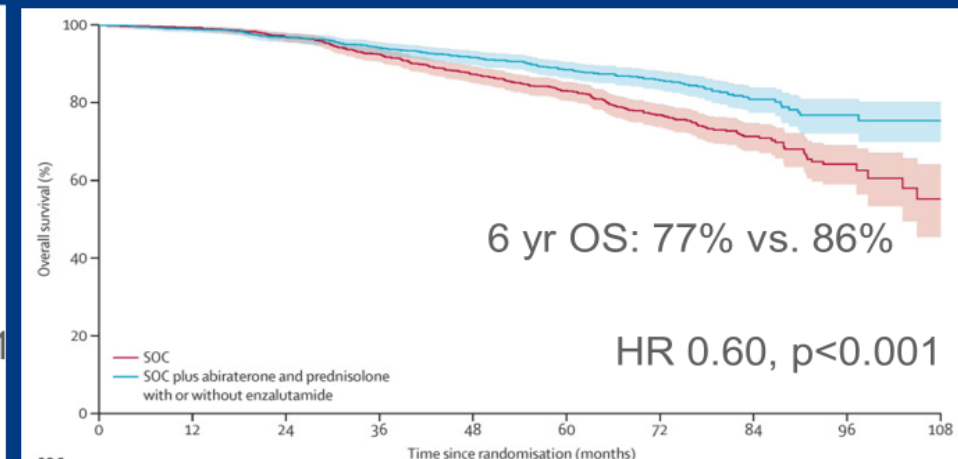
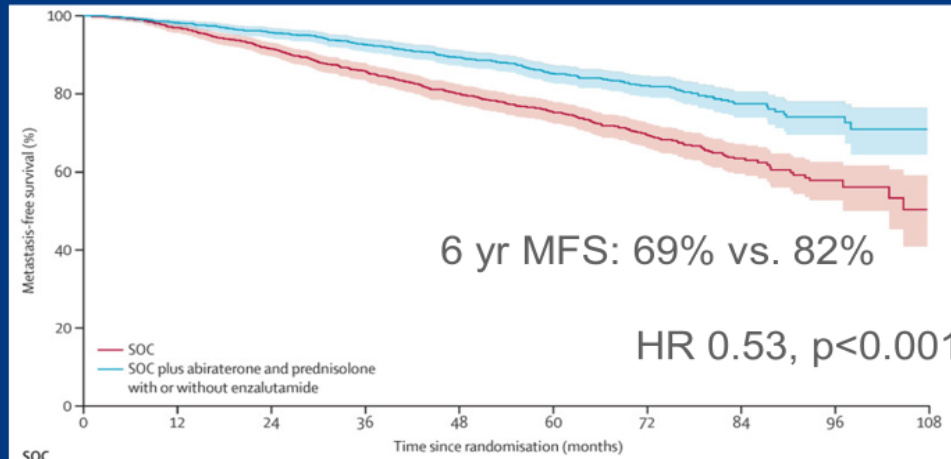
Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampededtrial.org

Lokalizasyon Yüksek Riskli Prostat Kanserinde Doz Yoğun Tedavi Gerekli

Improvement in PFS, MFS, and OS with the Addition of Abiraterone and Prednisolone 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

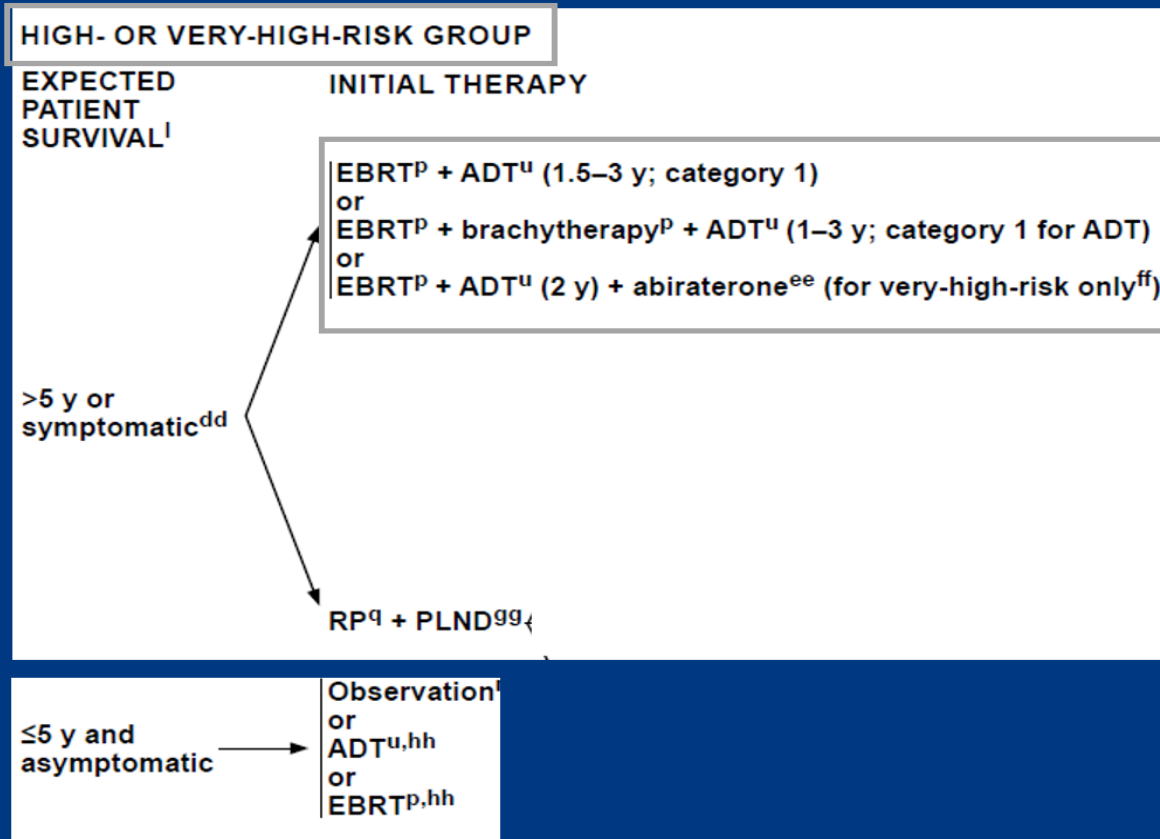
Overall survival

Median age 68. 73% T3/4. 79% G18-10. Median PSA 34. 39% Node-positive

No additional benefit to enzalutamide in addition to abiraterone.

Lokelize Yüksek Riskli Prostat Kanserinde Doz Yoğun Tedavi Gerekli

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 features
- >4 cores with Grade Group 4 or 5



National
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NCCN Guidelines Version 1.2023
Prostate Cancer

PSA persistansı olan hastalarda tedavi

Table 2 – Salvage treatments and outcomes of patients included in the 20 selected retrospective studies

Author [ref]	Comparator	Treatment received	Pre-sRT PSA level/ median time from RP to sRT	Biochemical outcomes			Metastasis-free survival			Cancer-specific survival			Overall survival			Predictive factors for survival					
				BCR rate	BCRFS	Time	95% CI	Metastasis rate	MFS	Time	95% CI	CSM rate	CSS	Time	95% CI	ACM rate	OS	Time	95% CI	Endpoint	Univariate analysis
Only pN0 included																					
Bartkowiak [12]		sRT: 100%	0.58/10 mo		49%	5 yr	NA	NA				NA			NA				BCRFS	Overall cohort	Overall cohort
																				(PSA persistence not correlated)	(PSA persistence not correlated)
																				Pre-sRT PSA Gleason score (6–7 vs >7)	Pre-sRT PSA Gleason score (6–7 vs >7)
	Versus undetectable PSA	sRT: 100%	0.27/30 mo		62%	5 yr	NA	NA												pT	pT
			p < 0.001 p = 0.250																		Risk-matched cohort (n = 224)
																				Pre-sRT PSA pT (PSA persistence not correlated)	pT stage
Fossati [17]		sRT (+ ADT): 100% (30%)	0.3*	52.4%					74% if GS 6–7 62% if GS 8–10	8 yr		NA			NA				MFS		Gleason score
										8 yr											PSA persistence PSA at sRT
			Detectable PSA: 1.0 Undetectable PSA: 0.2 p < 0.001																		ADT duration
																					Time from RP to detectable PSA
Lohm [19]		sRT: 100%	0.29		52.8%	3.5 yr		3.1%				0.6%			1.2%				BCRFS after RT	Pre-sRT PSA	
																				Gleason score (6 vs 7–10)	
	Versus undetectable PSA	sRT: 100%	0.34		65.4%	3.5 yr														PSADT	
Eisenberg [21]		NA	NA	30.4%	p = 0.215 67%	5 yr		NA				NA			NA				BCRFS		Pre-RP PSA
																					PSM
																					PSA persistence Gleason score (6 vs 7–10)

Biyokimyasal Rekürens olan hastalarda Salvage RT

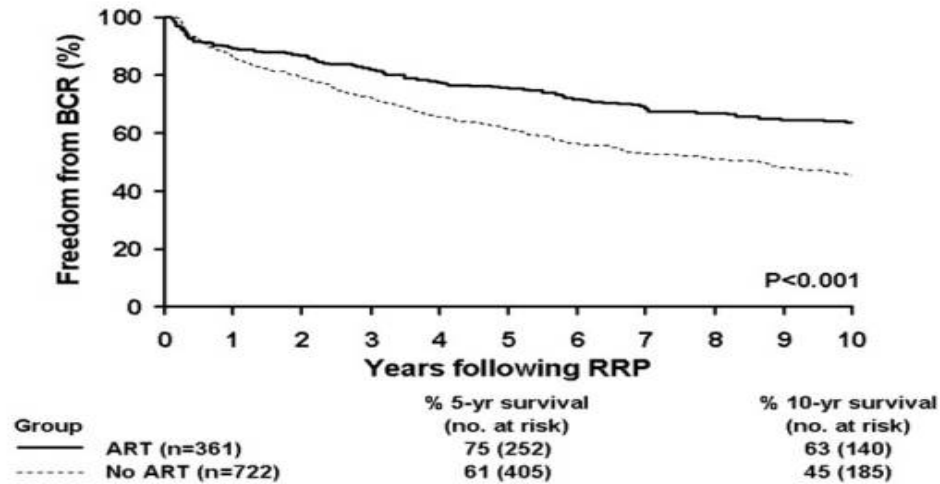


Figure 2. BCR-free survival in patients treated with ART vs controls.

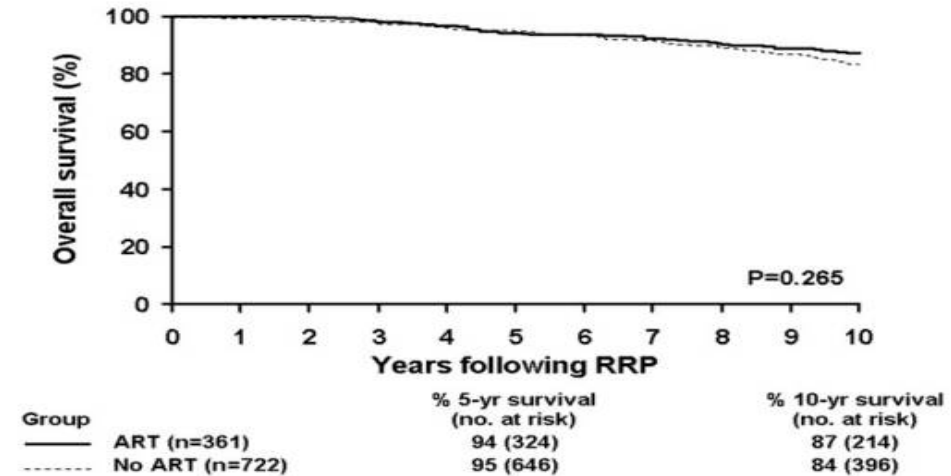


Figure 3. Overall survival in patients treated with ART vs controls.

End Point	Univariate Analysis		Multivariate Analysis*	
	HR† (95% CI)	p Value	HR† (95% CI)	p Value
BCR	0.57 (0.45–0.71)	<0.0001	0.53 (0.42–0.67)	<0.0001
Local recurrence	0.11 (0.05–0.24)	<0.0001	0.11 (0.05–0.23)	<0.0001
Systemic progression	0.97 (0.62–1.51)	0.88	0.93 (0.58–1.49)	0.76
Late ADT	0.60 (0.45–0.81)	0.0008	0.57 (0.42–0.78)	0.0003
Death from any cause	0.85 (0.63–1.15)	0.85	0.81 (0.59–1.10)	0.18

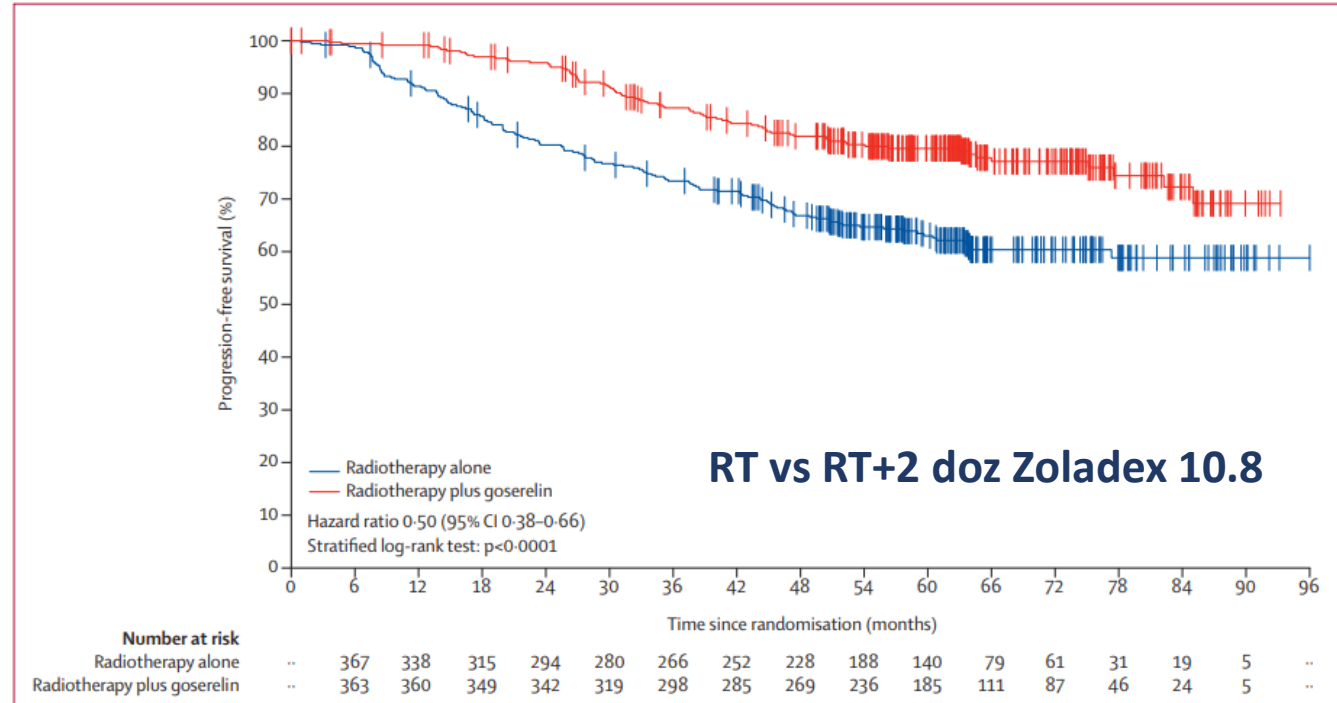
* Controlling for matching variables and late ADT.

† Association of ART and end point with no ART as referent (HR 1).

Biyokimyasal Rekürens ve PSA Persistansı

Prostat +/-pelvis RT+ADT

	Radiotherapy alone (n=373)	Radiotherapy and goserelin (n=369)
Age (years)	67 (52-85)	67 (49-80)
Gleason score		
<8	332 (89%)	329 (89%)
≥8	41 (11%)	40 (11%)
Pathological tumour stage (TNM 2005)		
pT2a	37 (10%)	29 (8%)
pT2b	76 (20%)	75 (20%)
pT2c	88 (24%)	92 (25%)
pT3a	121 (32%)	127 (34%)
pT3b	50 (13%)	44 (12%)
pT4 bladder neck involvement	0	1 (<1%)
Missing	1 (<1%)	1 (<1%)
Pathological node involvement (TNM 2005)		
pN0	274 (74%)	273 (74%)
pNX	99 (27%)	96 (26%)
Positive surgical margins	196 (53%)	175 (47%)
Seminal vesicle involvement	318 (85%)	312 (85%)
PSA doubling time >6 months	276 (74%)	270 (73%)
ECOG performance status		
0	345 (92%)	329 (89%)
1	13 (4%)	22 (6%)
Missing	15 (4%)	18 (5%)
PSA at baseline randomisation (µg/L), median (IQR)*	0.30 (0.20-0.50)	0.30 (0.20-0.50)
Time between surgery and relapse (months), median (IQR)*	29.99 (19-52)	33.98 (21-53)
Presurgery PSA (µg/L), median (IQR)†	8.10 (6-12)	8.35 (6-12)



Free-biochemical progression or clinical progression at 5 years (80% vs 62% [57-67]; HR 0.50 ; p<0.0001.

Biyokimyasal Rekürens ve PSA Persistansı Prostat +/-pelvis RT+ADT

	n	Univariate analysis		Multivariate analysis*	
		HR (95% CI)	p value†	HR (95% CI)	p value†
Age at randomisation			0.166		NS‡
≤65 years	283	Reference		Reference	
>65 years	459	0.83 (0.6–1.1)		..	
Gleason score			0.001		NS‡
<8	661	Reference		Reference	
≥8	81	1.81 (1.6–2.6)		..	
PSA at relapse (baseline)			<0.0001		<0.0001
≤0.5 µg/L	589	Reference		Reference	
0.5–1 µg/L	86	1.97 (1.4–2.8)		2.05 (1.4–3.0)	
≥1 µg/L	63	2.40 (1.6–3.6)		2.30 (1.5–3.4)	
Seminal vesicle			0.001		<0.0001
Non-involvement	630	Reference		Reference	
Involvement	112	1.88 (1.4–2.6)		1.93 (1.4–2.7)	
Surgical margins			0.003		0.010
Positive	371	Reference		Reference	
Negative	371	1.52 (1.2–1.99)		1.44 (1.1–1.9)	
PSA doubling time at relapse			0.002		0.007
≥6 months	546	Reference		Reference	
<6 months	196	1.57 (1.2–2.1)		1.48 (1.1–2.0)	
Delay between prostatectomy and recurrence			0.045		NS‡
>30 months	390	Reference		Reference	
≤30 months	348	1.32 (1.0–1.7)		..	

HR=hazard ratio. NS=non-significant. PSA=prostate-specific antigen. *Multivariate model including significant parameters at 20% significance level in the univariate procedure. †p value for overall trend on multiple categories of the predictor in the regression model. ‡Parameter not kept in the final model because of non-significant p value in the backward procedure.

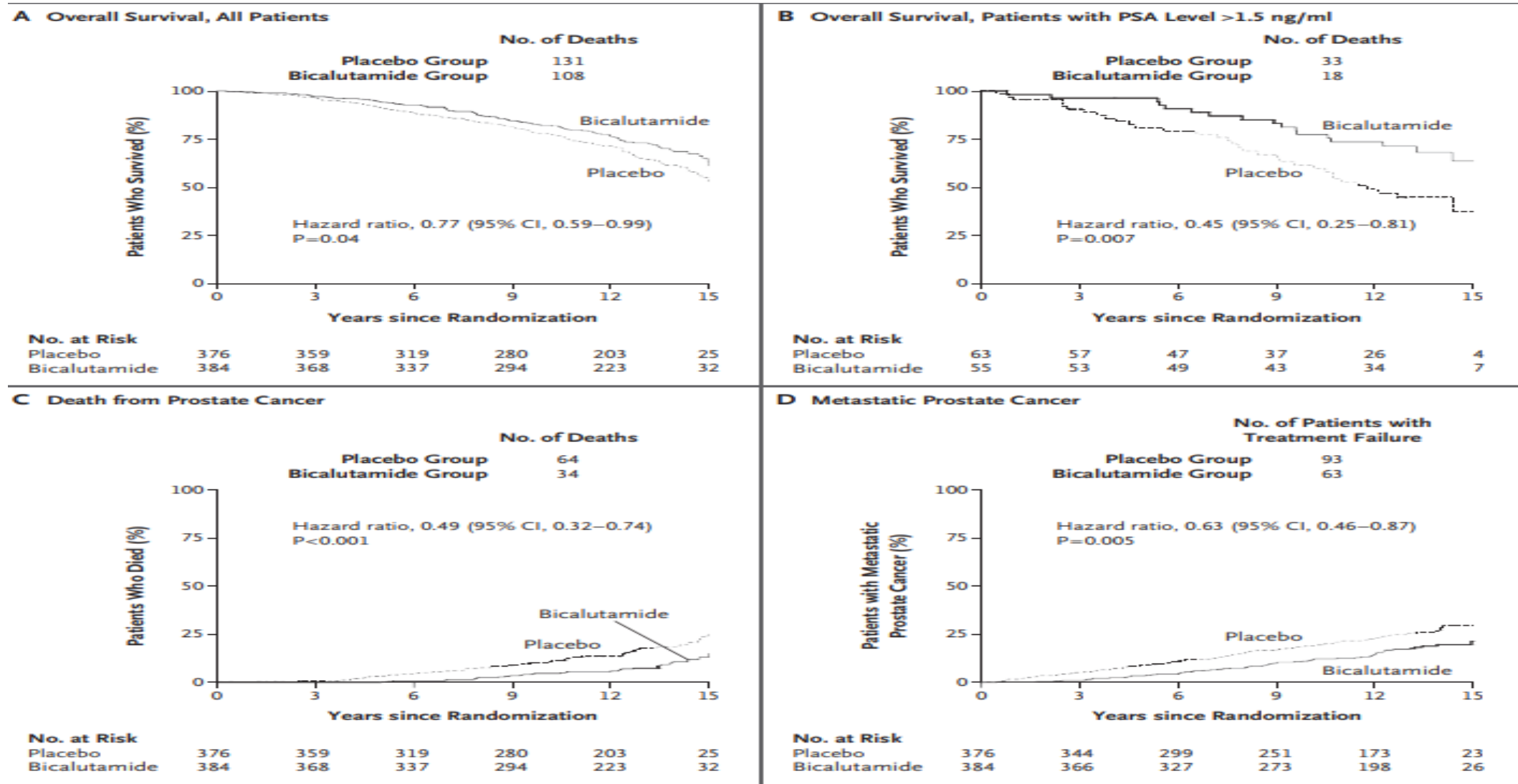
	Radiotherapy alone (n=372)		Radiotherapy plus goserelin (n=366)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Gynaecomastia	0	0	4 (1%)	0
Hot flushes	1 (<1%)	0	163 (45%)	3 (1%)
Breast pain	0	0	5 (1%)	0
Sweating	0	0	47 (13%)	1 (<1%)
Paraesthesia	0	0	0	0
Spinal-cord compression	0	0	0	0
Hypertension	1 (<1%)	0	21 (6%)	0
Muscular weakness	0	0	6 (2%)	0
Arthralgia	1 (<1%)	0	7 (2%)	0
Osteoarticular and muscular pain	6 (2%)	0	6 (2%)	0
Sexual disorders	4 (1%)	1 (<1%)	3 (1%)	0

Data are number of patients with at least one episode of that event (% of patients). No grade 4 or 5 events were reported.

Table 3: Acute adverse events previously associated with hormone therapy

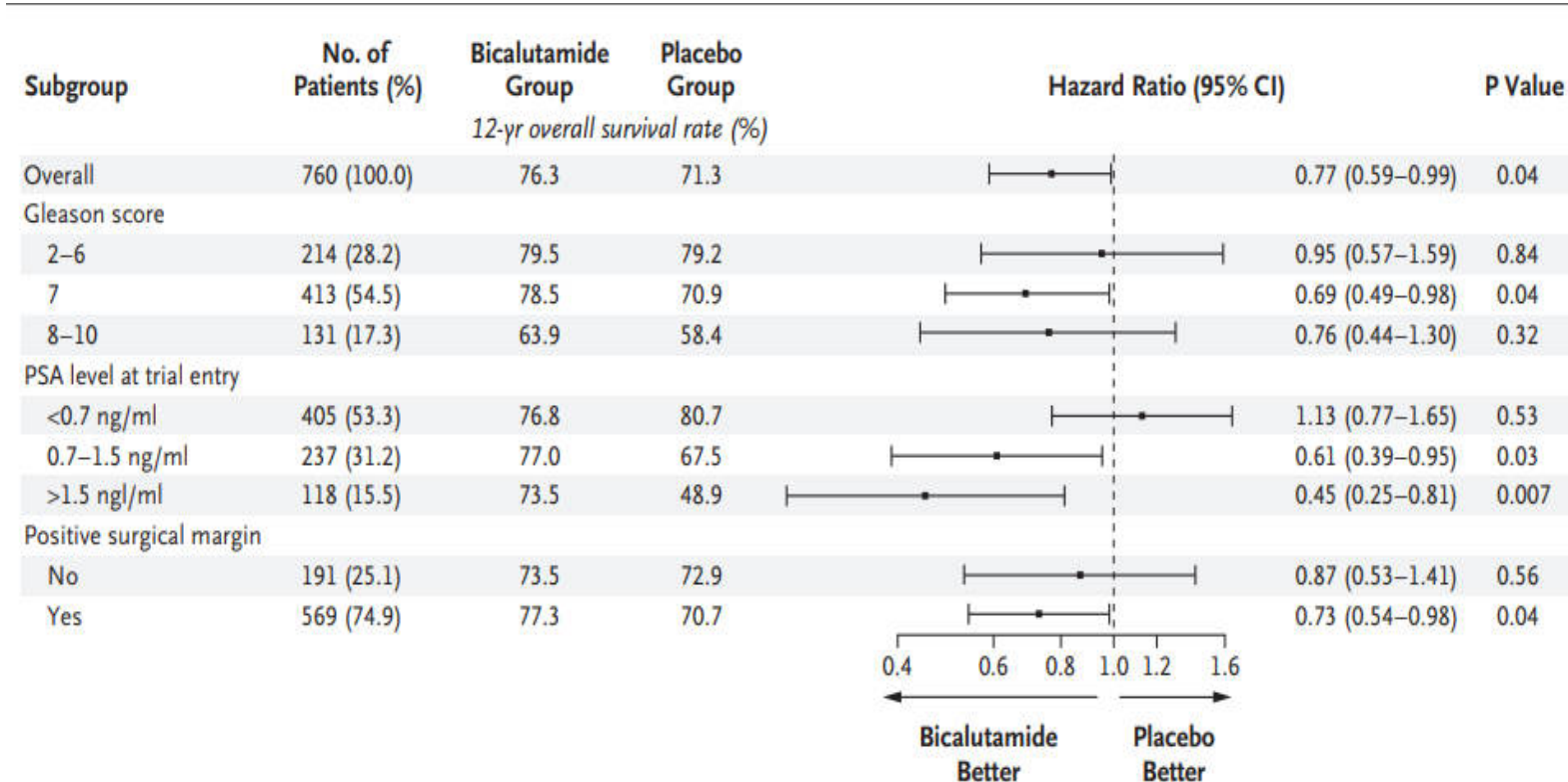
Biyokimyasal Rekürens ve PSA Persistansı

RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)



Biyokimyasal Rekürens ve PSA Persistansı

RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)



Resulting in 69.7% of the patients in the bicalutamide group having gynecomastia

The rate of cardiovascular deaths that were reported as adverse events was not significantly higher in the bicalutamide group than in the placebo group.

Biyokimyasal Rekürens ve PSA Persistansı RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)

Feng Reanalysis of RTOG 96-01 Suggests Decipher Identifies Men Who Benefit Most from ADT With Salvage RT

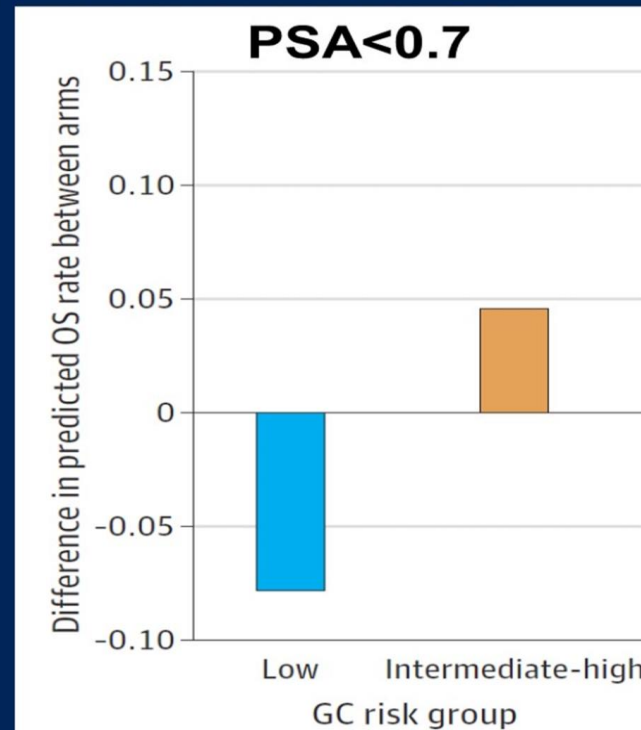
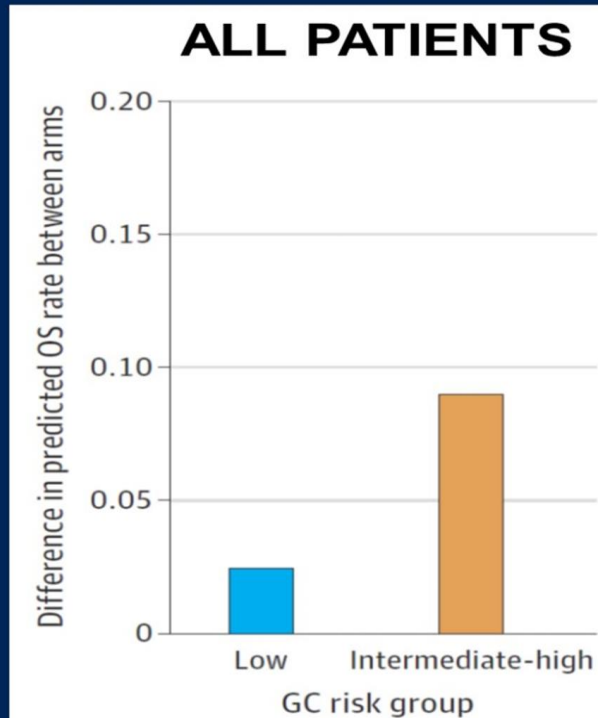
JAMA Oncology | Original Investigation

Validation of a 22-Gene Genomic Classifier in Patients With Recurrent Prostate Cancer An Ancillary Study of the NRG/RTOG 9601 Randomized Clinical Trial

Felix Y. Feng, MD; Huei-Chung Huang, MA; Daniel E. Spratt, MD; Shuang (George) Zhao, MD;
Howard M. Sandler, MD; Jeffry P. Simko, MD, PhD; Elai Davicioni, PhD; Paul L. Nguyen, MD; Alan Pollack, MD, PhD;
Jason A. Efstathiou, MD, PhD; Adam P. Dicker, MD, PhD; Tamara Todorovic, MSc; Jennifer Margrave, BSc;
Yang (Seagle) Liu, PhD; Bashar Dabbas, MD; Darby J. S. Thompson, PhD; Rajdeep Das, MD, PhD;
James J. Dignam, PhD; Christopher Sweeney, MD; Gerhardt Attard, PhD; Jean-Paul Bahary, MD;
Himanshu R. Lukka, MD; William A. Hall, MD; Thomas M. Pisansky, MD; Amit B. Shah, MD;
Stephanie L. Pugh, PhD; William U. Shipley, MD; Phuoc T. Tran, MD, PhD

Biyokimyasal Rekürens ve PSA Persistansı RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)

Among PSA <0.7, Only Decipher Int/High Has OS Benefit from ADT



Bars show %
Difference in OS
by Treatment Arm

Biyokimyasal Rekürens ve PSA Persistansı

Prostat+pelvis RT+ADT Sonuçları

1-PBRT

2-PBRT+4-6 ay
LHRH

3-PBRT+PLNRT+2-
4 ay LHRH

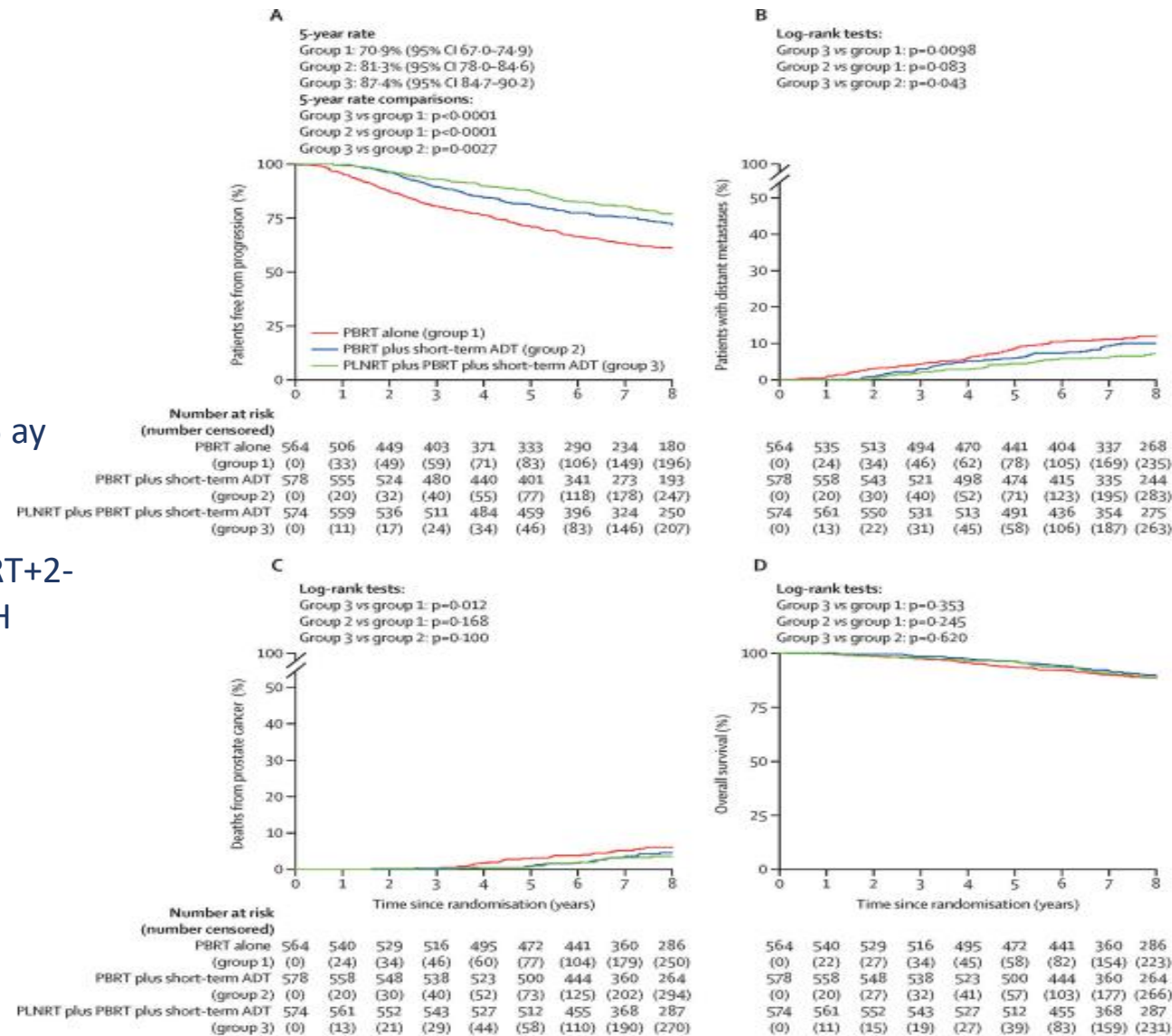


Figure 2:
Kaplan-Meier estimates and cumulative incidence curves: (A) Freedom from progression,

pT2/pT3

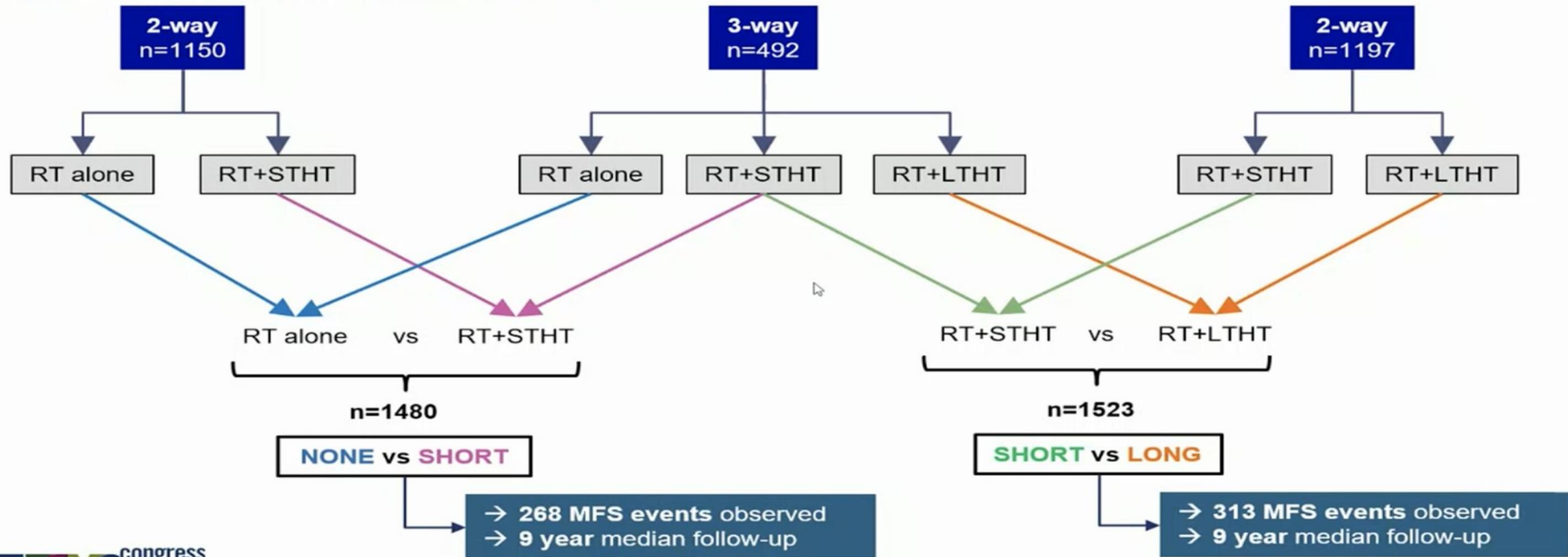
Overall, about 15% had pT3b disease, 53% had pT2 disease, 50% had positive margins, and 17% had Gleason score ≥ 8 disease. **Pelvic lymphadenectomy was done in 65%**, with a median number of lymph nodes removed of 6. The median PSA at protocol registration was 0.35 and 25% had a value of 0.2 or less.

The 5 yr FFP rates for all 1716 eligible patients were **71%, 81% and 87%** for Arms 1, 2 and 3, respectively

Acute grade 2+ and 3+ adverse events increased significantly from Arm 1 to Arm 2 to Arm 3; however, only significant late grade 2+ **blood/bone marrow events were attributable to the use of PLNRT**

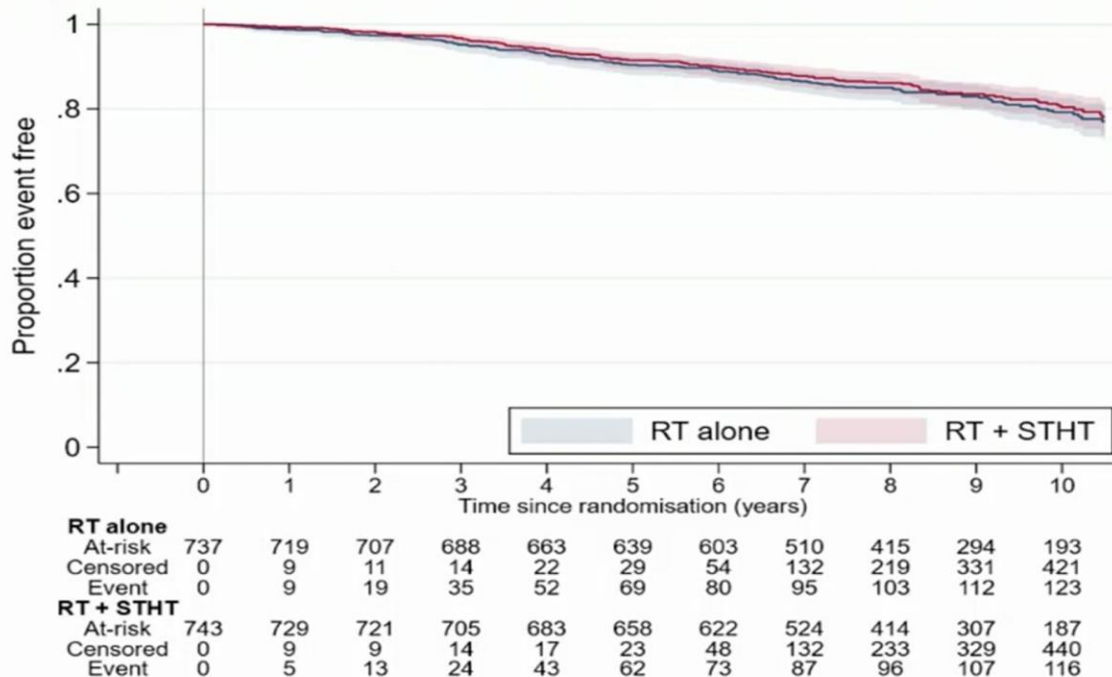
Biyokimyasal Rekürens ve PSA Persistansı RT+uzun dönem ADT

RADICALS-HD: Duration of ADT with post-op RT for prostate cancer Recruitment and Randomisation



Biyokimyasal Rekürens ve PSA Persistansı RT+uzun dönem ADT

RADICALS-HD: Duration of ADT with post-op RT for prostate cancer None vs Short: Metastases-Free Survival (MFS)



NONE vs SHORT		
	RT alone (n=737)	RT+STHT (n=743)
Events	142	126
HR (95%CI)	0.89 (0.69 to 1.14)	
P-value	0.35	
10yr event free	79%	80%

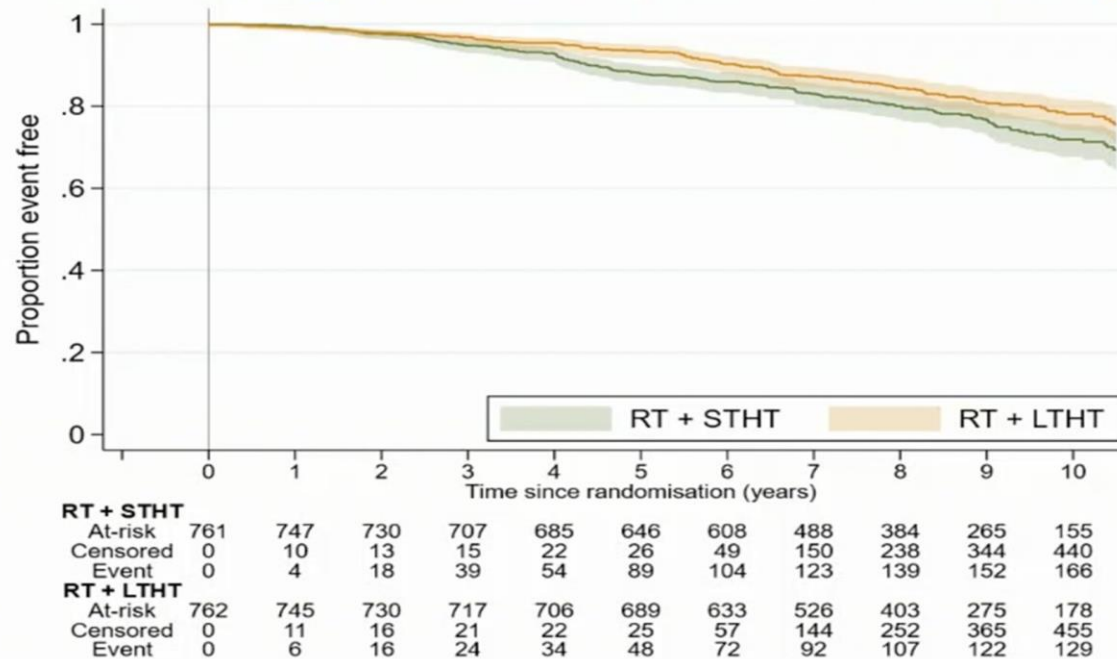
Note: HR < 1 favour RT+STHT
Note: predicted 10yr MFS = 80%

29% Received *Adjuvant RT*

11% Gleason 8-10

Biyokimyasal Rekürens ve PSA Persistansı RT+uzun dönem ADT

RADICALS-HD: Duration of ADT with post-op RT for prostate cancer Short vs Long: Metastases-Free Survival (MFS)



SHORT vs LONG

	RT+STHT (n=761)	RT+LTHT (n=762)
Events	174	139
HR (95%CI)	0.77 (0.61 to 0.97)	
P-value	0.03	
10yr event free	72%	78%

Note: HR < 1 favour RT+LTHT
Note: predicted 10yr MFS = 75%

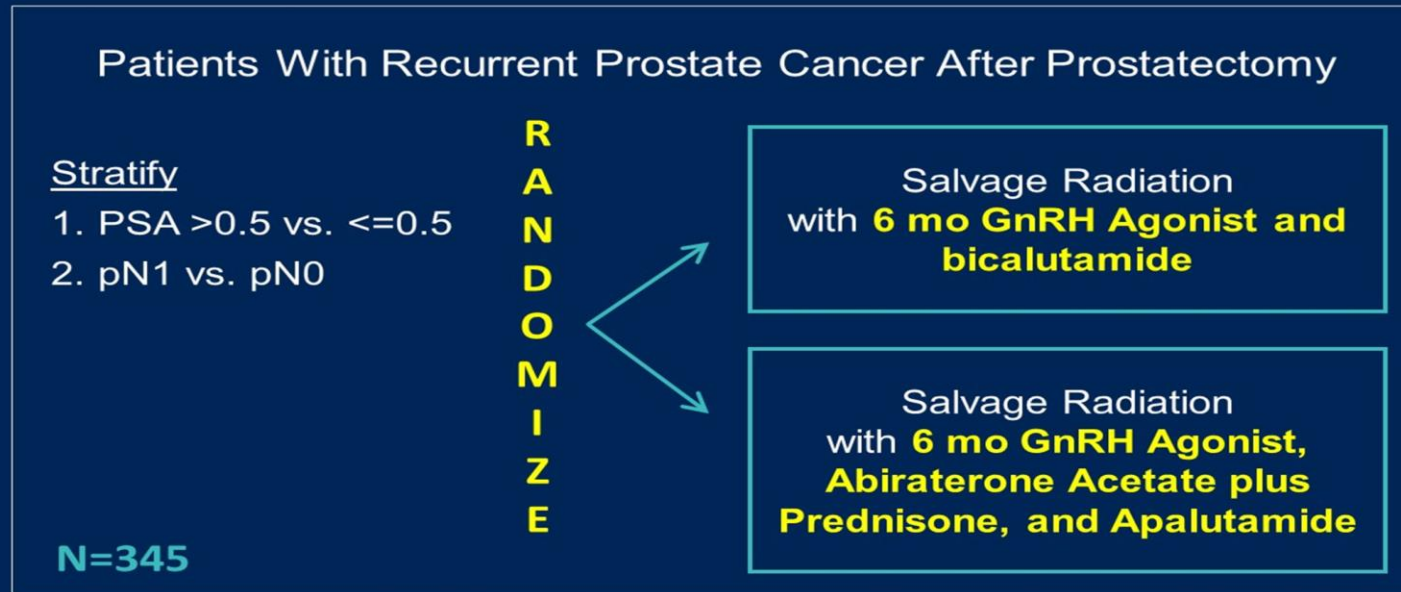
43% Received *Adjuvant RT*
28% Gleason 8-10

İzole PSA nüksünde hangi hastalar tedavi edilmeli

Risk group	Characteristics
BCR after radical prostatectomy	
Low-risk BCR	PSA-DT >1 yr and pGS <8 (ISUP grade <4)
High-risk BCR	PSA-DT ≤1 yr or pGS 8–10 (ISUP grade 4–5)
BCR after radiation therapy	
Low-risk BCR	IBF > 18 mo and bGS <8 (ISUP grade <4)
High-risk BCR	IBF ≤ 18 mo or bGS 8–10 (ISUP grade 4–5)
BCR = biochemical recurrence; PSA-DT = prostate-specific antigen doubling time; pGS = pathological Gleason score; ISUP = International Society of Urological Pathology; IBF = interval from primary therapy to biochemical failure; bGS = biopsy Gleason score.	

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

FORMULA 509 Schema



Primary outcome: Progression-free survival

Secondary outcomes: Metastasis-free survival, Physician-reported toxicity,
Patient-reported toxicity



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Patient Characteristics

	ADT + Bical (N=172)	ADT + AAP/Apa (N=173)	Overall (N=345)
Age at Enrollment			
Mean (SD)	64.2 (6.8)	63.2 (7.4)	63.7 (7.1)
Median (Range)	65.0 (47.1 – 78.9)	63.0 (43.6 – 81.8)	64.7 (43.6 – 81.8)
Race			
Asian	2 (1.2%)	4 (2.3%)	6 (1.7%)
Black	18 (10.5%)	13 (7.5%)	31 (9.0%)
White	146 (84.9%)	150 (86.7%)	296 (85.8%)
More than one race	3 (1.7%)	2 (1.2%)	5 (1.5%)
Other	3 (1.7%)	4 (2.3%)	7 (2.0%)
Gleason Score			
6	2 (1.2%)	2 (1.1%)	4 (1.2%)
7	86 (50.0%)	96 (55.5%)	182 (52.7%)
8	17 (9.9%)	20 (11.6%)	37 (10.7%)
9	67 (38.9%)	54 (31.2%)	121 (35.1%)
10	0 (0%)	1 (0.6%)	1 (0.3%)
PSA at Enrollment			
Mean (SD)	0.9 (1.7)	0.8 (1.6)	0.9 (1.6)
Median (Range)	0.3 (0 – 11.58)	0.3 (0.1 – 9.1)	0.3 (0 – 11.58)
Pathologic Nodal Status			
pN0	123 (71.5%)	123 (71.1%)	246 (71.3%)
pN1	49 (28.5%)	50 (28.9%)	99 (28.7%)

- Median age 65
- 35% Gleason 9
- Median PSA 0.3
- 31% PSA >0.5
- 29% pN1



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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Radiation Treatment

	ADT + Bical (N=172)	ADT + AAP/Apa (N=173)	Overall (N=340*)
Radiation Dose Median	69.2 Gy	68.4 Gy	68.4 Gy
Pelvic Nodal Treatment Yes	40 (23.5%)	49 (28.8%)	89 (26.2%)
No	130 (76.5%)	121 (71.2%)	251 (73.8%)

*5 pts without
radiation details

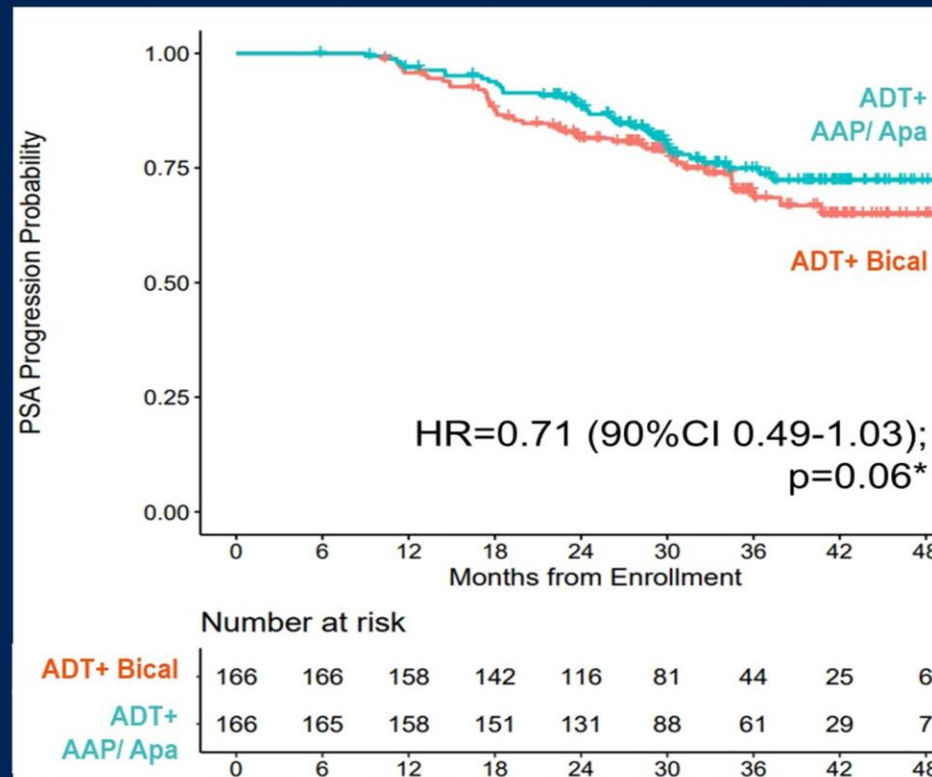


Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

9

Progression Free Survival

- Median follow-up 34 months [range 6-53]



3 year PFS
74.9% vs. 68.5%

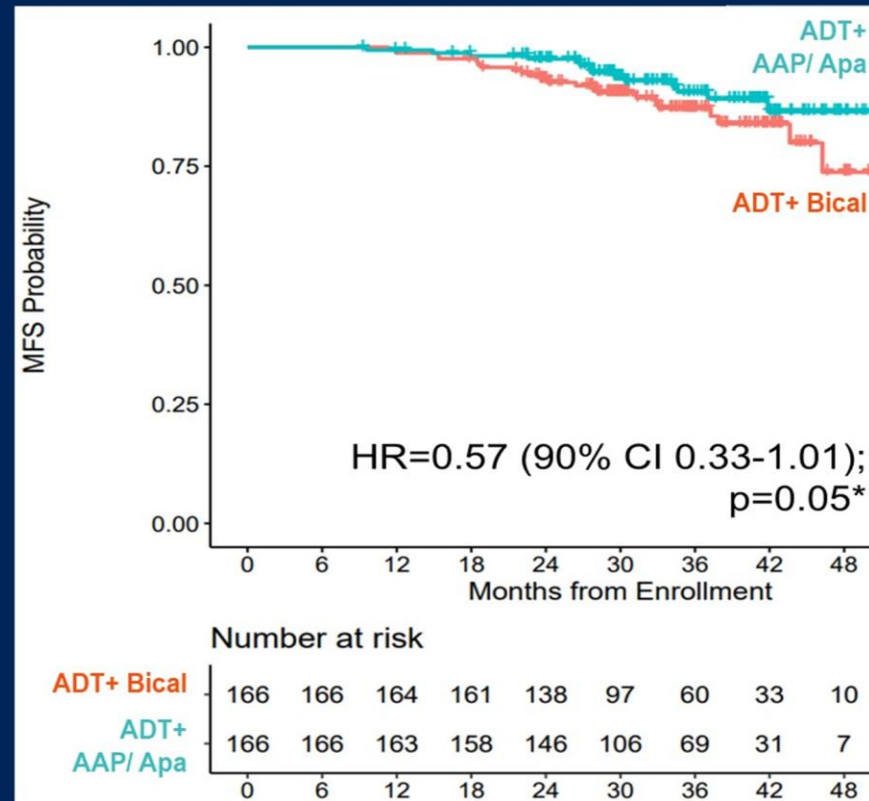
*one-sided



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Metastasis-Free Survival

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3 year MFS
90.6% vs. 87.2%

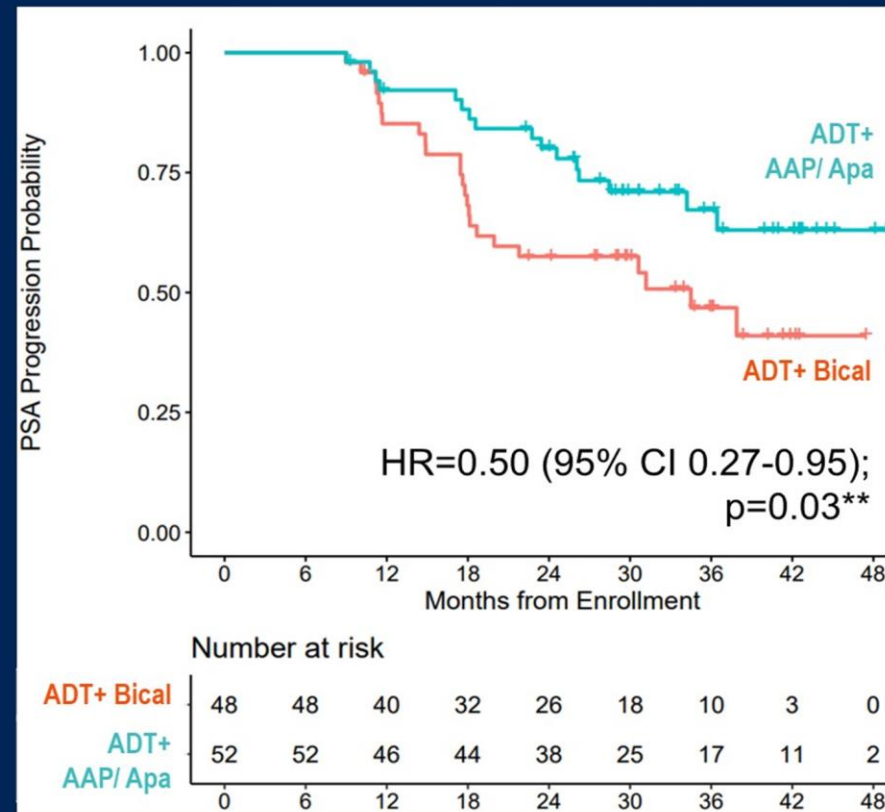
*one-sided



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PFS Benefit Among PSA >0.5 (n=100)

11



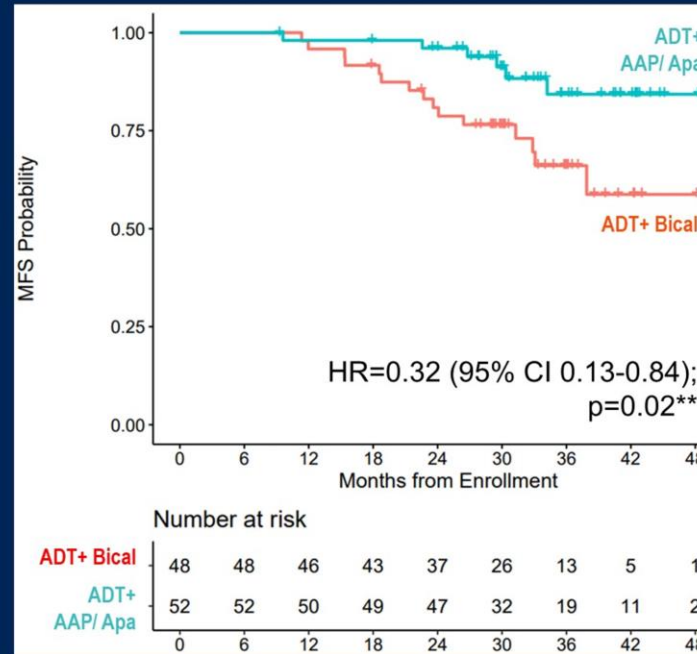
3 year PFS
67.2% vs. 46.8%

**two-sided



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

MFS Benefit Among PSA >0.5 (n=100)



3 year MFS
84.3% vs. 66.1%

Absolute improvement
18.2% at 3 years

NNT = 5

**two-sided



ASCO Genitourinary
Cancers Symposium

#GU23

PRESENTED BY: Paul Nguyen, MD, MBA; FORMULA 509 Trial
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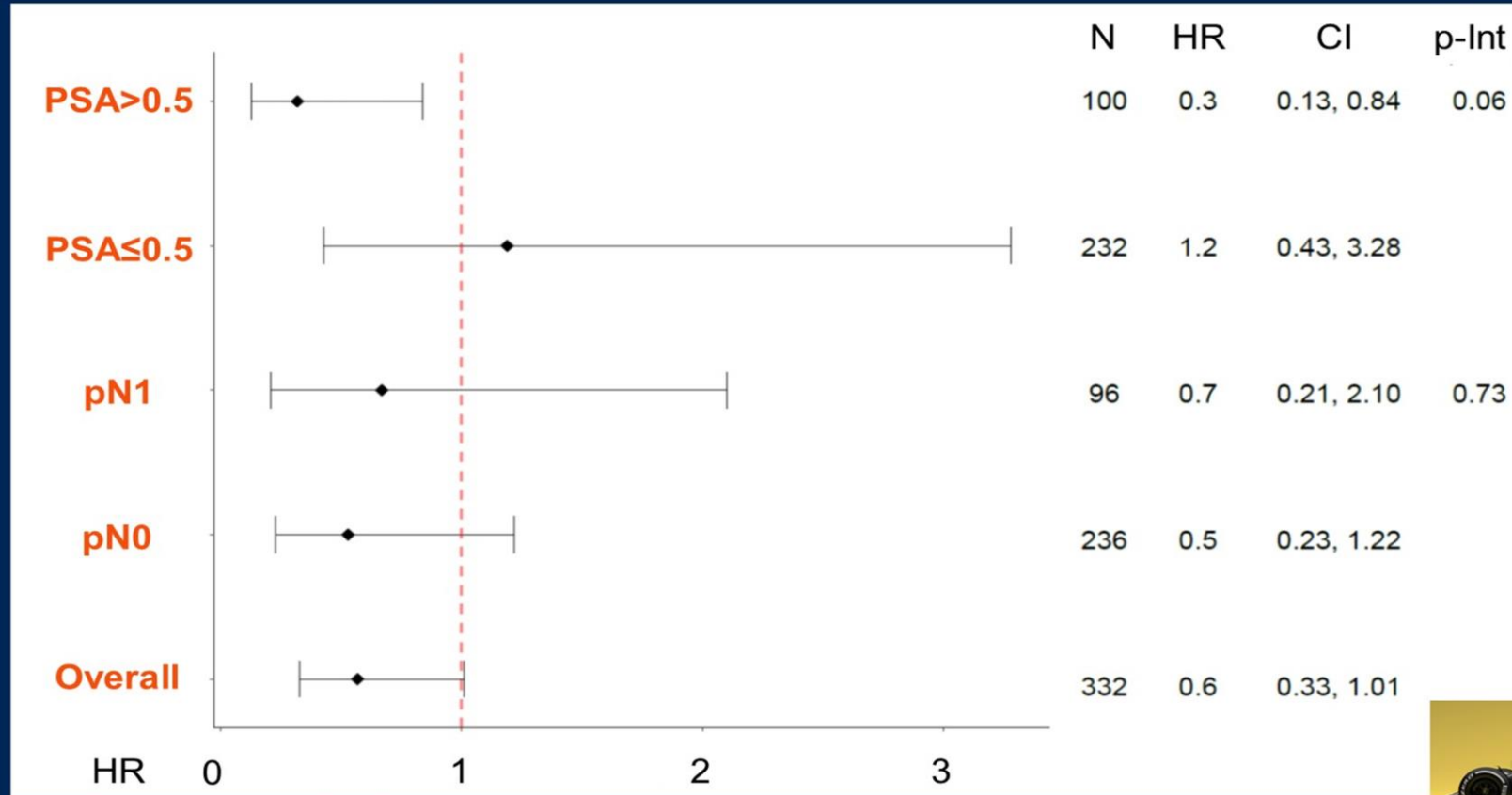
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Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

MFS Results by Pre-Planned Stratified Subgroups

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Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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Comparison of FORMULA-509 & RADICALS-HD

	Trial	Experimental ADT Arm	MFS HR vs 6 mos of ADT
All Patients	RADICALS HD	24 mos ADT	0.77, p=0.03**
	FORMULA-509	6 mos ADT/AAP/Apa	0.57, p=0.05*
PSA>0.5 Subgroup	RADICALS HD	24 mos ADT	0.67, p=0.04**
	FORMULA-509	6 mos ADT/AAP/Apa	0.32, p=0.02**

*one-sided
**two-sided

- For patients with higher risk features intensifying 6 months of ADT may be an appealing alternative to lengthening ADT duration to 24 months
- This concept will be tested in the PROSTATE-IQ Study
 - PIs Karen Hoffman (MDACC) & Marisa Kollmeier (MSKCC) & Paul Nguyen

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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6 Months of ADT+AAP+Apa May be Another Way to Intensify Beyond 6 Months of ADT

Trial	Experimental ADT Arm	MFS HR vs 6 mos of ADT
RADICALS HD all patients	24 mos ADT	0.77, p=0.03**
FORMULA-509 all patients	6 mos ADT/AAP/Apa	0.57, p=0.05*
RADICALS HD PSA>0.5 Subgroup	24 mos ADT	0.67, p=0.04**
FORMULA-509 PSA>0.5 subgroup	6 mos ADT/AAP/Apa	0.32, p=0.02**

*one-sided
**two-sided

- This concept will be tested in the PROSTATE-IQ Study
 - PIs Karen Hoffman (MDACC) & Marisa Kollmeier (MSKCC) & Paul Nguyen

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

63

New Paradigm For ADT With Post-op Salvage RT Now Mirrors ADT With Intact Prostate RT (At Last)

	LOW RISK	INTERMEDIATE RISK	HIGH RISK
INTACT PROSTATE	NO ADT	Short Term ADT	Long Term ADT
POST-OP PROSTATE	NO ADT	Short Term ADT	Long Term ADT

RISK DEFINED BY COMBINATION OF CLINICAL AND GENOMIC/PATH AI FEATURES

RISK CUTPOINTS WILL BE DIFFERENT FOR INTACT VS POST-OP

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

64

New Paradigm For ADT With Post-op Salvage RT Now Mirrors ADT With Intact Prostate RT (At Last)

	LOW RISK	INTERMEDIATE RISK	HIGH RISK
INTACT PROSTATE	NO ADT	Short Term ADT	Long Term ADT
POST-OP PROSTATE	NO ADT	Short Term ADT	Long Term ADT ??6 mos ADT +AAP/Apa??

RISK DEFINED BY COMBINATION OF CLINICAL AND GENOMIC/PATH AI FEATURES

RISK CUTPOINTS WILL BE DIFFERENT FOR INTACT VS POST-OP

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

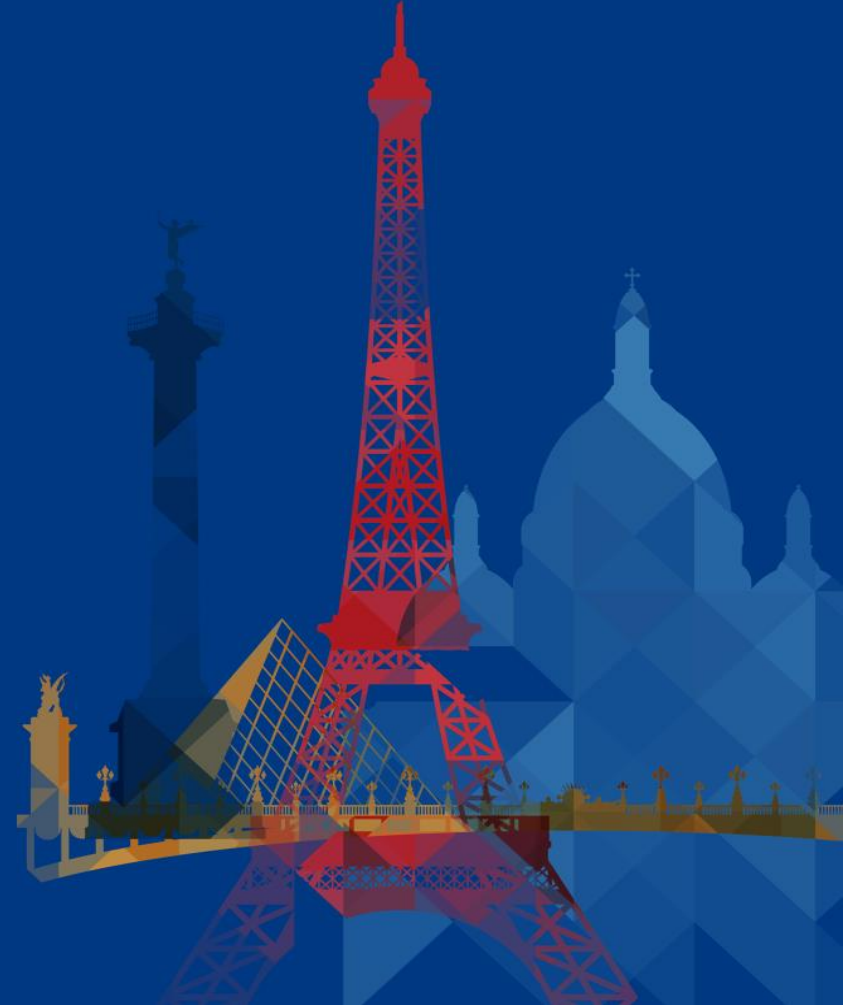
PARIS
2022

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



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Study Schema

Prior radical
prostatectomy

Biochemical recurrence
with PSA > 0.5 ng/mL

PSA-DT ≤ 9 months

No metastases on
conventional imaging

Last dose of ADT > 9
months prior to study
entry

Serum T > 150 ng/dL

Randomize 1:1:1

Arm A:
LHRH Analog

Arm B:
LHRH Analog +
Apalutamide

Arm C:
LHRH Analog +
Apalutamide + Abiraterone
Acetate + Prednisone

Follow up for PSA
Progression

Treatment per Investigator
Discretion

Long Term Follow Up

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

52 Weeks

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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

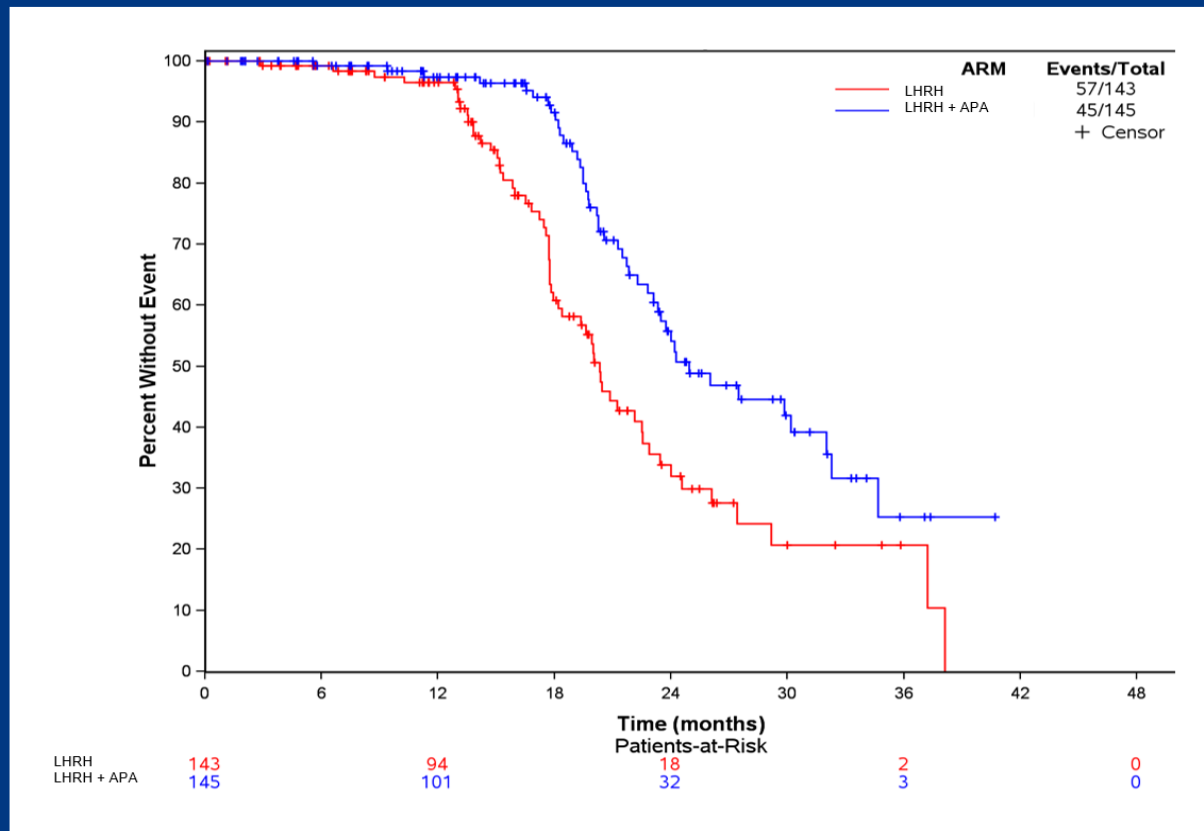
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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)

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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)

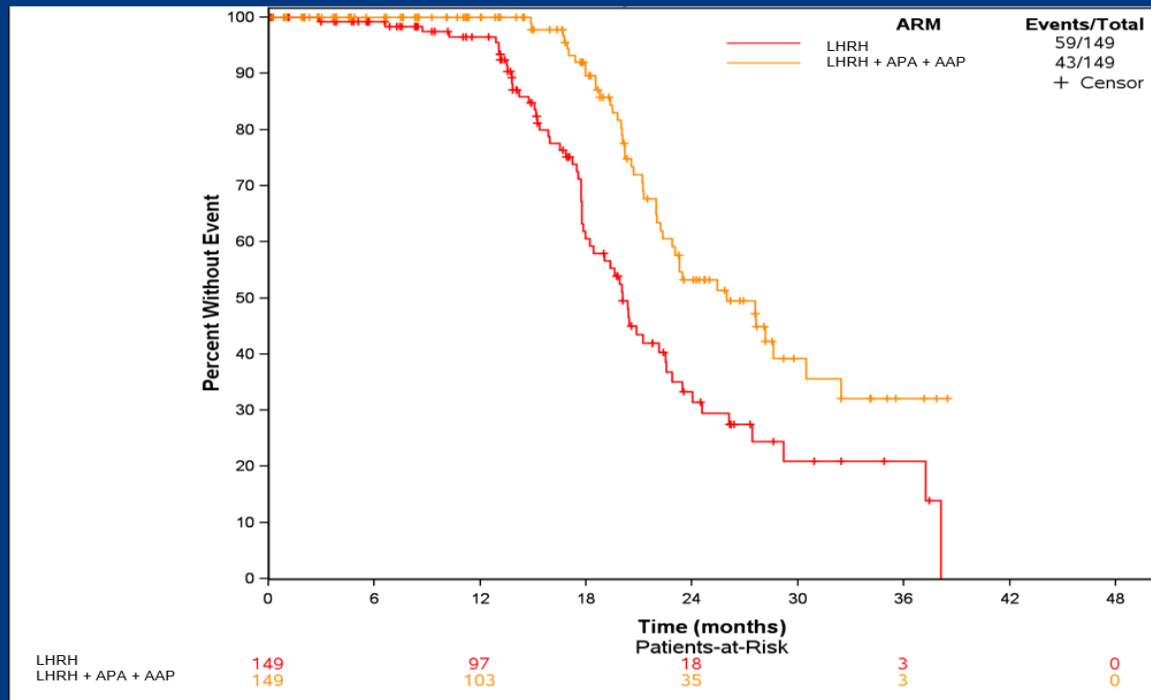
ADT alone = 20.3 months
(95% CI: 18.2 – 22.9)

**Hazard ratio 0.52 (95%
CI: 0.35 – 0.77)**

One-sided p-value =
0.00047)

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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



Median follow up 21.3 months

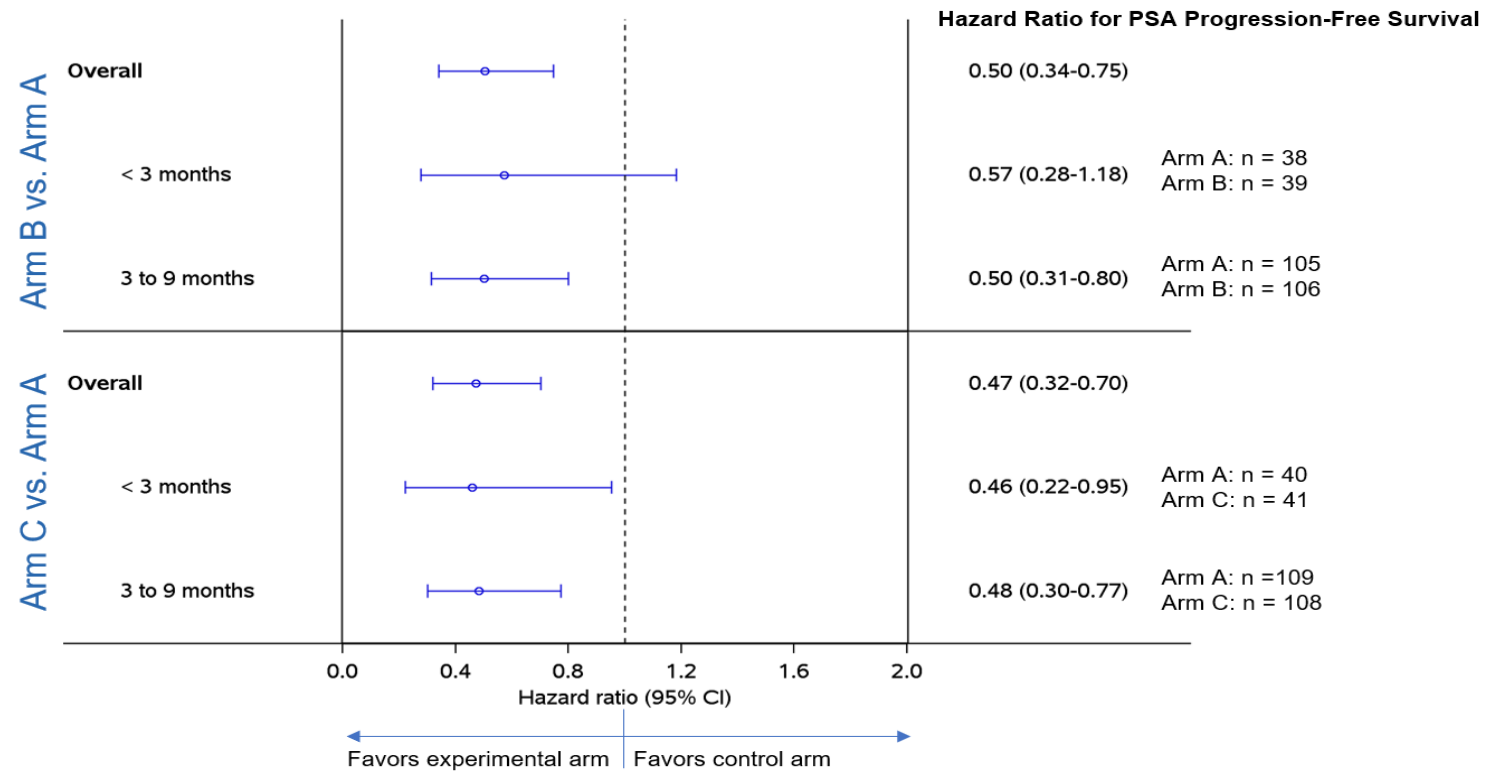
102 PSA PFS events

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PSA Progression-Free Survival by PSA Doubling Time



Biyokimyasal Rekürens ve PSA Persistansı

Doz Yoğun Tedavi

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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EMBARK study design

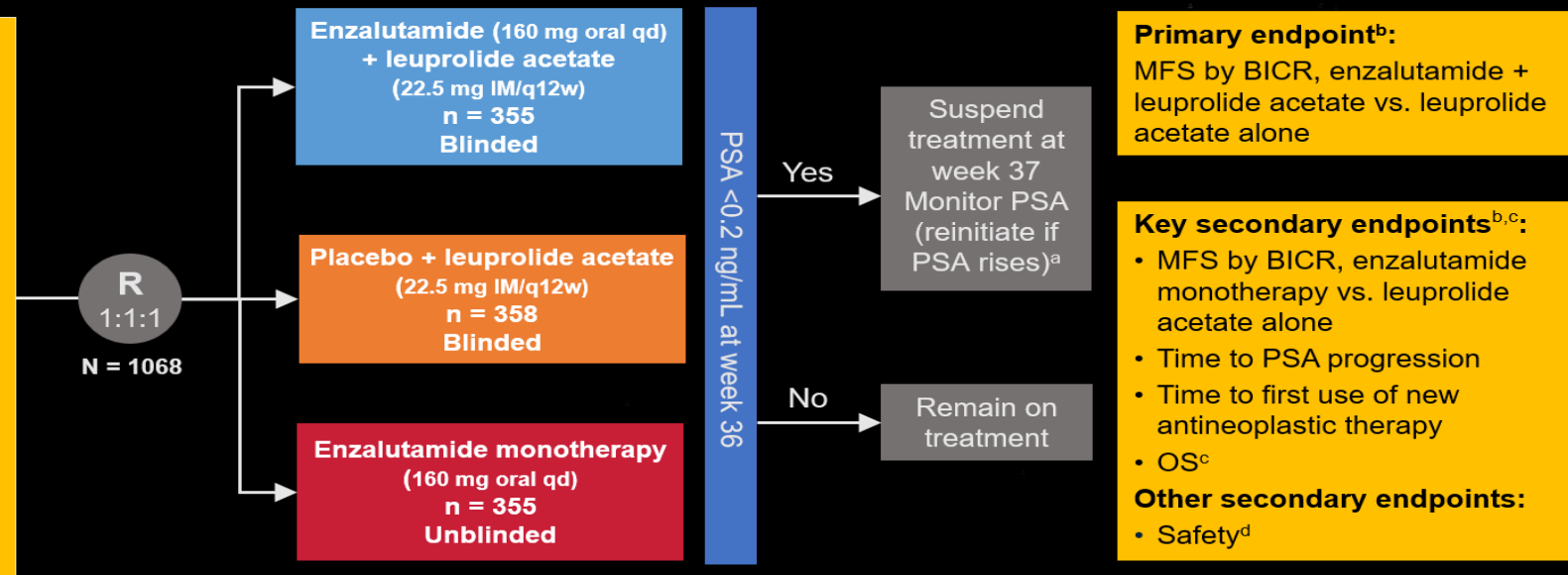


Patient population:

- 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)



^aStudy 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). ^bIntent-to-treat population. ^cPrimary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. ^dP-value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. ^eSafety 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.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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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)

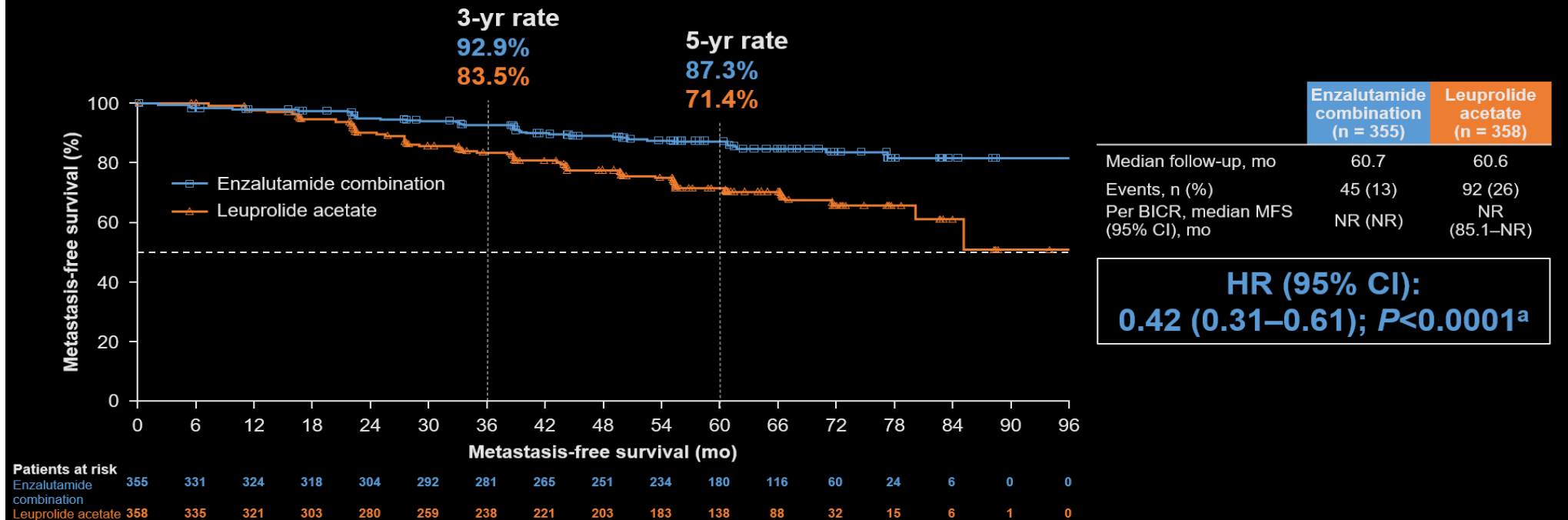
^aNot reported included: enzalutamide combination, n = 10 (2.8%); leuprolide acetate, n = 5 (1.4%); enzalutamide monotherapy, n = 14 (3.9%). ^bIncludes patients who identified as multiple races (enzalutamide combination, n = 5; leuprolide acetate, n = 9; enzalutamide monotherapy, n = 5), American Indian 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). ^cMissing included n = 1 (0.3%) for each treatment group. ^dMissing included: leuprolide acetate, n = 2; enzalutamide monotherapy, n = 1. RT, radiation therapy; yr, year.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



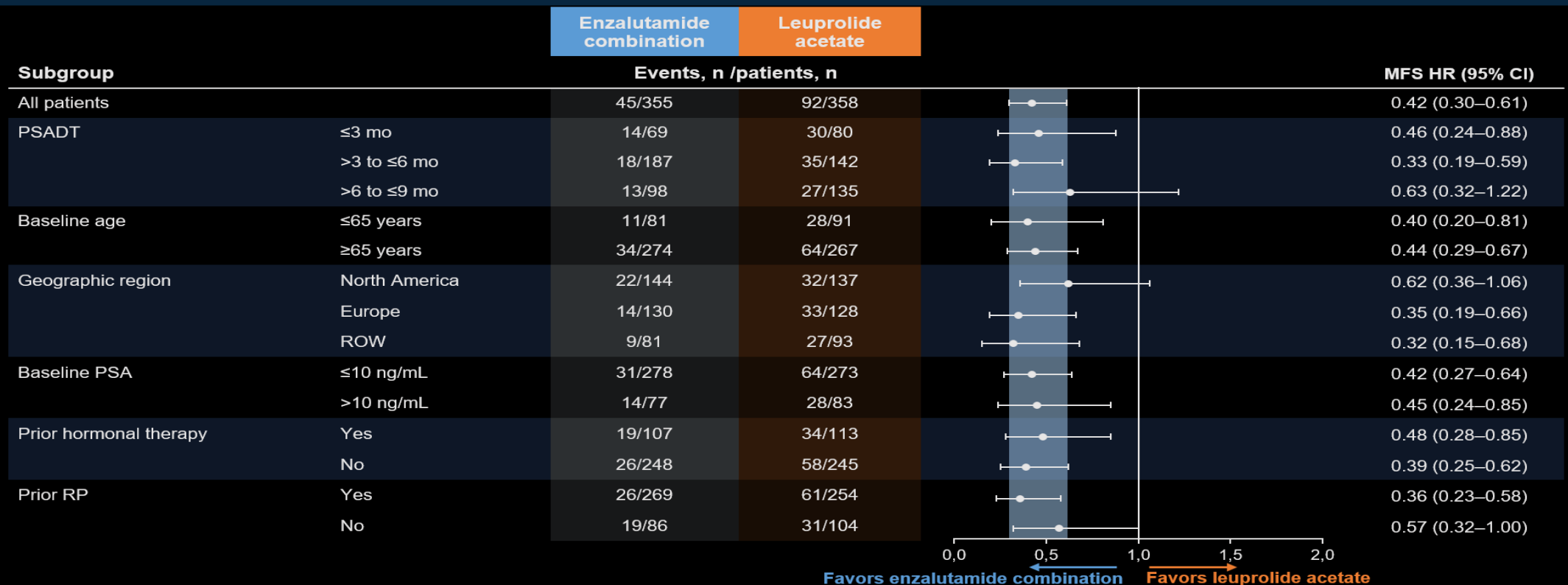
A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); $P < 0.0001$

Data cutoff: January 31, 2023. Symbols indicate censored data. ^aHR 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.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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Subgroup analysis of MFS for enzalutamide combination vs. leuprolide acetate



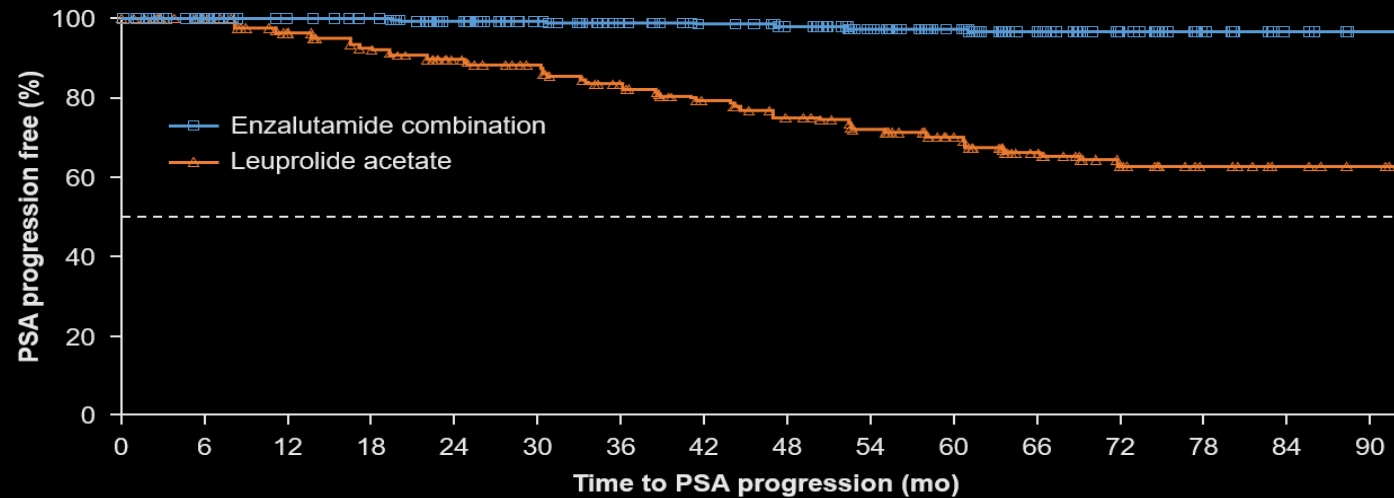
Data cutoff: January 31, 2023. For all patients, HR and 95% CI are based on stratified Cox regression model stratified by randomization stratification factors; for subgroups, HR and 95% CI are based on unstratified Cox regression model.

Shore N et al. AUA 2023; Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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



	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); $P < 0.0001^a$**

Patients at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
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

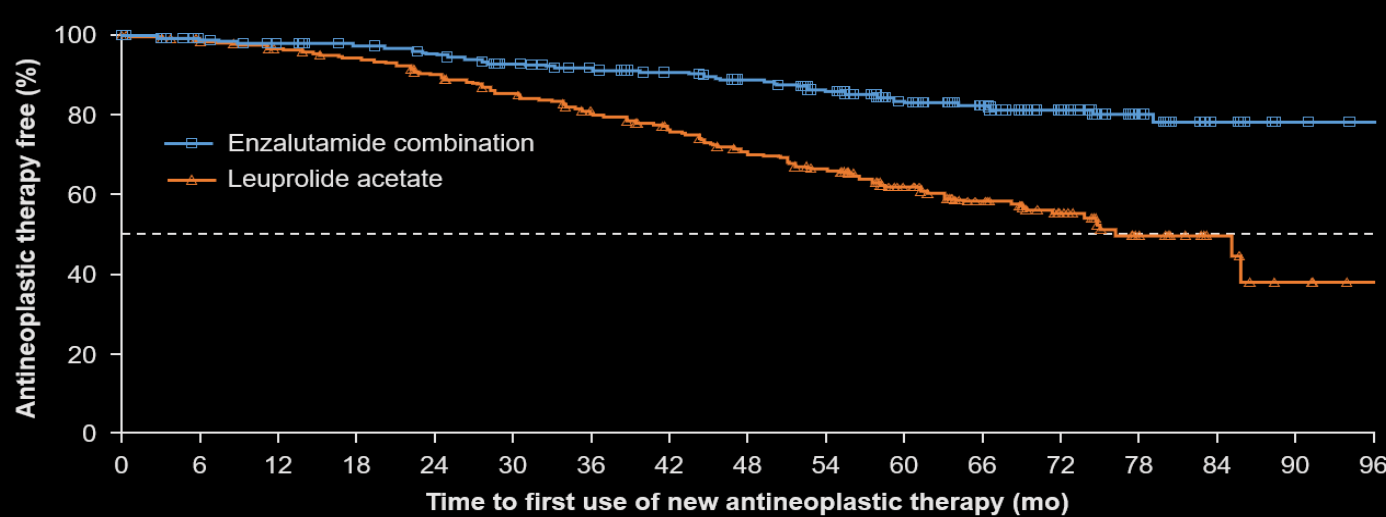
Data cutoff: January 31, 2023. Symbols indicate censored data. ^aThe HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination;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

Shore N et al. AUA 2023; Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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



	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); $P < 0.0001^a$**

Time to first use of new androgenic therapy (mo)																	
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

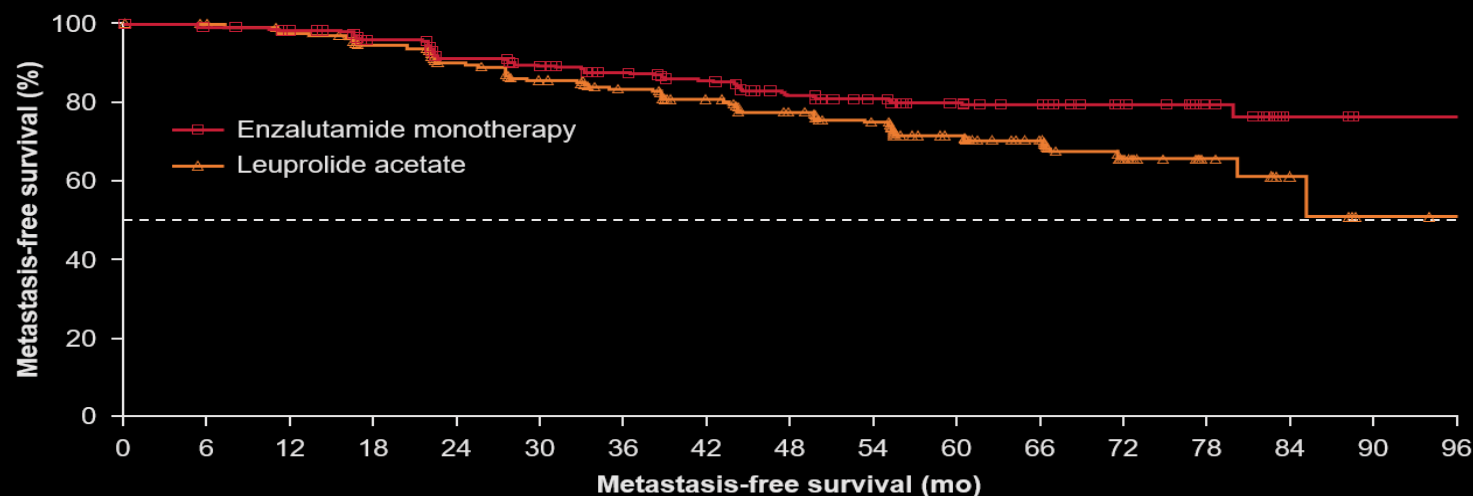
Data cutoff: January 31, 2023. Symbols indicate censored data. ^aThe HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination;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

Shore N et al. AUA 2023; Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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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); $P=0.0049^a$**

Patients at risk		355	342	328	309	287	273	260	247	228	209	171	108	52	26	5	0	0
Enzalutamide monotherapy	358	335	321	303	280	259	238	221	203	183	138	88	32	15	6	1	0	0
Leuprolide acetate																		

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

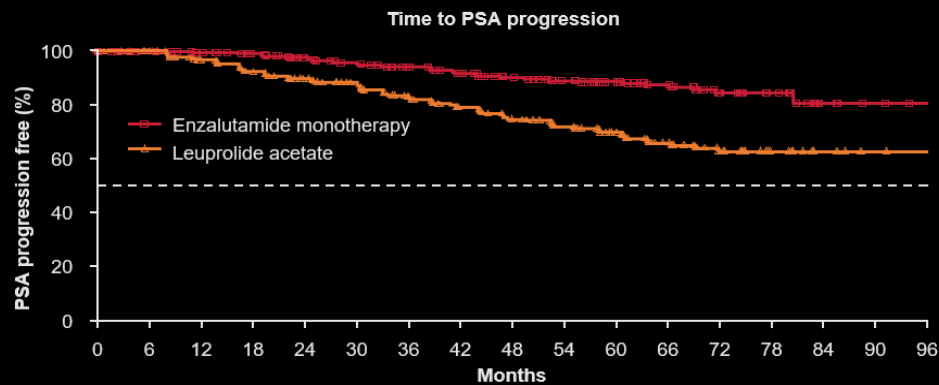
Data cutoff: January 31, 2023. Symbols indicate censored data. ^aThe HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy;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

Shore N et al. AUA 2023;Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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Key secondary endpoints — Enzalutamide monotherapy vs. leuprolide acetate

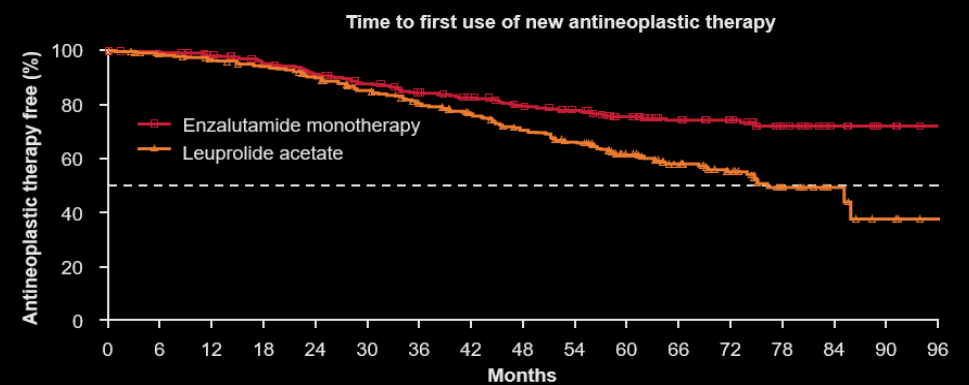


Patients at risk

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); $P < 0.0001^a$**



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. ^aThe 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.

Shore N et al. AUA 2023; Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı

Doz Yoğun Tedavi

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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. ^aPercentages 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.

Shore N et al. AUA 2023; Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı

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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. ^aPercentages 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. ^bFatigue events included asthenia. ^cThe most common (≥10% of patients) TEAEs. ^dMusculoskeletal events included back pain, arthralgia, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal stiffness, muscular weakness, and muscle spasms. ^eFractures excluded tooth fracture and fracture of the penis. ^fLoss of consciousness included syncope and presyncope. ^gOther selected CV events included hemorrhagic central nervous system vascular conditions, ischemic central nervous system vascular conditions, and cardiac failure. CV, cardiovascular.

Shore N et al. AUA 2023; Abstract LBA02-09.

Sonuç 1

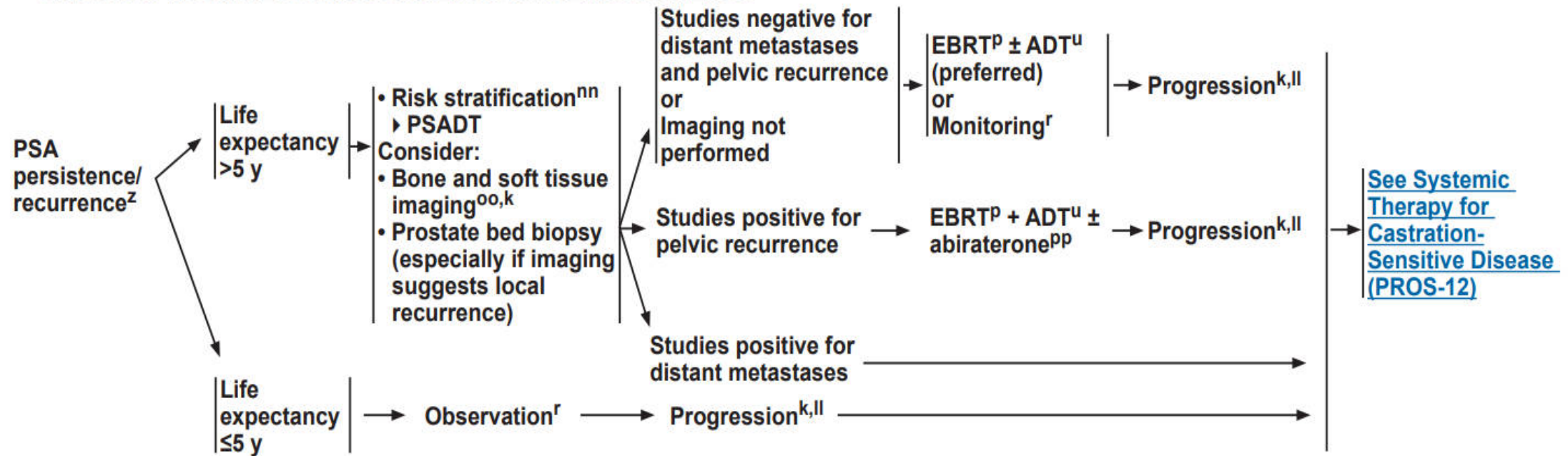


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RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE



Sonuç 2

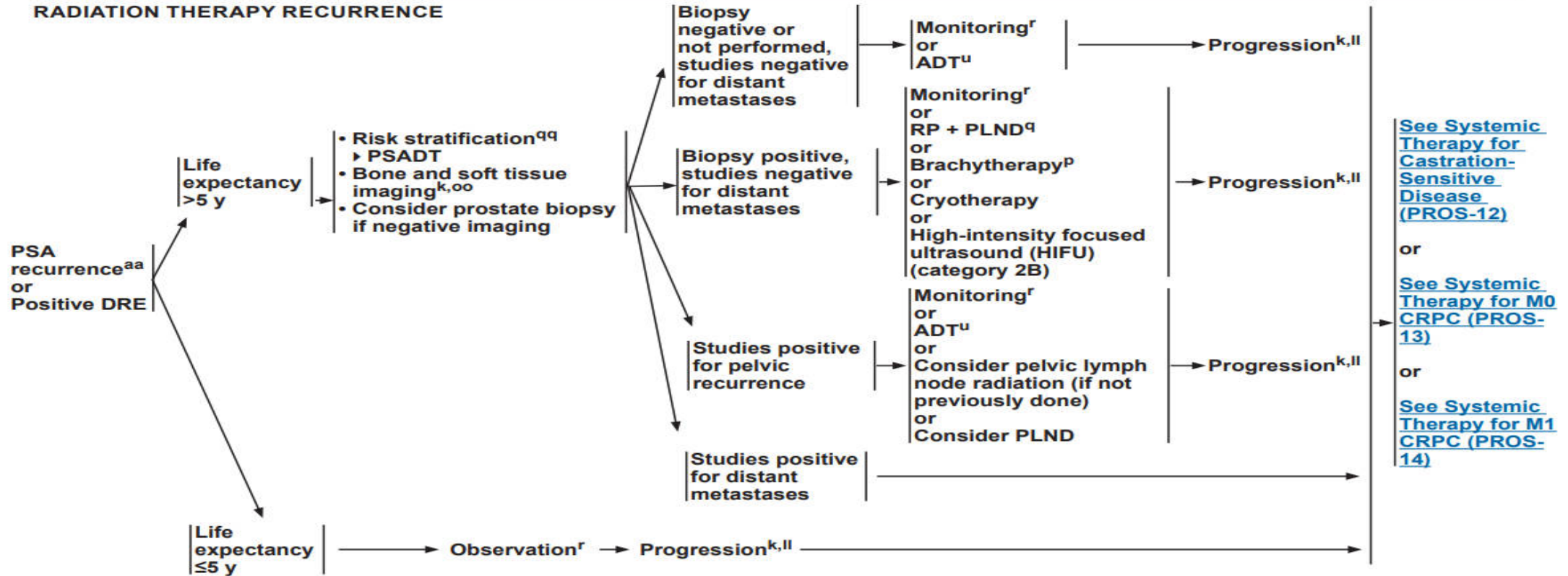


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RADIATION THERAPY RECURRENCE



RT sonrası Biyokimyasal Rekürens

CAD vs IAD : Trials With Uniform Population & Survival End Point

Trial (Year)	Patient Population	# pts Randomized	Median f/u (Y)	Primary Endpoint	Median Survival (Y)
NCIC PR7 (2012)	PSA relapse after RT	1386	6.9	OS non inferiority	IAD: 8.8 CAD: 9.1
TAP22 (2012)	Metastatic	173	3.7	OS superiority	IAD: 3.5 CAD: 4.3
SWOG 9346 (2013)	Metastatic (3040 pts)	1535	9.8	OS non inferiority	IAD: 5.1 CAD: 5.8

İntermittent ADT , sürekli ADT göre inferior değil. Yaşam kalitesi sonuçları daha iyi

RT sonrası Biyokimyasal Rekürens

Intermittent Androgen Deprivation for Biochemically Recurrent Prostate Cancer: First Do No Harm

70

Table 1 – Trials comparing iADT to cADT

Trial	Patient population	mFU (yr)	Primary endpoint			Trial design	HR for primary endpoint (iADT vs cADT) ^a		NI or SUP achieved?
			Median (yr)		PST		HR (95% CI)		
			cADT	iADT					
nmPC									
NCIC-CTG PR.7 [2]	PSA relapse after pRT or sRT	6.9	OS	9.1	8.8	NI for iADT vs cADT	<1.25	1.02 (0.86–1.21)	Yes
nmPC + mPC									
SEUG 9401 [7]	LA PC 70%, mPC 30%	4.3	PFS	NR	NR	SUP for iADT vs cADT	0.70	1.23 (0.95–1.59)	No
Finn Prostate VII [6]	LA PC 50%, mPC 50%	5.4	PFS	2.5	2.9	SUP for iADT vs cADT	0.74	0.93 (0.78–1.11)	No
SEUG 9901 [6]	LA PC 89%, mPC 11%	5.5	OS	NR	NR	NI for iADT vs cADT	<1.21	1.16 (0.93–1.47)	No
mPC									
TAP22 [6]	mPC	3.7	OS	4.3	3.5	SUP for iADT vs cADT	0.51	NR	No (<i>p</i> = 0.75)
SWOG 9346 [7]	mPC	9.8	OS	5.8	5.1	NI for iADT vs cADT)	<1.20	1.10 (0.99–1.23) ^b	No

ADT = androgen deprivation therapy; cADT = continuous ADT; CI = confidence interval; HR = hazard ratio for ; iADT = intermittent ADT; LA PC = locally advanced prostate cancer; mFU = median follow-up; mPC = metastatic prostate cancer; NI = noninferiority; nmPC = nonmetastatic prostate cancer; NR = not reported; OS = overall survival; PFS = progression-free survival; pRT = primary RT; PST = prespecified target; RT, radiation therapy; sRT = salvage RT; SUP = superiority.

^a HR > 1 favors cADT, HR < 1 favors iADT.

^b Represents 90% CI.

Sonuç 3

Table 2 – APCCC 2022 questions concerning PSA persistence and biochemical recurrence after definitive treatment that have reached a consensus

Question	Answers	Voting results, % (n)
34. In the majority of patients with PSA persistence 4–8 wk after radical prostatectomy (pN0) and M0 on preoperative imaging, do you recommend PSMA PET?	1. Yes	91 (90), strong consensus
	2. No	9 (9)
36. What do you recommend for a patient with PSA persistence 4–8 wk after radical prostatectomy (pN0 and ≥ 2 risk factors: R1, pT3, ISUP grade group 4–5), M0 on preoperative imaging, and negative postoperative PSMA PET, provided that the patient has regained continence?	1. Salvage radiation therapy	10 (10)
	2. Salvage radiation therapy plus systemic hormonal treatment	77 (76), consensus
	3. Systemic hormonal treatment alone	1 (1)
	4. No immediate active treatment, PSA surveillance	12 (12)
42. For the majority of patients with rising PSA after radical prostatectomy and PSA-DT <1 yr or pathological ISUP grade group 4–5 (EAU high risk), at what confirmed rising PSA level do you recommend PSMA PET imaging?	1. PSA below 0.2 ng/ml	11 (11)
	2. PSA >0.2–0.5 ng/ml	80 (78), consensus
	3. PSA >0.5 ng/ml	9 (9)
	4. No imaging	0 (0)
44. For the majority of patients with rapidly rising PSA (eg, PSA-DT <3 mo) after radical prostatectomy (ISUP grade group 4–5 and/or pT3/4) with negative PSMA PET or no PSMA PET imaging available, what is your management recommendation?	1. Active monitoring and treat only in case of a positive lesion on follow-up imaging	8 (8)
	2. Salvage RT alone	6 (6)
	3. Salvage RT plus systemic therapy	75 (75), consensus
	4. Systemic therapy alone	11 (11)
49. In the majority of patients with a PSA rise after radical prostatectomy ($\pm$ salvage RT of the prostate bed) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your treatment recommendation?	1. Locoregional treatment alone	10 (10)
	2. Systemic therapy alone	5 (5)
	3. Locoregional treatment plus systemic therapy	85 (84), consensus
50. If you voted for locoregional treatment in the previous question in the majority of patients with a PSA rise after radical prostatectomy ($\pm$ salvage RT of the prostate bed) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your	1. Radiation therapy	92 (85), strong consensus

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	2. Systemic therapy alone	5 (5)
	3. Locoregional treatment plus systemic therapy	85 (84), consensus
50. If you voted for locoregional treatment in the previous question in the majority of patients with a PSA rise after radical prostatectomy ($\pm$ salvage RT of the prostate bed) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your preferred strategy?	1. Radiation therapy	92 (85), strong consensus
	2. Surgery	8 (7)
51. Outside of clinical trials, do you recommend the use of a molecular classifier (eg, Decipher) for patients with undetectable postoperative PSA after radical prostatectomy but subsequently rising PSA?	1. Yes	18 (17)
	2. No	82 (78), consensus
52. Outside of clinical trials, do you recommend the use of a molecular classifier (eg, Decipher) for patients with PSA persistence (never achieved undetectable postoperative PSA) after radical prostatectomy?	1. Yes	20 (19)
	2. No	80 (75), consensus
54. If you recommend systemic therapy in combination with salvage radiation therapy in the majority of patients with rising PSA after radical prostatectomy and negative PSMA PET, what do you recommend?	1. ADT (LHRH agonist or antagonist)	85 (80), consensus
	2. ADT plus AR pathway inhibitor	10 (9)
	3. Bicalutamide monotherapy	5 (5)
55. If you recommend systemic hormonal treatment in combination with salvage radiation therapy in the majority of patients with rising PSA after radical prostatectomy and negative PSMA PET, which duration of AR blockade do you recommend for the majority of patients?	1. Short term (eg, 6 mo)	80 (76), consensus
	2. Long term (eg, 18–24 mo)	20 (19)
57. Which imaging modality do you recommend as a first imaging step for patients with rising PSA after radical radiation therapy of the prostate with an interval to biochemical failure of >18 mo and biopsy ISUP grade group <4 (EAU low risk), assuming that all imaging modalities are available?	1. MRI of the pelvis alone	11 (12)
	2. CT and/or bone scintigraphy	9 (9)
	3. Whole-body MRI alone/choline/fluciclovine PET/CT	1 (1)
	4. PSMA PET	78 (80), consensus
	5. I do not recommend imaging in this situation	1 (1)
60. Which imaging modality do you recommend as a first imaging step for patients with rising PSA after radical radiation therapy of the prostate with an interval to biochemical failure of <18 mo or biopsy ISUP grade group 4–5 (EAU high risk), assuming that all imaging modalities are available?	1. MRI of the pelvis alone	5 (5)
	2. CT and/or bone scintigraphy	10 (10)
	3. Whole-body MRI alone/choline/fluciclovine PET	1 (1)
	4. PSMA PET	84 (87), consensus
	5. I do not recommend imaging in this situation	0 (0)

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Table 2 (continued)

Question	Answers	Voting results, % (n)
65. What do you recommend in patients with rising PSA after definitive local therapy (RP ± salvage RT, RT of the prostate), with no local salvage therapy options available and no detectable metastases on imaging, and in a lower-risk setting (PSA-DT ≥12 mo and/or ISUP grade group ≤3)?	1. Start immediate systemic therapy for the majority of patients	11 (11)
	2. Monitor by PSA and imaging until detection of metastases	89 (89), consensus
69. In the majority of patients with PSA rise after radical local radiation of the prostate alone (no pelvic RT) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your treatment recommendation?	1. Locoregional treatment alone	19 (19)
	2. Systemic therapy alone	6 (6)
	3. Locoregional treatment plus systemic therapy	75 (73), consensus
70. If you voted for locoregional treatment in the majority of patients with PSA rise after radical local radiation of the prostate alone (no pelvic RT) and 1–3 positive lymph nodes in the pelvis alone on PSMA PET, what is your preferred strategy?	1. Radiation therapy	82 (74), consensus
	2. Surgery	18 (16)

ADT = androgen deprivation therapy; APCCC = Advanced Prostate Cancer Consensus Conference; AR = androgen receptor; CT = computed tomography; EAU = European Association of Urology; ISUP = International Society of Urological Pathology; LHRH = luteinising hormone-releasing hormone; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; RT = radiation therapy.

Özet

- ❑Biyokimyasal Rekürens ve PSA Persistansı olan hastada PSMA PET/CT ile evreleme yapılmalıdır.
- ❑Prostatektomi sonrası Biyokimyasal Rekürens olan gleason skoru ≥ 8 ya da PSA double time değeri $12\text{ay} \leq$ olanlarda tedavi düşünülmelidir
- ❑Gleason skoru 4+3 olanlar ? Decipher ve benzeri genomik analizler
- ❑Salvage RT ve ADT (6ay)düşünülmelidir
- ❑Uzun dönem 24 ay ADT($pT3 \geq$ ve gleason skoru ≥ 8)?
- ❑Pelvik RT nüks riski yüksek hastalarda düşünülebilir(Gleason ≥ 8 , $\geq pT3$, cerrahi sınır pozitifliği)
- ❑Enzalutamid , double time ≤ 9 ay, Metastatik free survival üzerinde etkili

Özet

- ❑ RT sonrası Biyokimyasal Rekürens olan hastalarda
- ❑ PSA değeri ≥ 2 ng/ml olan hastalar için
- ❑ İntermittent ADT önerilir
- ❑ PSA double time ≤ 9 ay olanlarda enzalutamid önerilebilir