Biyokimyasal Rekürens ve PSA Persistansı

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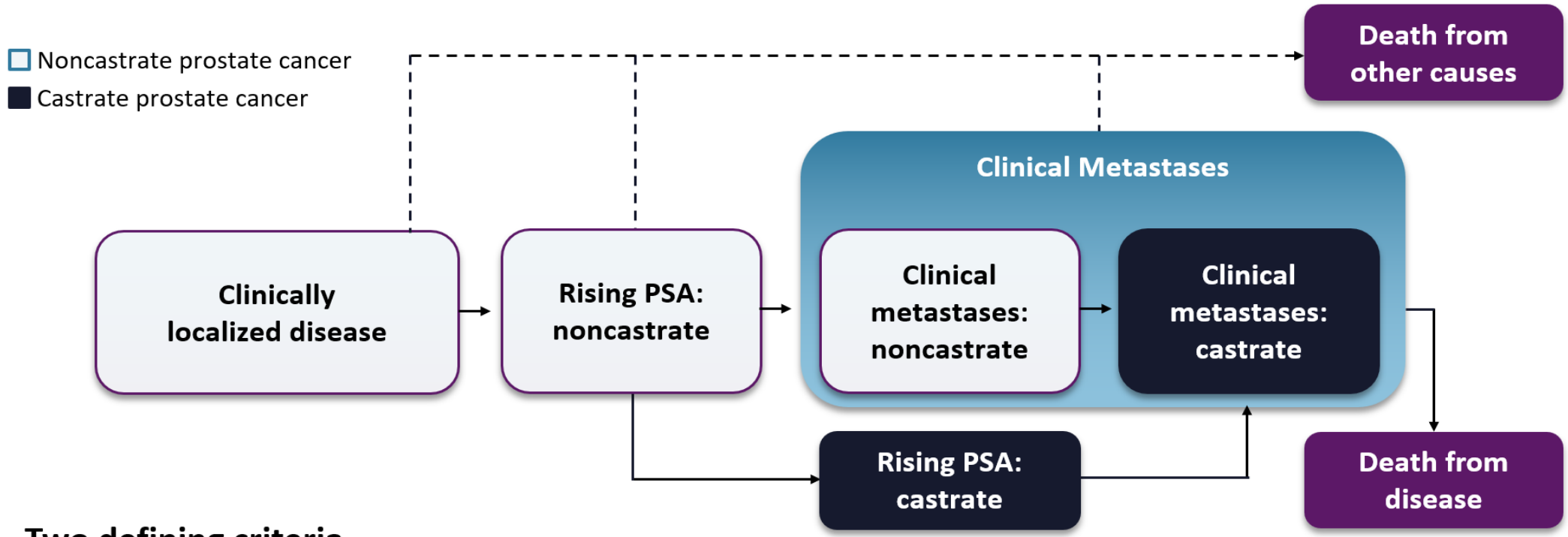
Tıbbi Onkoloji

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 Cancer[1]



Two defining criteria

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

1. Adapted from Scher HI et al. *J Clin Oncol.* 2008;26:1148-1159.

Courtesy of Matthew R Smith, MD, PhD

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, özelikle PSA ≥0.2 ng/ml olan hastalarda
- ❑ PSA persistansın olan hastaların %74 PSA artışı devam eder ve metastaz riski bu grup için yüksek

Mottet N, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer—2020 Update, Eur Urol 2020

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 ≤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≥, Gleason skoru>, cerrahi sınır+, lenf nodu+ olanlarda kötü sonuç ile ilişkili

Felix Preisser, European Association of Urology 2019

PSA Persistansı sağkalım sonuçları

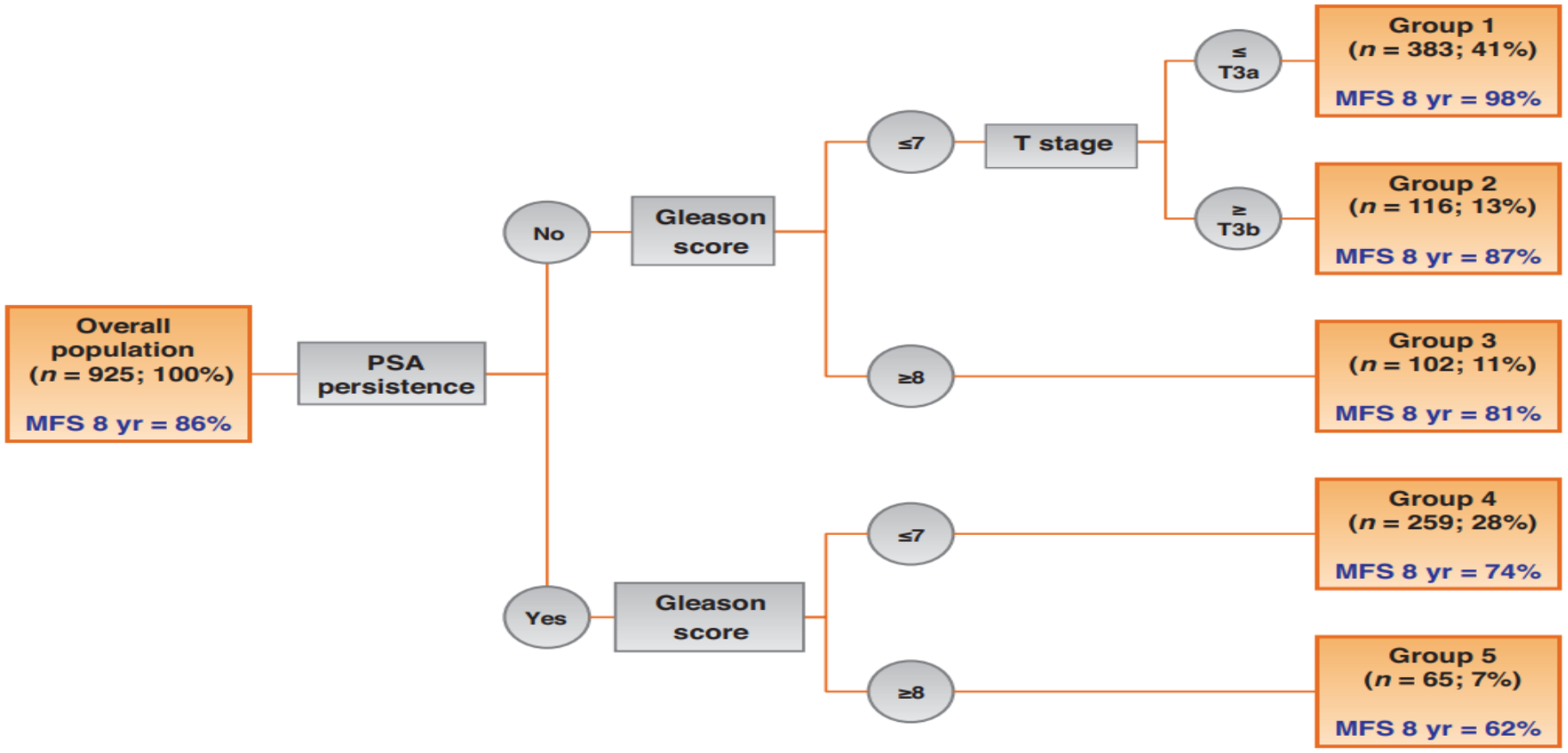


Fig. 1 – A risk stratification tree assessing metastasis-free survival (MFS), based on 925 patients treated with salvage radiation therapy for prostate-specific antigen (PSA) rise after radical prostatectomy.

Nicola Fossati, Eur Urol (2017)

Biyokimyasal Rekürens

Tanım

- ❶ 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

- ❷ NCCN tanımlaması; Prostatektomi sonrası PSA değeri nadir düzeye düşen hastalarda PSA değerinin artarak ≥0.1 ng/ml olarak ölçülmesi ve bunun birkaç ölçümle doğrulanması

- ❷ 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.

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

❷ 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.

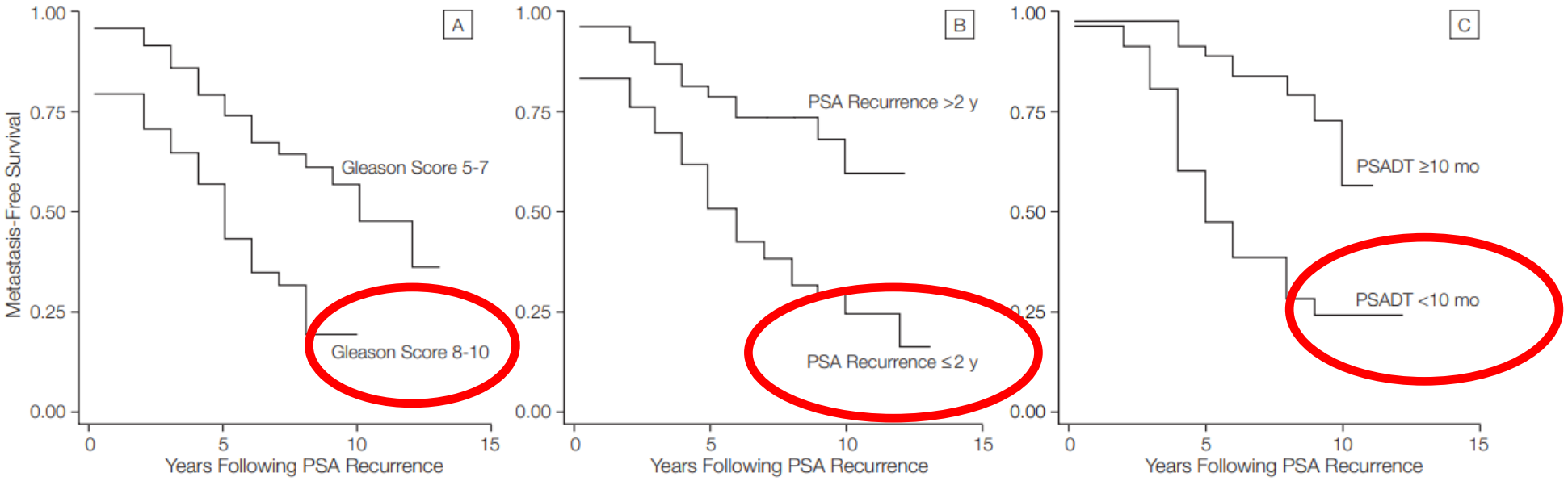
Definition			
Low risk	Intermediate risk	High risk	
PSA < 10 ng/mL and ISUP grade 1 (GS < 7) and cT1-2a	PSA 10–20 ng/ml or ISUP grade 2/3 (GS 7) or cT2b	PSA > 20 ng/mL or ISUP grade 4/5 (GS > 7) or cT2c	Any PSA, any GS (any ISUP grade), cT3–4, or cN+
Localised			Locally advanced

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) ($P<.001$).

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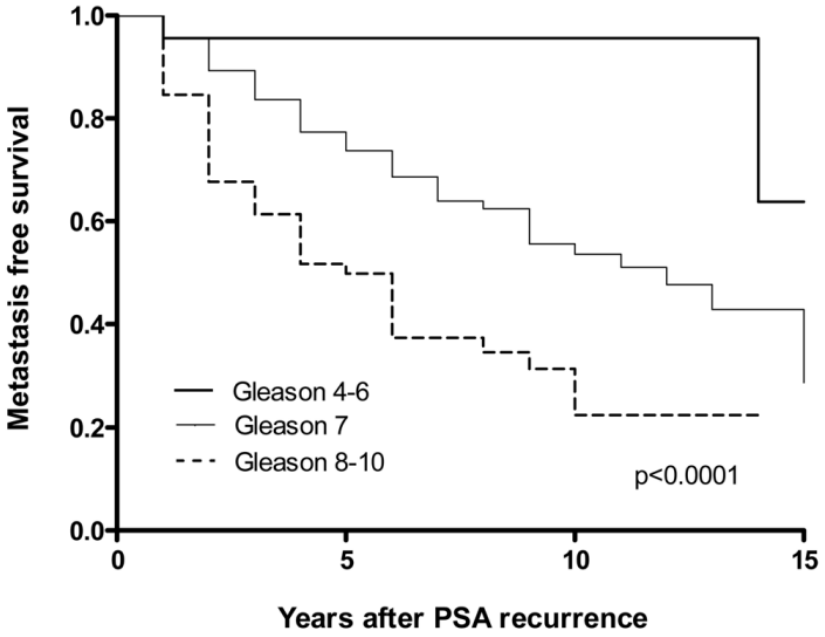
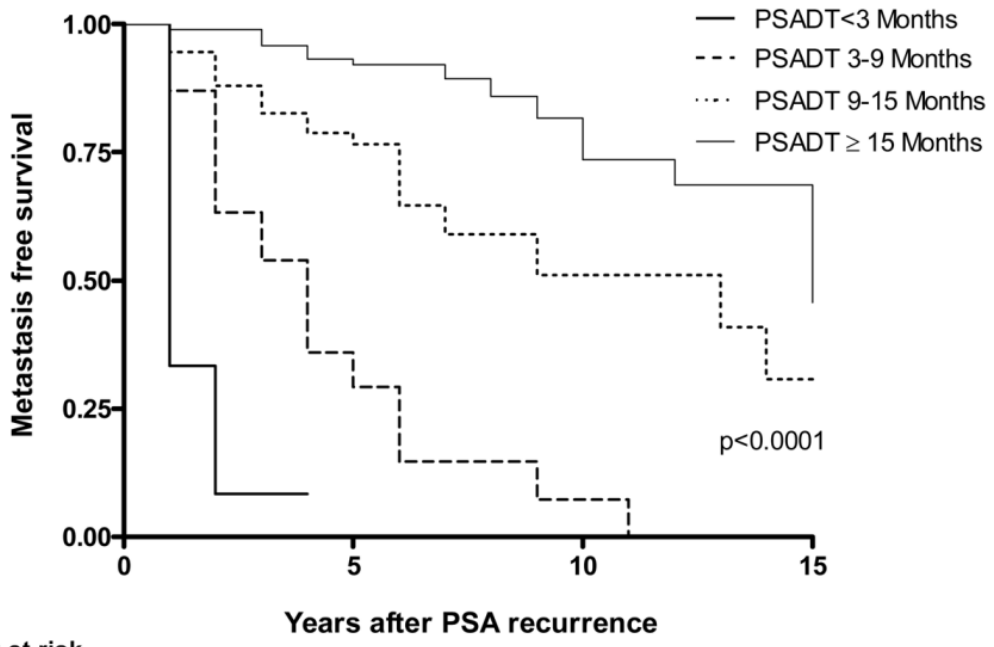
Biyokimyasal Rekürens Metastaz riski



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

Emmanuel S. Antonarakis, BJU Int. 2012

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

	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)

- ❑ PSA double time
- ❑ Gleason skoru≥ 8
- ❑ Gleason skoru 7?

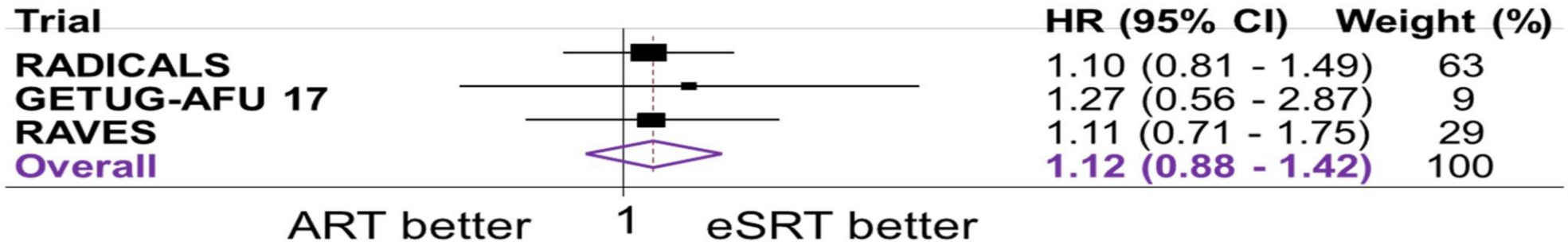
metastaz arasında güçlü ilişki mevcut

Emmanuel S. Antonarakis, BJU Int. 2012

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)



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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

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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

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Radikal Prostatektomi sonrası Adjuvan RT> Salvage RT

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

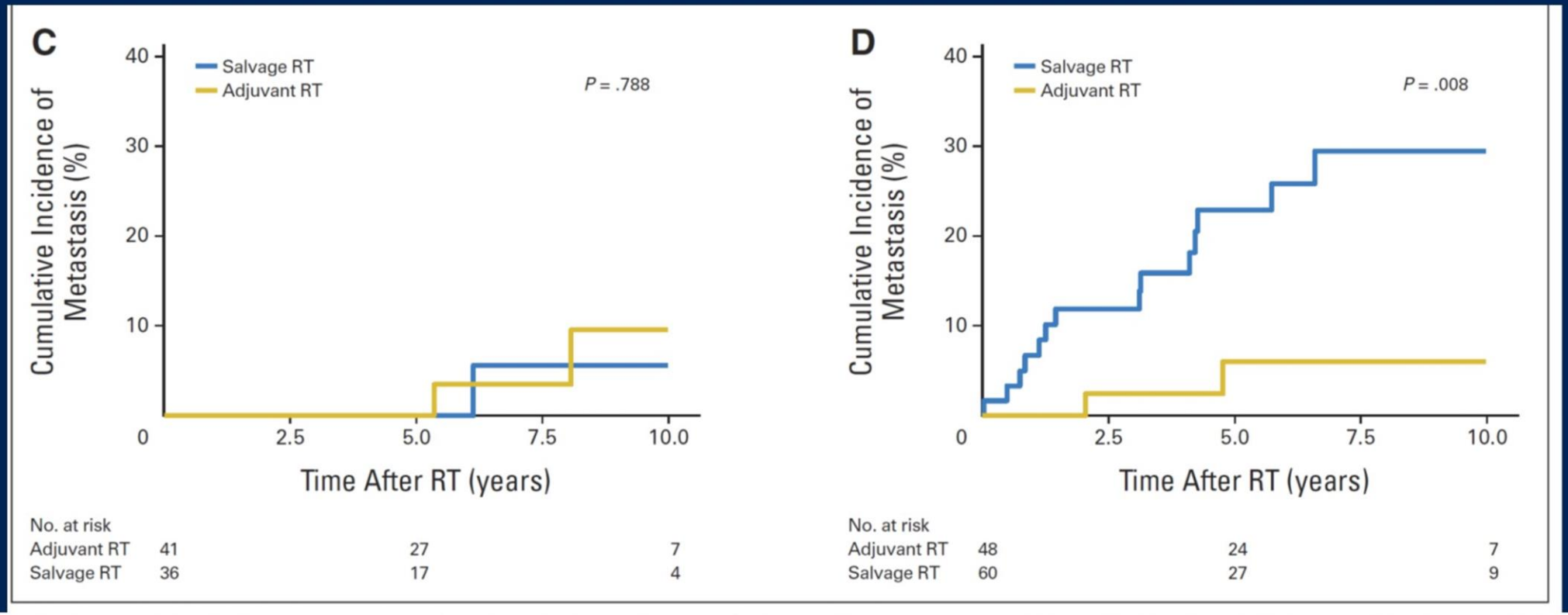
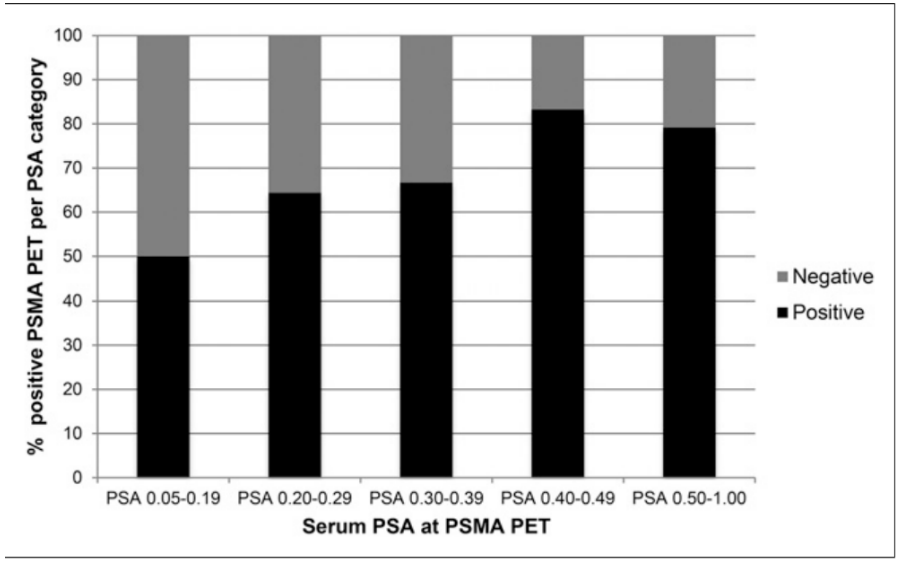


Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (C and D) genomic classifier (GC).

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)



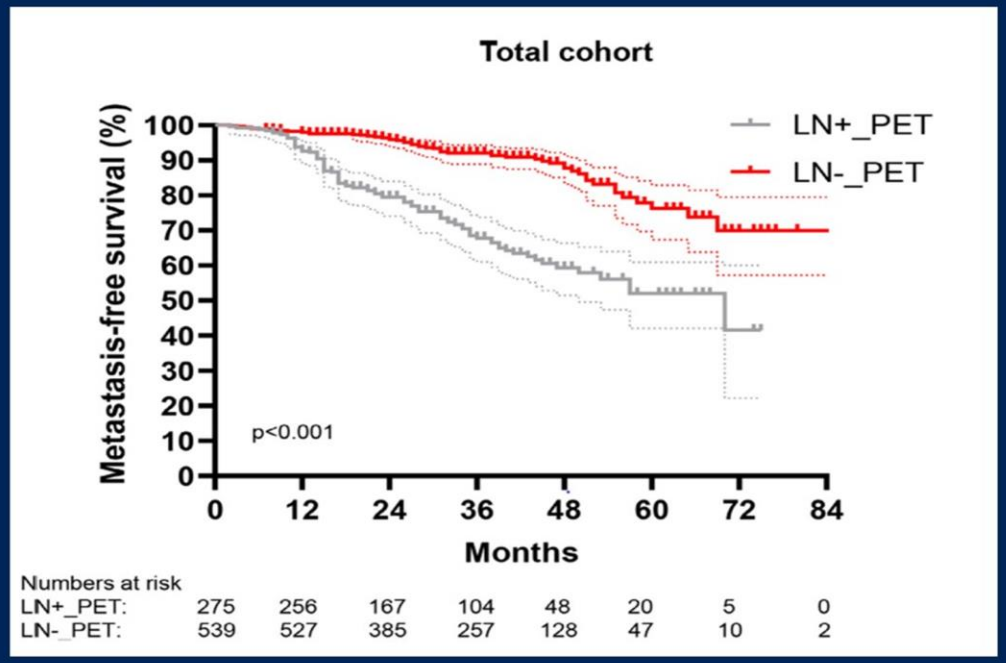
Variable	Odds ratio	Significance (*P*)
PSMA PET: negative/local, lymph nodes, distant disease	0.15	0.001
PSA at PSMA PET	0.026	0.02
pT stage	0.98	0.98
Gleason score	0.91	0.91
Surgical margins	0.80	0.80

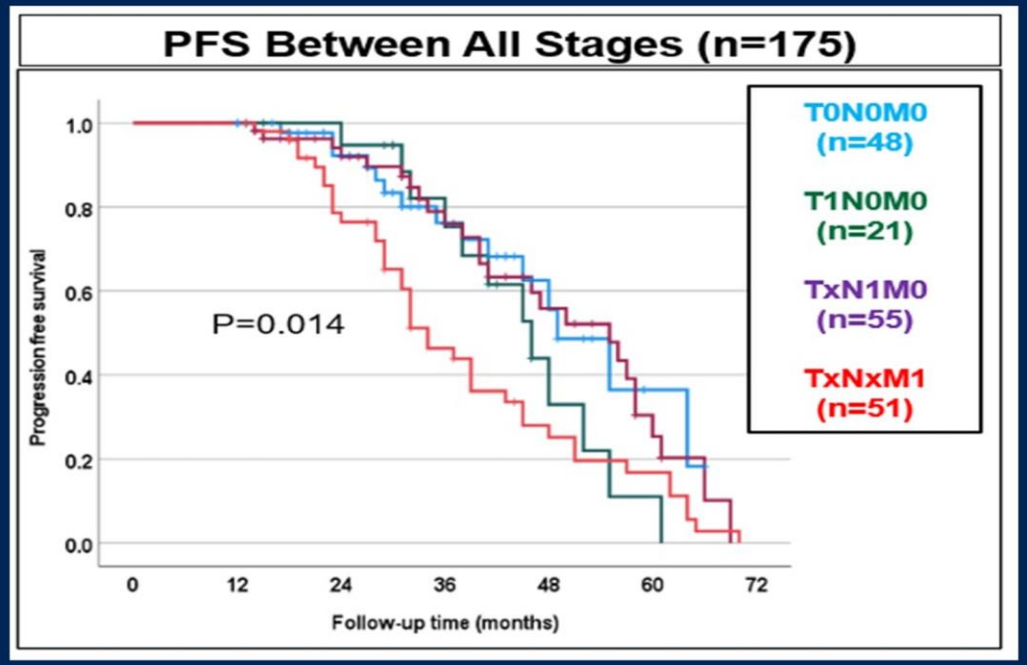
PSMA PET negatif olması salvage RT için prediktif değeri var

Louise Emmett at al, J Nucl Med 2017

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

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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**

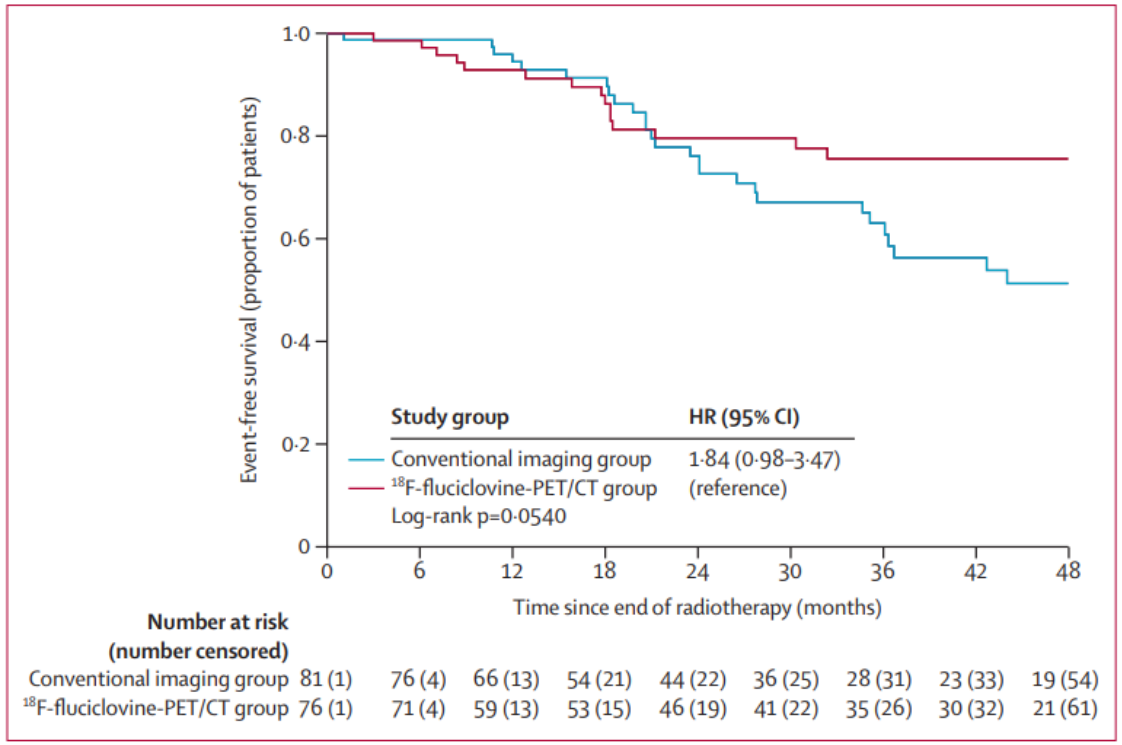

Figure 2: **3 year event-free survival**
Figure shows Kaplan-Meier curves for event-free survival among the modified intention-to-treat population, consisting of all patients assigned to a study group who received radiotherapy.

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

EMPIRE-1 trial, Lancet 2021

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

PRESENTED BY: David M. Nanus, M.D., Professor of Medicine and Urology, Weill Cornell Medicine
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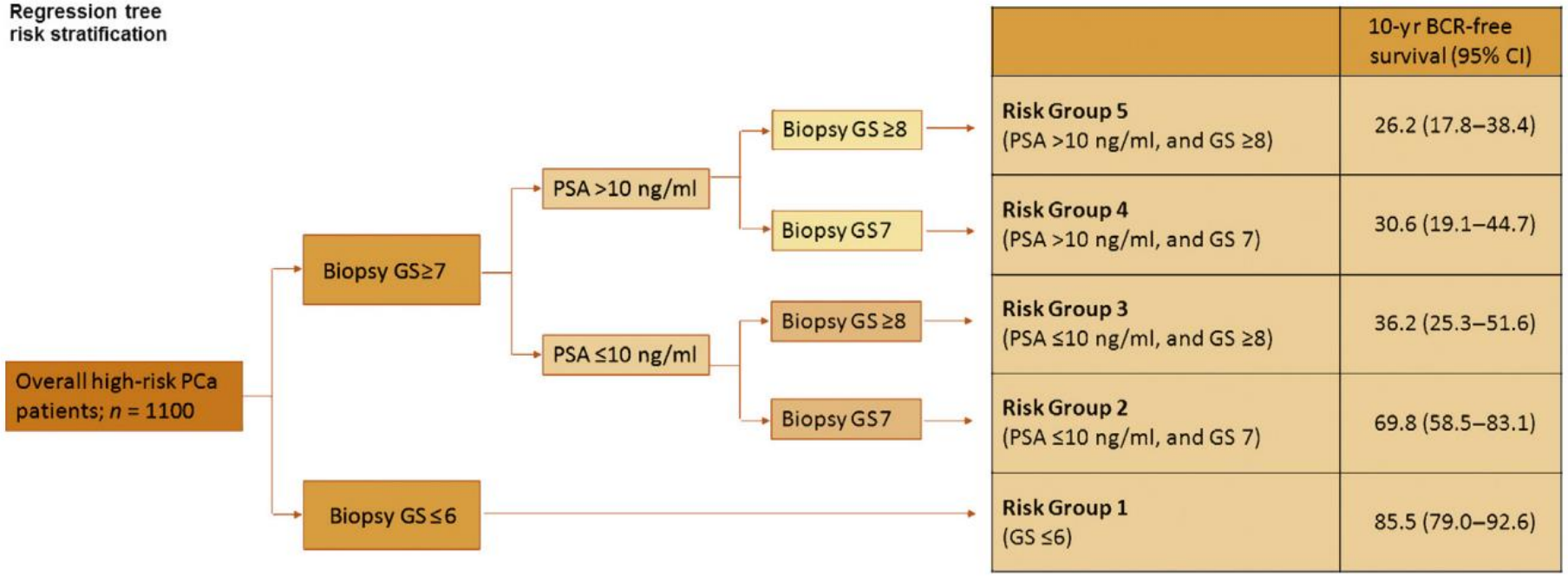
Lokalize Yüksek Riskli Prostat Kanseri

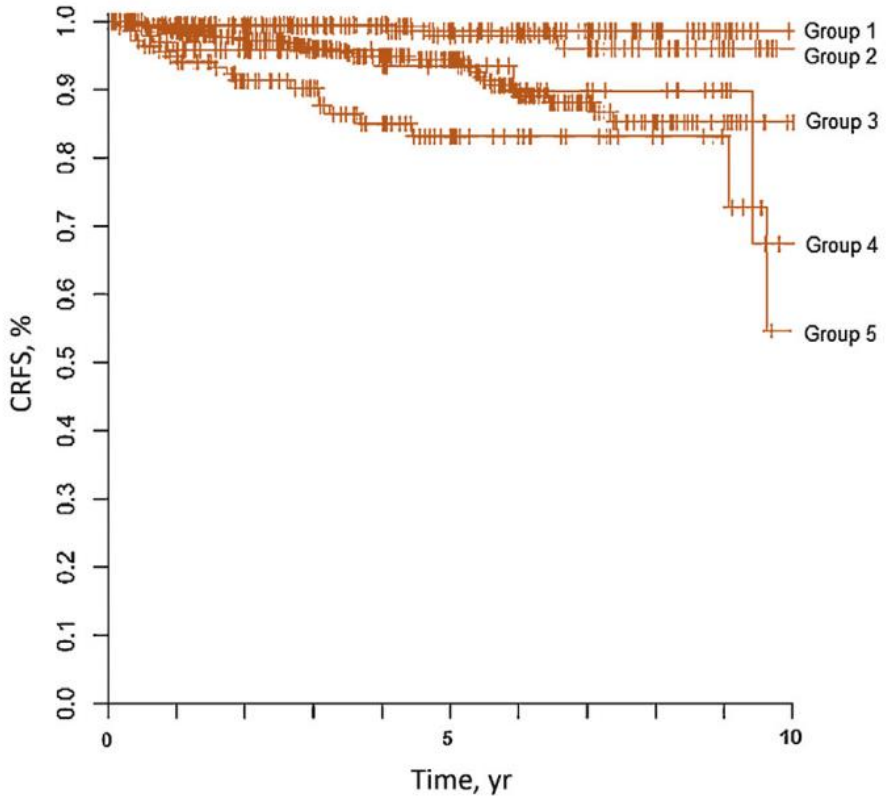


	10-yr BCR-free survival (95% CI)
Risk Group 5 (PSA >10 ng/ml, and GS ≥8)	26.2 (17.8–38.4)
Risk Group 4 (PSA >10 ng/ml, and GS 7)	30.6 (19.1–44.7)
Risk Group 3 (PSA ≤10 ng/ml, and GS ≥8)	36.2 (25.3–51.6)
Risk Group 2 (PSA ≤10 ng/ml, and GS 7)	69.8 (58.5–83.1)
Risk Group 1 (GS ≤6)	85.5 (79.0–92.6)

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.

Lokalize Yüksek Riskli Prostat Kanseri

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



RISK GROUP		CRFS (95% CI)		
		1 yr	5 yr	10 yr
Risk Group 1 (GS ≤6)	CRFS (95% CI)	99.5 (98.5–100)	98.6 (96.7–100)	98.6 (96.7–100)
	At Risk	189	100	17
Risk Group 2 (PSA ≤10 ng/ml, and GS7)	CRFS (95% CI)	99.3 (98.0–100)	98.0 (95.1–100)	96.0 (91.4–100)
	At Risk	132	71	14
Risk Group 3 (PSA ≤10 ng/ml, and GS ≥8)	CRFS (95% CI)	98.5 (97.3–99.6)	94.4 (92.0–96.9)	85.3 (79.5–91.4)
	At Risk	435	179	18
Risk Group 4 (PSA >10 ng/ml, and GS7)	CRFS (95% CI)	95.9 (92.0–99.9)	93.5 (87.6–99.7)	67.4 (37.9–100)
	At Risk	89	45	11
Risk Group 5 (PSA >10 ng/ml, and GS ≥8)	CRFS (95% CI)	94.9 (91.2–98.6)	83.2 (75.7–91.3)	54.6 (36.9–77.9)
	At Risk	121	37	5

$p < 0.001$
Harrell's C = 0.69

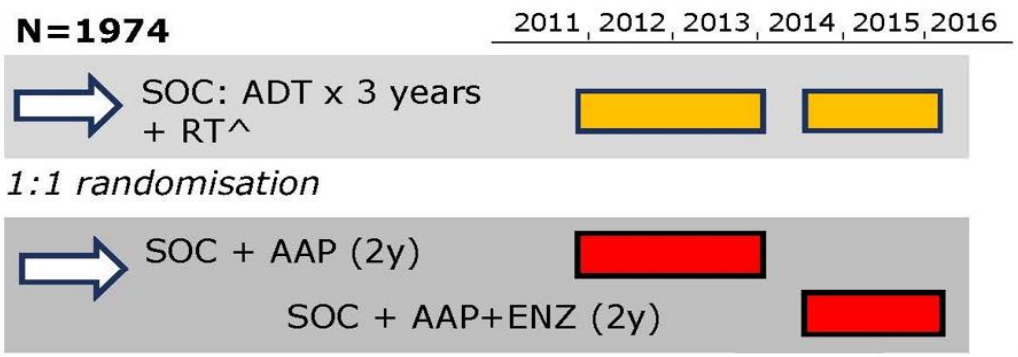
Fig. 3 – Kaplan-Meier curve for clinical recurrence–free survival in (A) the overall cohort and (B) after stratification according to the novel regression tree model.
CI = confidence interval; CRFS = clinical recurrence–free survival; GS = Gleason score; PSA = prostate-specific antigen.

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 1ary 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]

Courtesy of Neal D Shore, MD

Attard, et al. Lancet, 2022

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≥40ng/ml
  Gleason 8, 9 or 10

Relapsing after previous RP or RT
Any of:
- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

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

Full criteria: www.stampedetrial.org

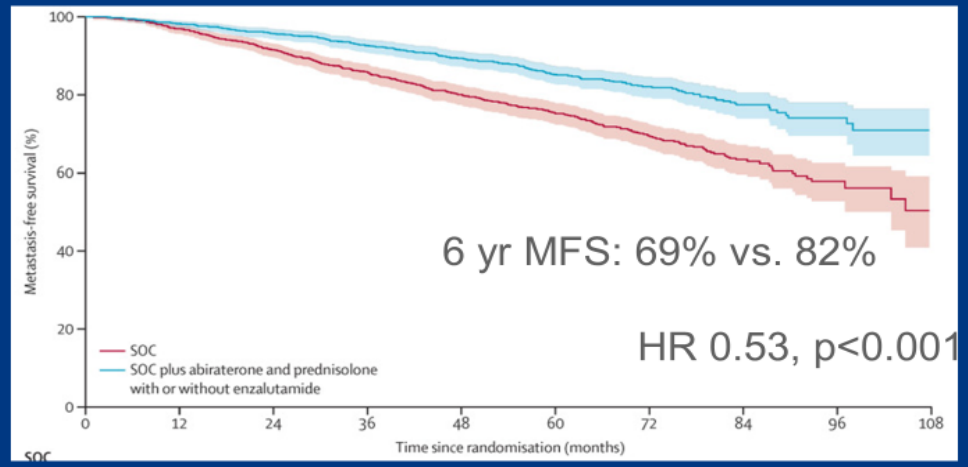
Attard G, et al. ESMO 2021.

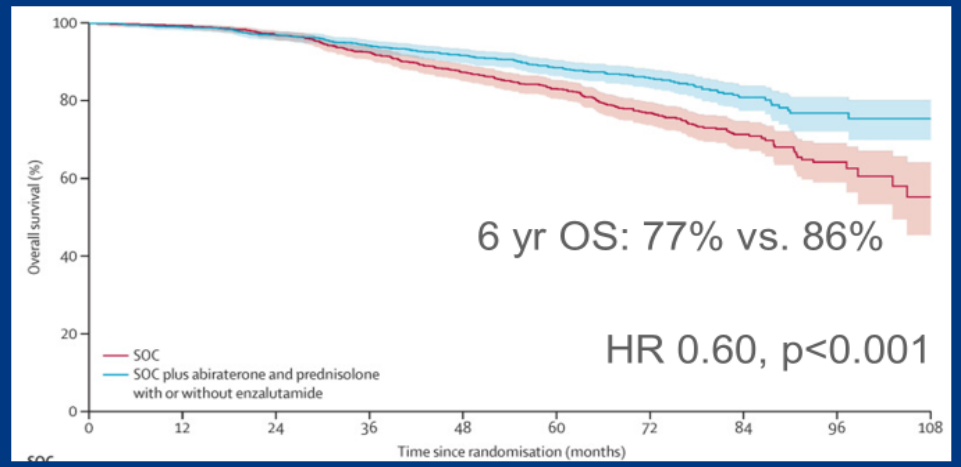
2021 ESMO congress

Lokalize 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

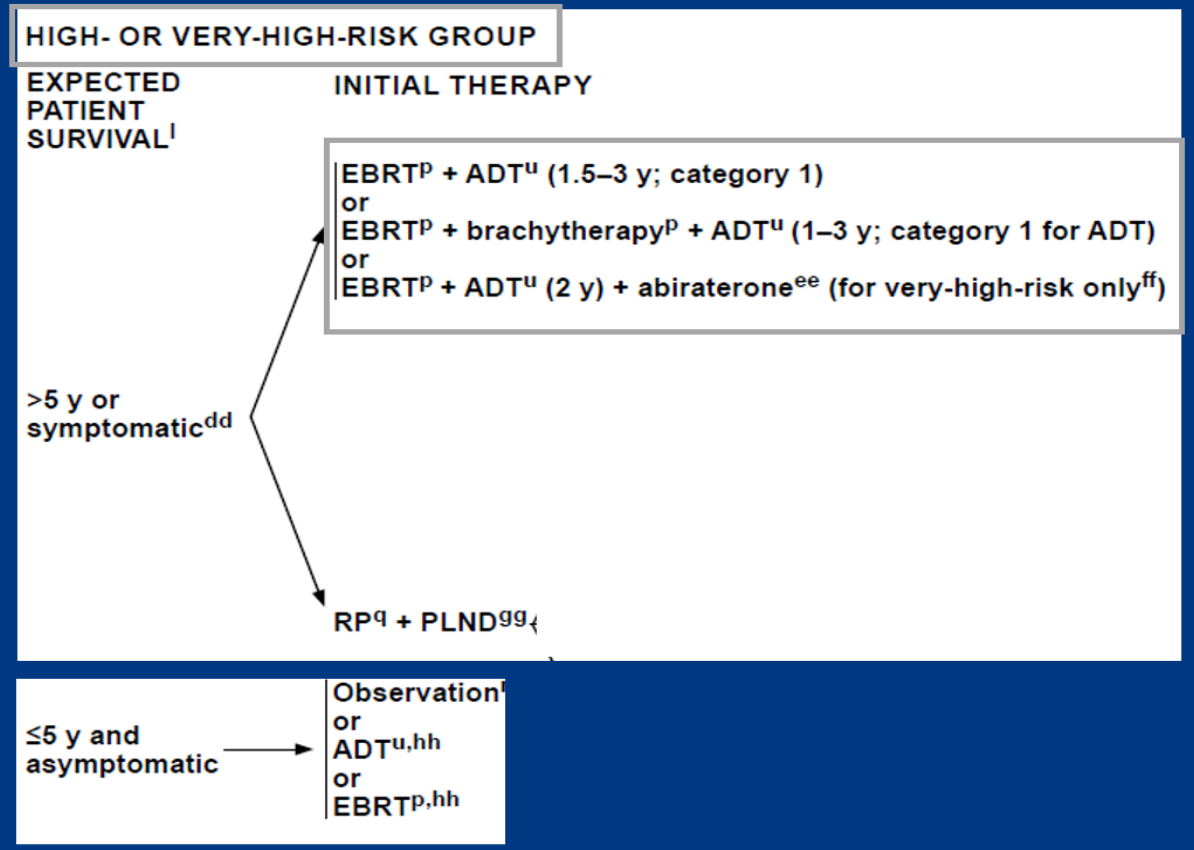
Median age 68. 73% T3/4. 79% GI8-10. Median PSA 34. 39% Node-positive

No additional benefit to enzalutamide in addition to abiraterone.

Attard G Lancet 2021; 399:447.

Lokalize 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

NCCN National Comprehensive Cancer Network®

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]	Comparato	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	Multivariate 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	Pre-sRT PSA
																					Gleason score (6–7 vs >7)	Gleason score (6–7 vs >7)
	Versus undetectabl PSA	sRT: 100%	0.27/30 mo		62%	5 yr	NA	NA													pT	pT
																						Risk-matched cohort (n = 224)
			$p < 0.001$																			Pre-sRT PSA
			$p = 0.250$																			pT
																						(PSA persistence not correlated)
Fossati [17]		sRT (+ ADT): 100% (30%)	0.3[a]	52.4%					74% if GS 6–7	8 yr		NA				NA				MFS		pT stage
									62% if GS 8–10	8 yr												Gleason score
																						PSA persistence
			Detectable PSA: 1.0																			PSA at sRT
			Undetectable PSA: 0.2																			ADT duration
			$p < 0.001$																			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)	
																					PSADT	
	Versus undetectabl PSA	sRT: 100%	0.34		65.4%	3.5 yr																
					$p = 0.215$																	
Eisenberg [21]		NA	NA	30.4%	67%	5 yr		NA				NA				NA				BCRFS		Pre-RP PSA
																						PSM
																						PSA persistence
																						Gleason score (6 vs 7–10)

EUROPEAN UROLOGY ONCOLOGY 4 (2021) 150–169

Biyokimyasal Rekürens olan hastalarda Salvage RT

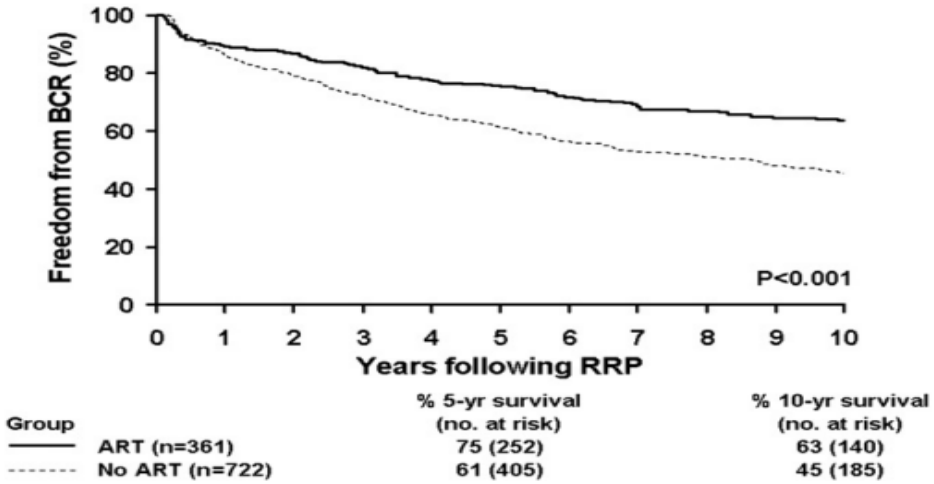


Figure 2. BCR-free survival in patients treated with ART vs controls.

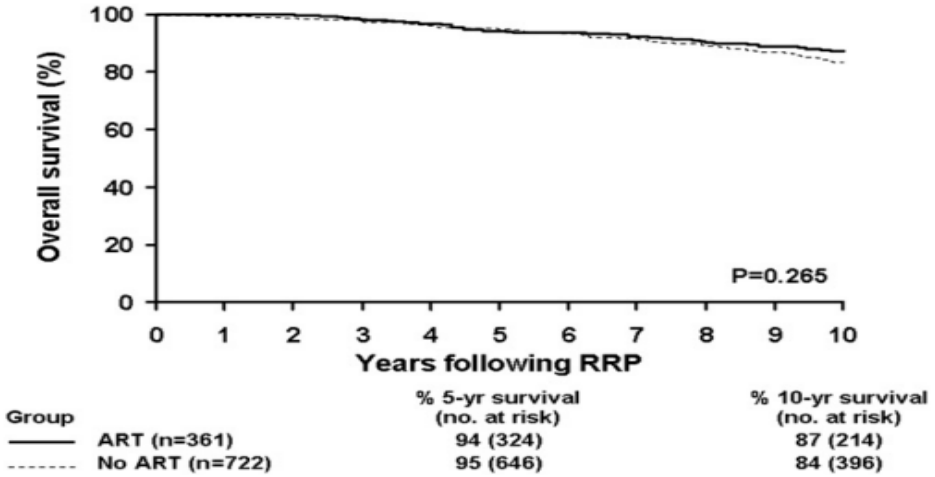


Figure 3. Overall survival in patients treated with ART vs controls.

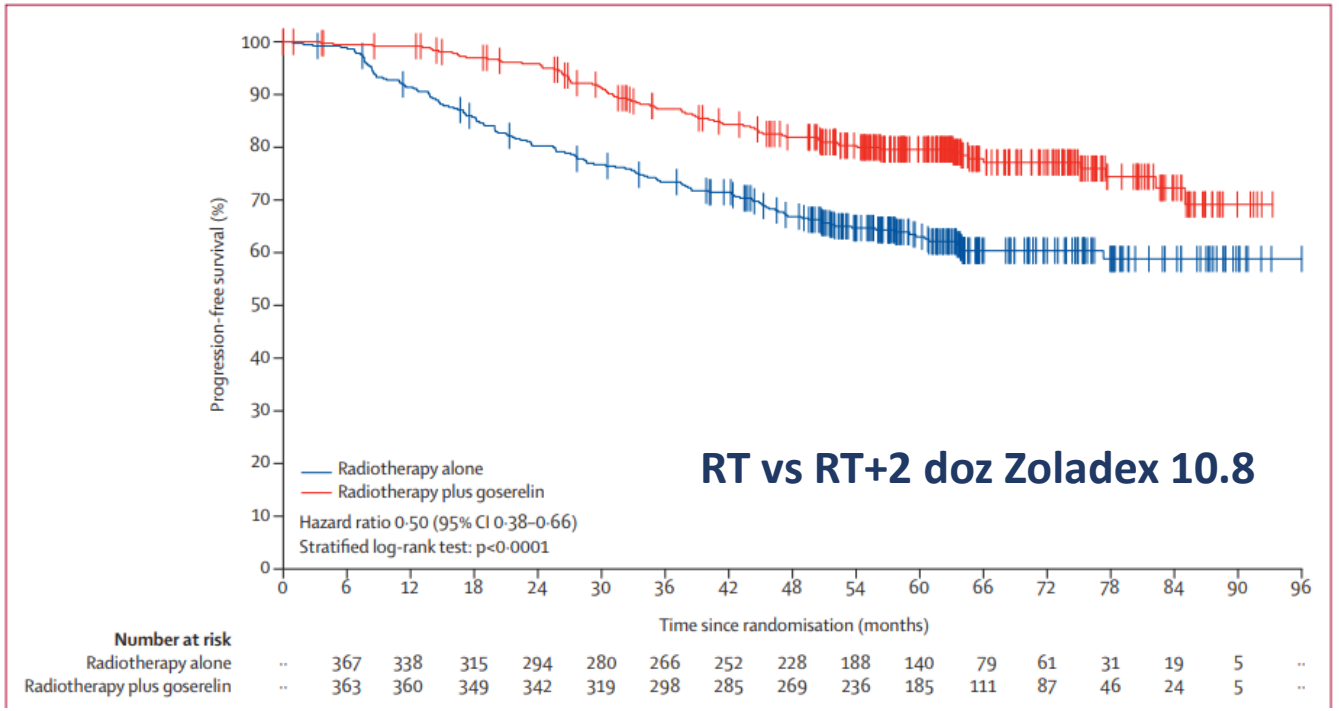
	Univariate Analysis		Multivariate Analysis*	
End Point	HR† (95% CI)	p Value	HR† (95% CI)	p Value
BCR	0.57 (0.45–0.71)	<0.0001	0.53 (0.42–0.67)	<0.0001
Local recurrence	0.11 (0.05–0.24)	<0.0001	0.11 (0.05–0.23)	<0.0001
Systemic progression	0.97 (0.62–1.51)	0.88	0.93 (0.58–1.49)	0.76
Late ADT	0.60 (0.45–0.81)	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).

Boorjian at al, THE JOURNAL OF UROLOGY 2009

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)



RT vs RT+2 doz Zoladex 10.8

Free-biochemical progression or clinical progression at 5 years (80% vs 62% [57–67]; HR 0·50 ; p<0·0001.

GETUG-AFU 16, Lancet Oncol 2016

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.

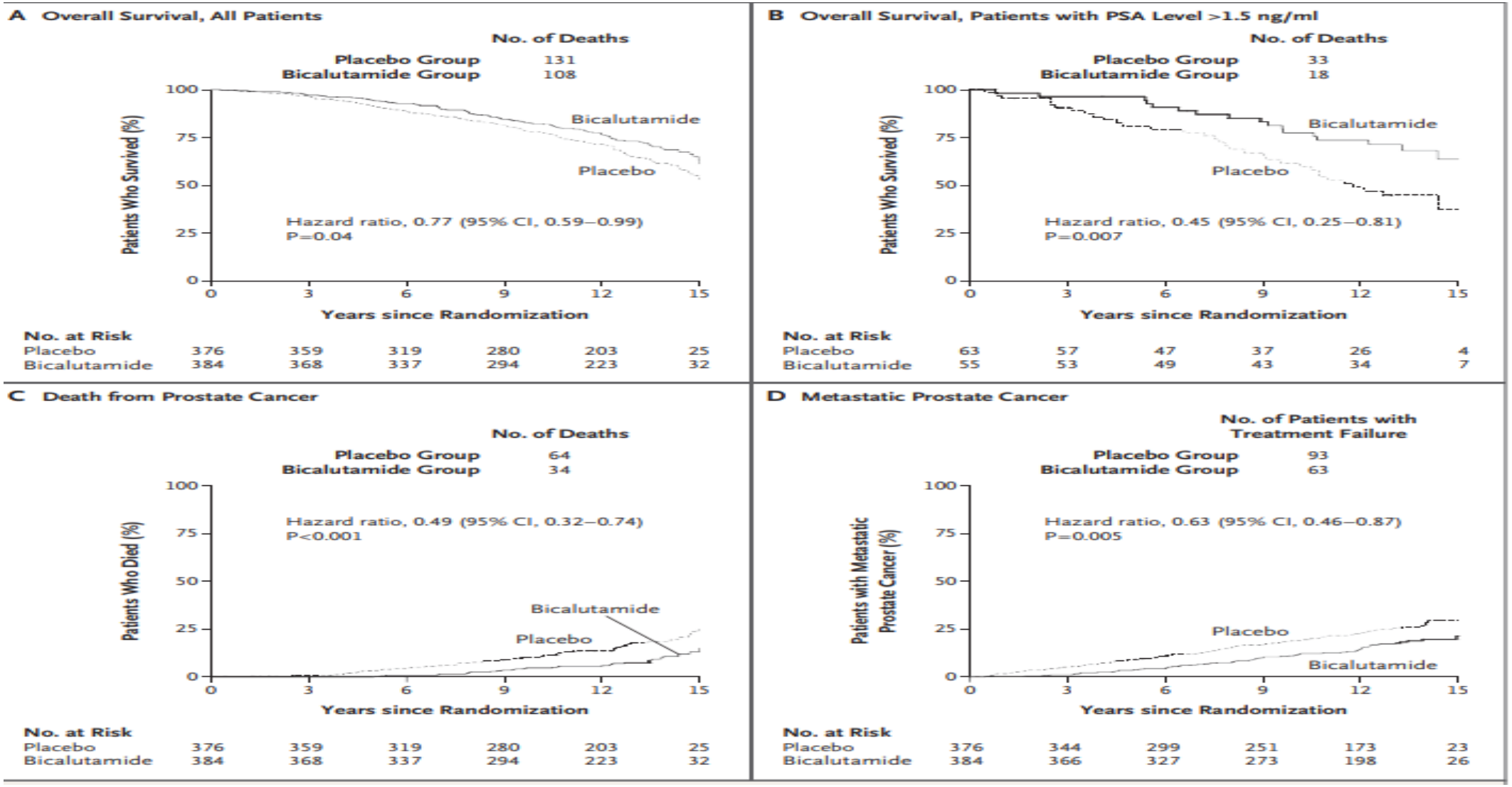
	Radiotherapy alone (n=372)		Radiotherapy plus goserelin (n=366)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Gynaecomastia	0	0	4 (1%)	0
Hot flushes	1 (<1%)	0	163 (45%)	3 (1%)
Breast pain	0	0	5 (1%)	0
Sweating	0	0	47 (13%)	1 (<1%)
Paraesthesia	0	0	0	0
Spinal-cord compression	0	0	0	0
Hypertension	1 (<1%)	0	21 (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**

GETUG-AFU 16, Lancet Oncol 2016

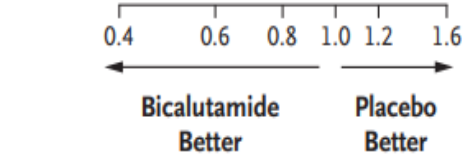
Biyokimyasal Rekürens ve PSA Persistansı
RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)



RTOG 9601, N Engl J Med 2017

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

Subgroup	No. of Patients (%)	Bicalutamide Group	Placebo Group	Hazard Ratio (95% CI)	P Value
		12-yr overall survival rate (%)			
Overall	760 (100.0)	76.3	71.3	0.77 (0.59–0.99)	0.04
Gleason score					
2–6	214 (28.2)	79.5	79.2	0.95 (0.57–1.59)	0.84
7	413 (54.5)	78.5	70.9	0.69 (0.49–0.98)	0.04
8–10	131 (17.3)	63.9	58.4	0.76 (0.44–1.30)	0.32
PSA level at trial entry					
<0.7 ng/ml	405 (53.3)	76.8	80.7	1.13 (0.77–1.65)	0.53
0.7–1.5 ng/ml	237 (31.2)	77.0	67.5	0.61 (0.39–0.95)	0.03
>1.5 ngl/ml	118 (15.5)	73.5	48.9	0.45 (0.25–0.81)	0.007
Positive surgical margin					
No	191 (25.1)	73.5	72.9	0.87 (0.53–1.41)	0.56
Yes	569 (74.9)	77.3	70.7	0.73 (0.54–0.98)	0.04



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.

RTOG 9601, N Engl J Med 2017

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

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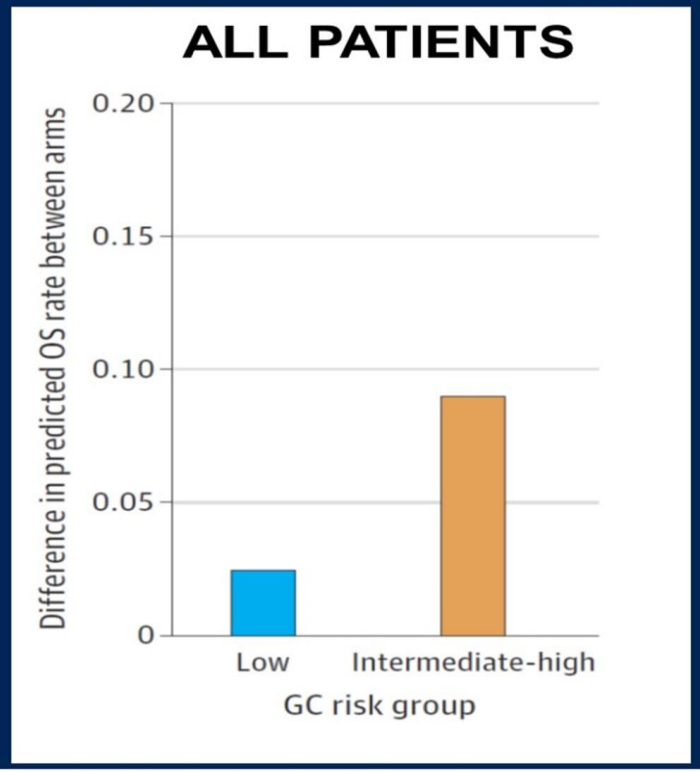
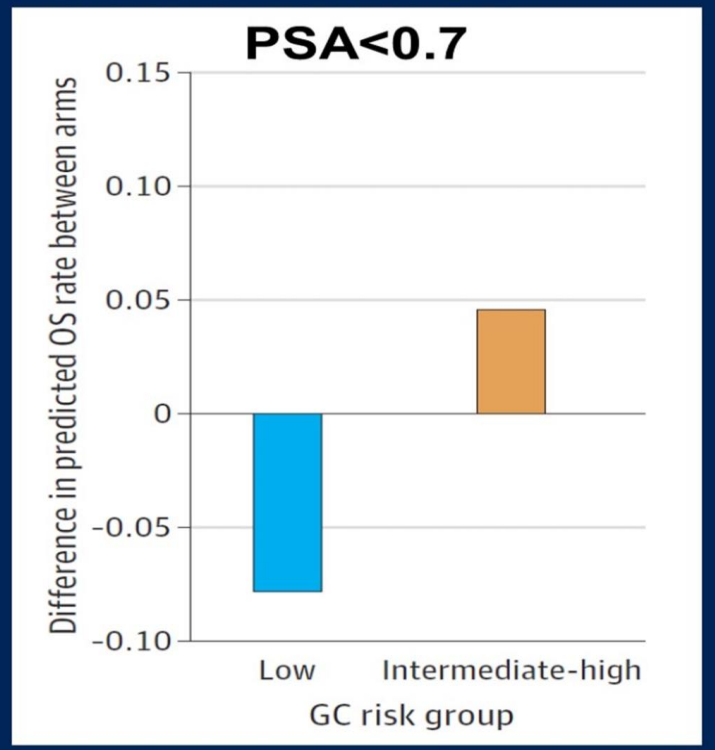
Biyokimyasal Rekürens ve PSA Persistansı RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)

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





Bars show % Difference in OS by Treatment Arm

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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

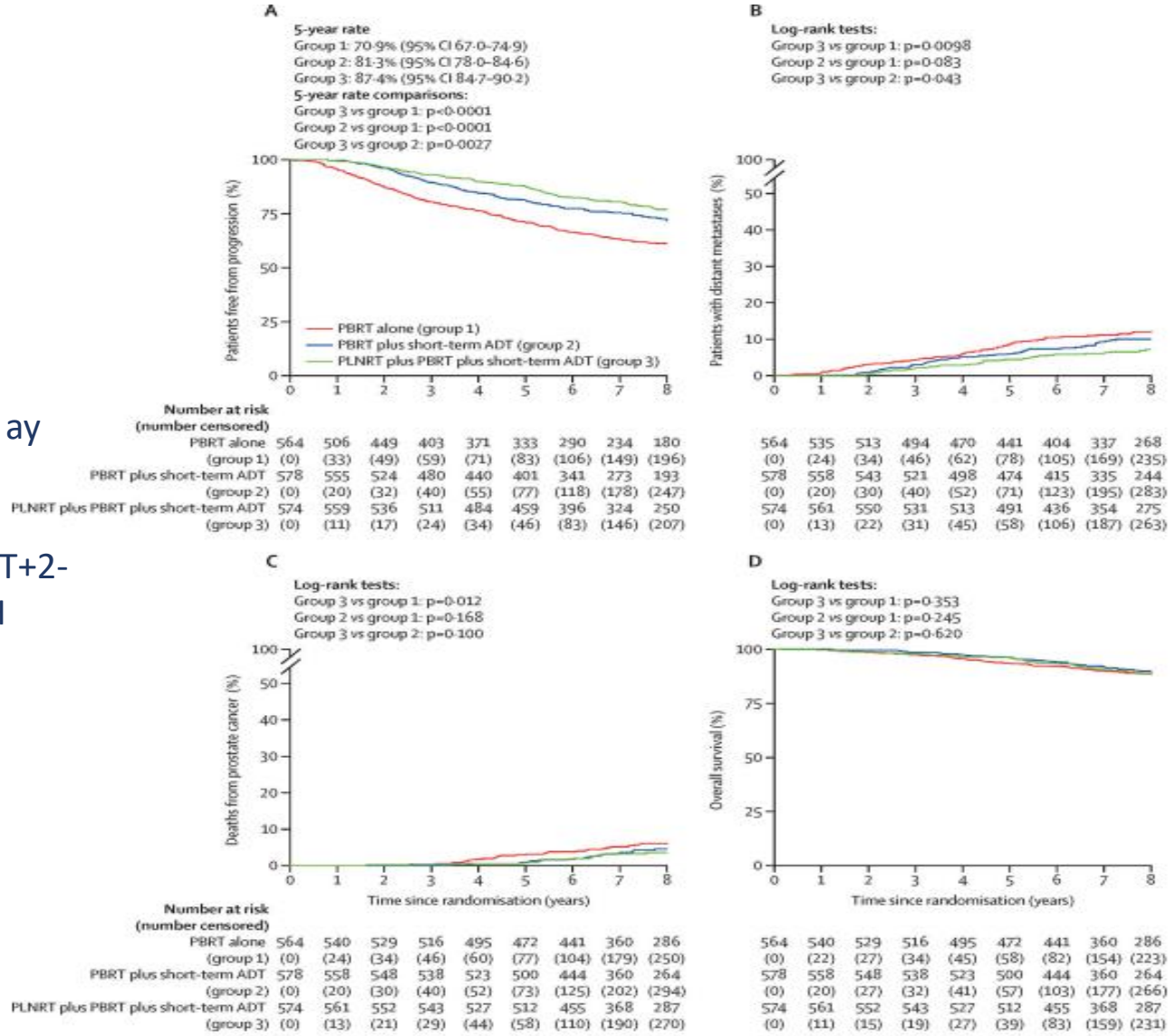


Figure 2:
Kaplan-Meier estimates and cumulative incidence curves: (A) Freedom from progression,

pT2/pT3

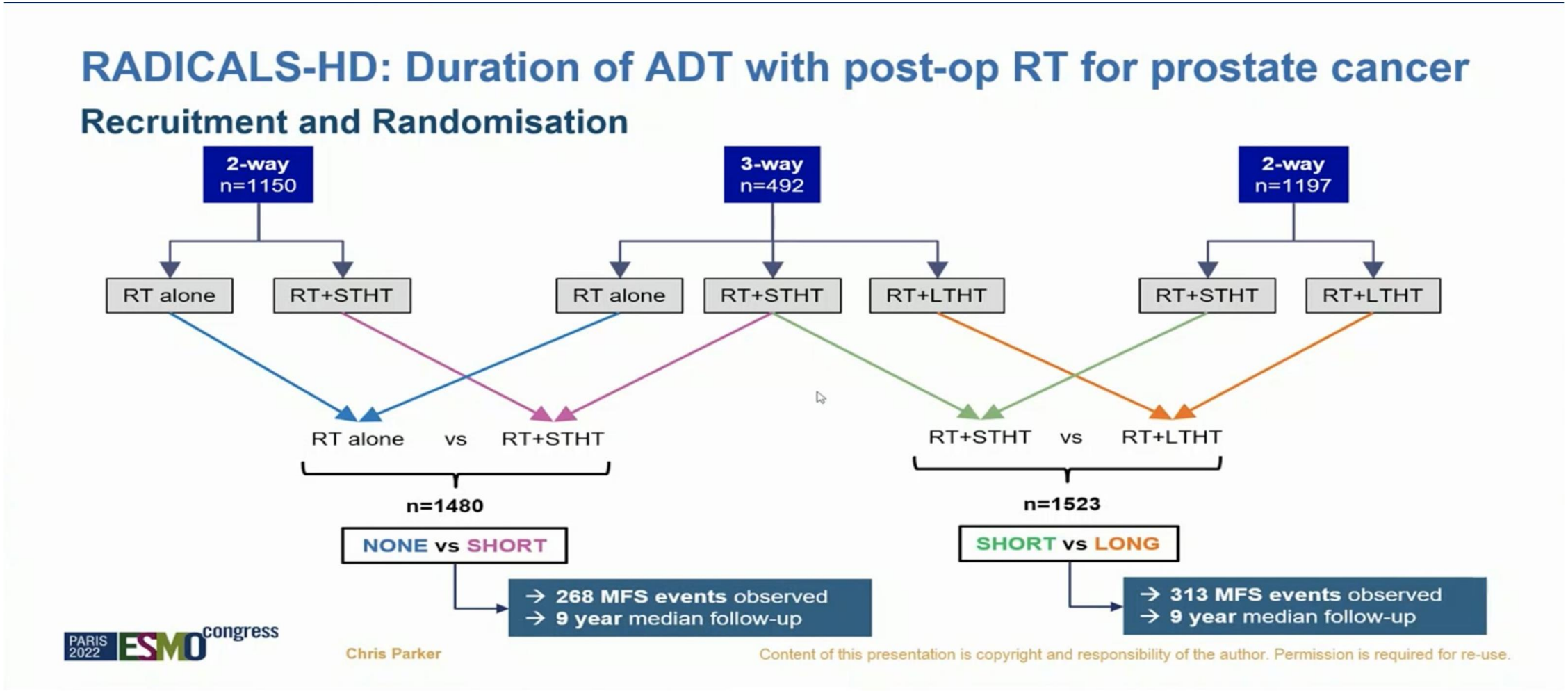
Overall, about 15% had pT3b disease, 53% had pT2 disease, 50% had positive margins, and 17% had Gleason score ≥8 disease. Pelvic lymphadenectomy was done in 65%, with a median number of lymph nodes removed of 6. The median PSA at protocol registration was 0.35 and 25% had a value of 0.2 or less.

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

RTOG 0534 SPPORT, Lancet. 2022

Biyokimyasal Rekürens ve PSA Persistansı RT+uzun dönem ADT



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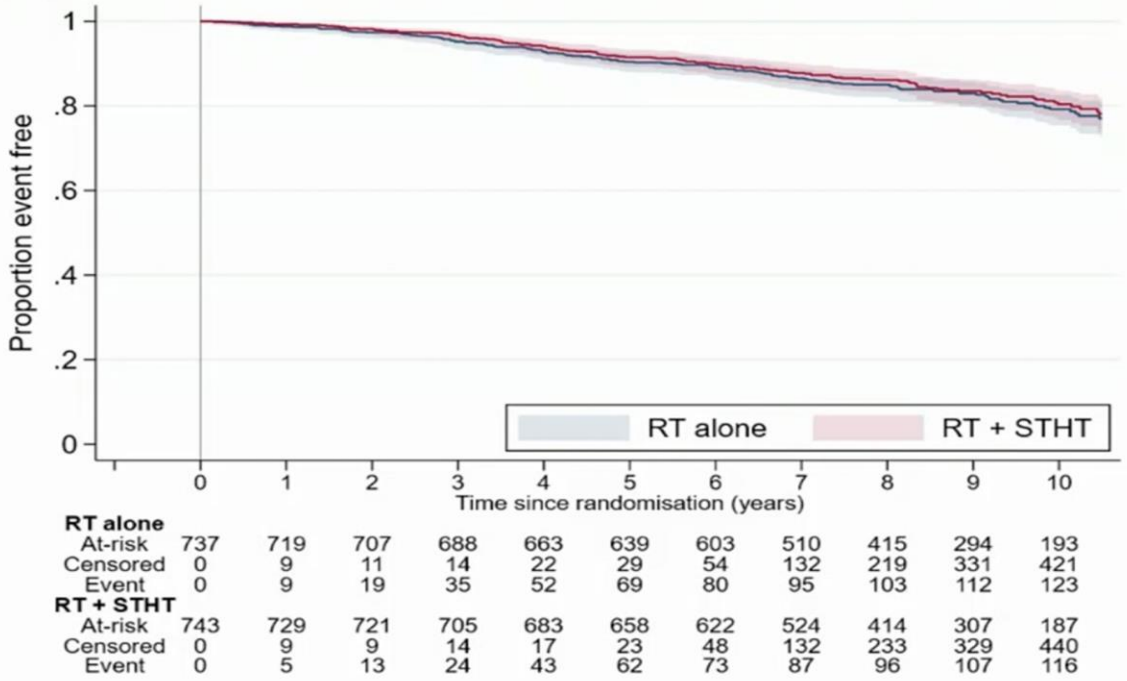
Biyokimyasal Rekürens ve PSA Persistansı
RT+uzun dönem ADT

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

None vs Short: Metastases-Free Survival (MFS)



RT alone										
At-risk	737	719	707	688	663	639	603	510	415	294	193
Censored	0	9	11	14	22	29	54	132	219	331	421
Event	0	9	19	35	52	69	80	95	103	112	123
RT + STHT										
At-risk	743	729	721	705	683	658	622	524	414	307	187
Censored	0	9	9	14	17	23	48	132	233	329	440
Event	0	5	13	24	43	62	73	87	96	107	116

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

PARIS 2022 ESMO congress

Chris Parker

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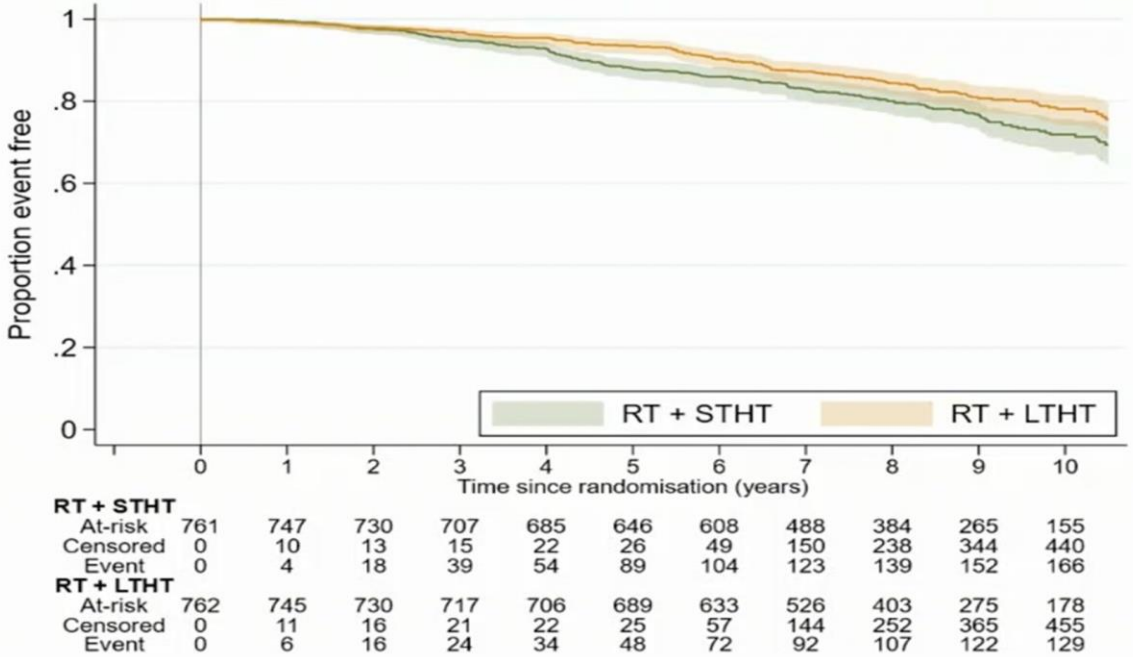
Biyokimyasal Rekürens ve PSA Persistansı
RT+uzun dönem ADT

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

Short vs Long: Metastases-Free Survival (MFS)



RT + STHT											
At-risk	761	747	730	707	685	646	608	488	384	265	155
Censored	0	10	13	15	22	26	49	150	238	344	440
Event	0	4	18	39	54	89	104	123	139	152	166
RT + LTHT											
At-risk	762	745	730	717	706	689	633	526	403	275	178
Censored	0	11	16	21	22	25	57	144	252	365	455
Event	0	6	16	24	34	48	72	92	107	122	129

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

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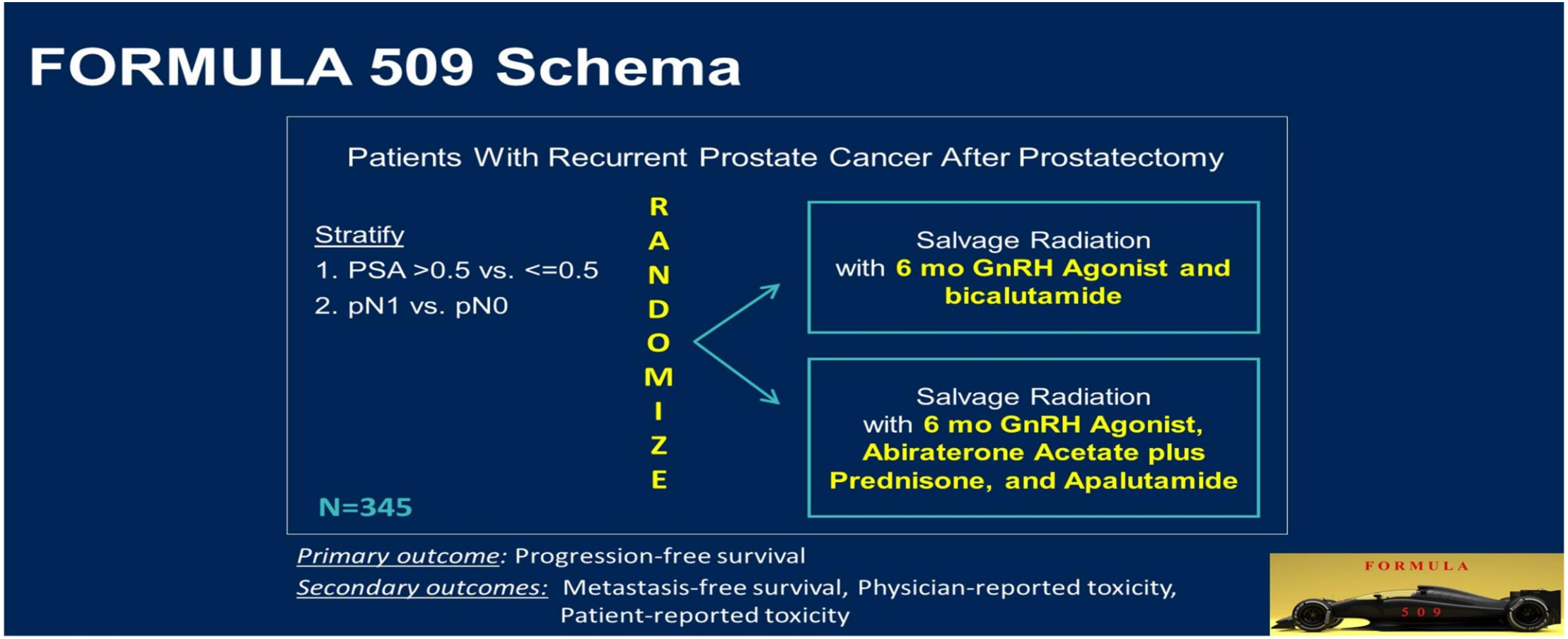
İzole PSA nüksünde hangi hastalar tedavi edilmeli

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



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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

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Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

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 No	 40 (23.5%) 130 (76.5%)	 49 (28.8%) 121 (71.2%)	 89 (26.2%) 251 (73.8%)

*5 pts without radiation details

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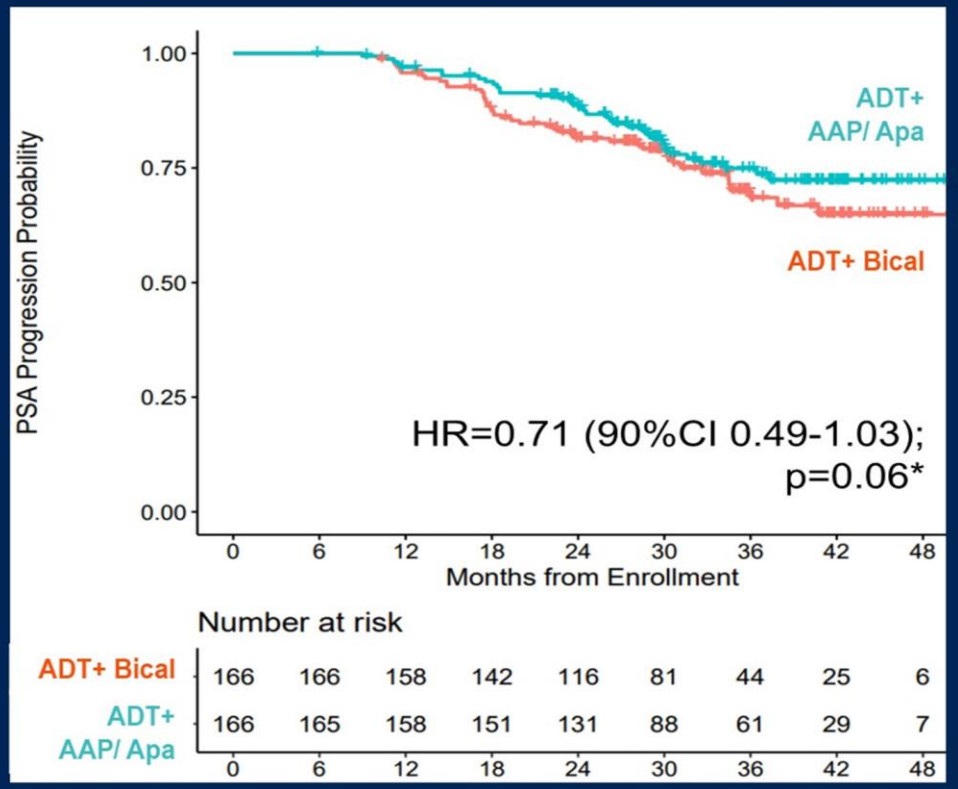
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Progression Free Survival

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



3 year PFS

74.9% vs. 68.5%

*one-sided

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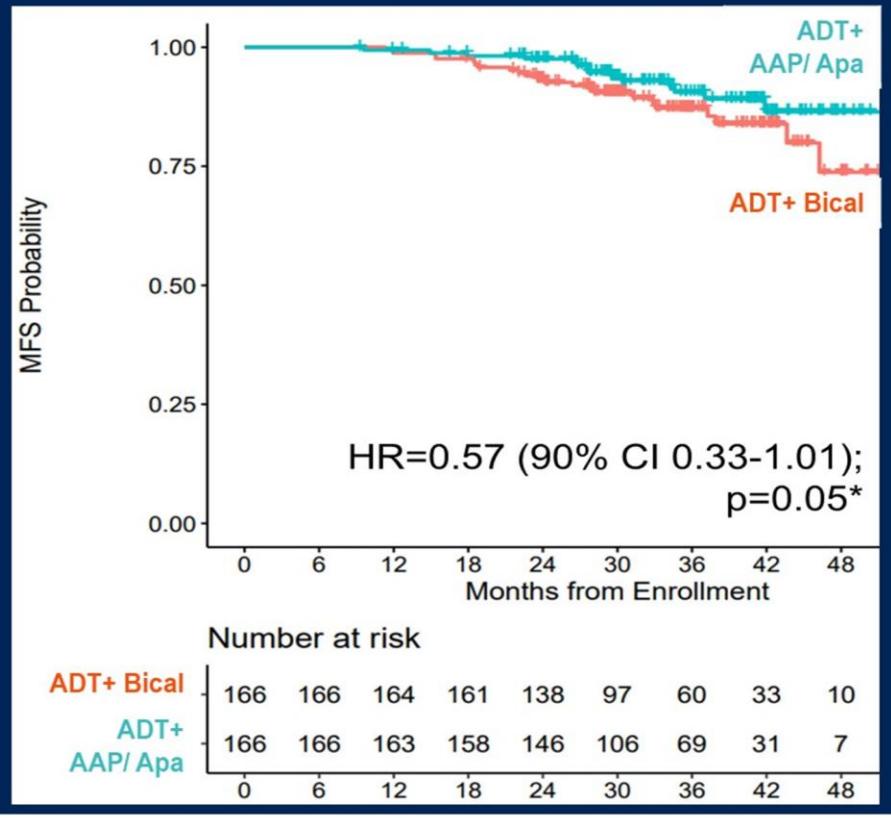
Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

Metastasis-Free Survival



3 year MFS

90.6% vs. 87.2%

*one-sided

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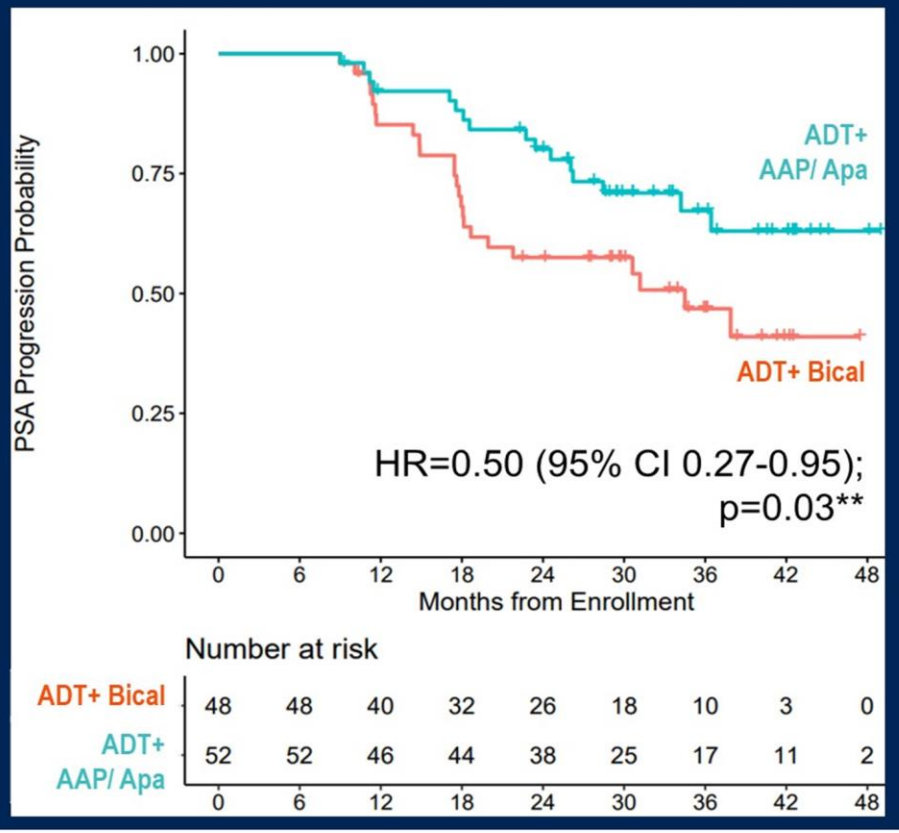
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PFS Benefit Among PSA >0.5 (n=100)



3 year PFS

67.2% vs. 46.8%

**two-sided

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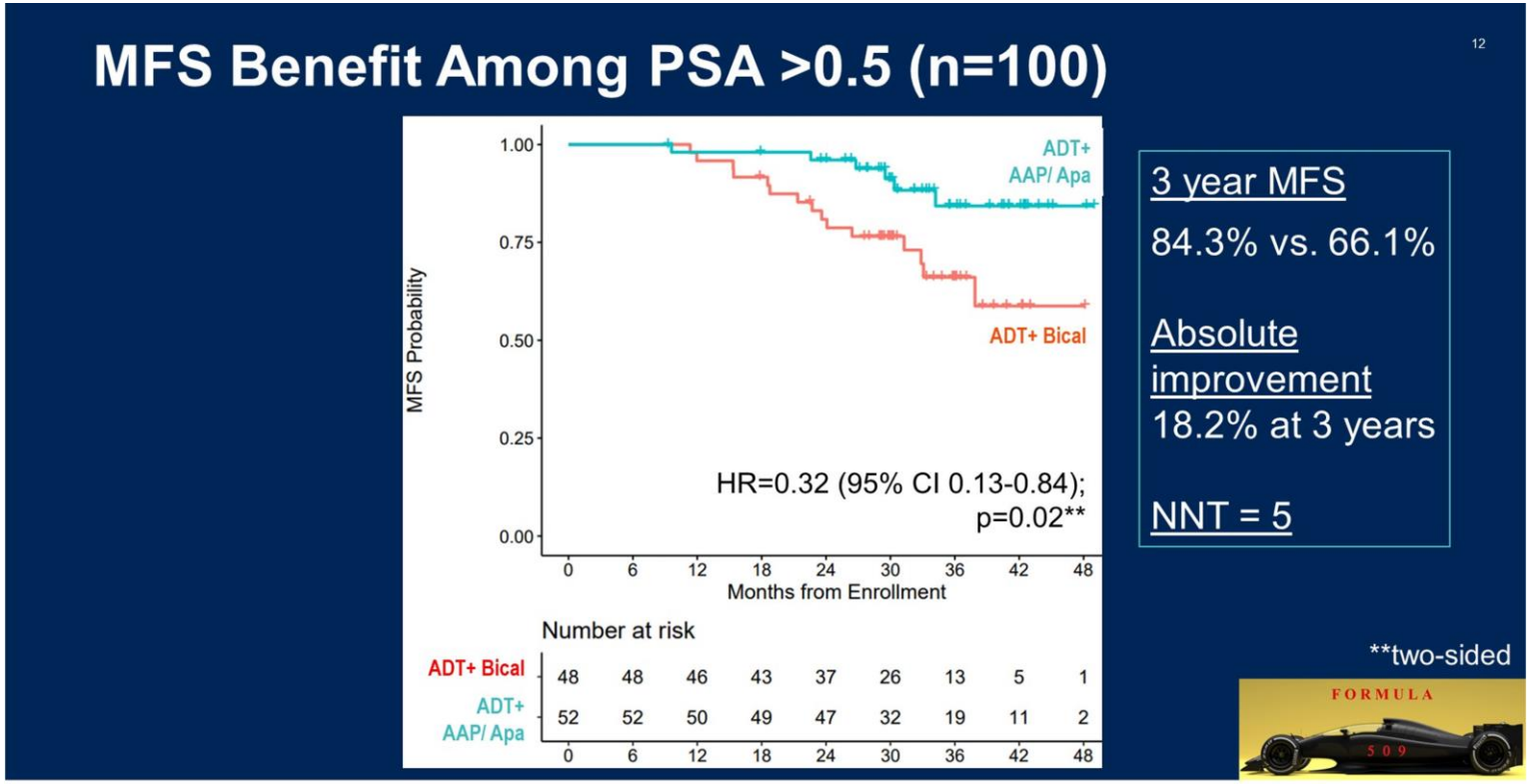
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi



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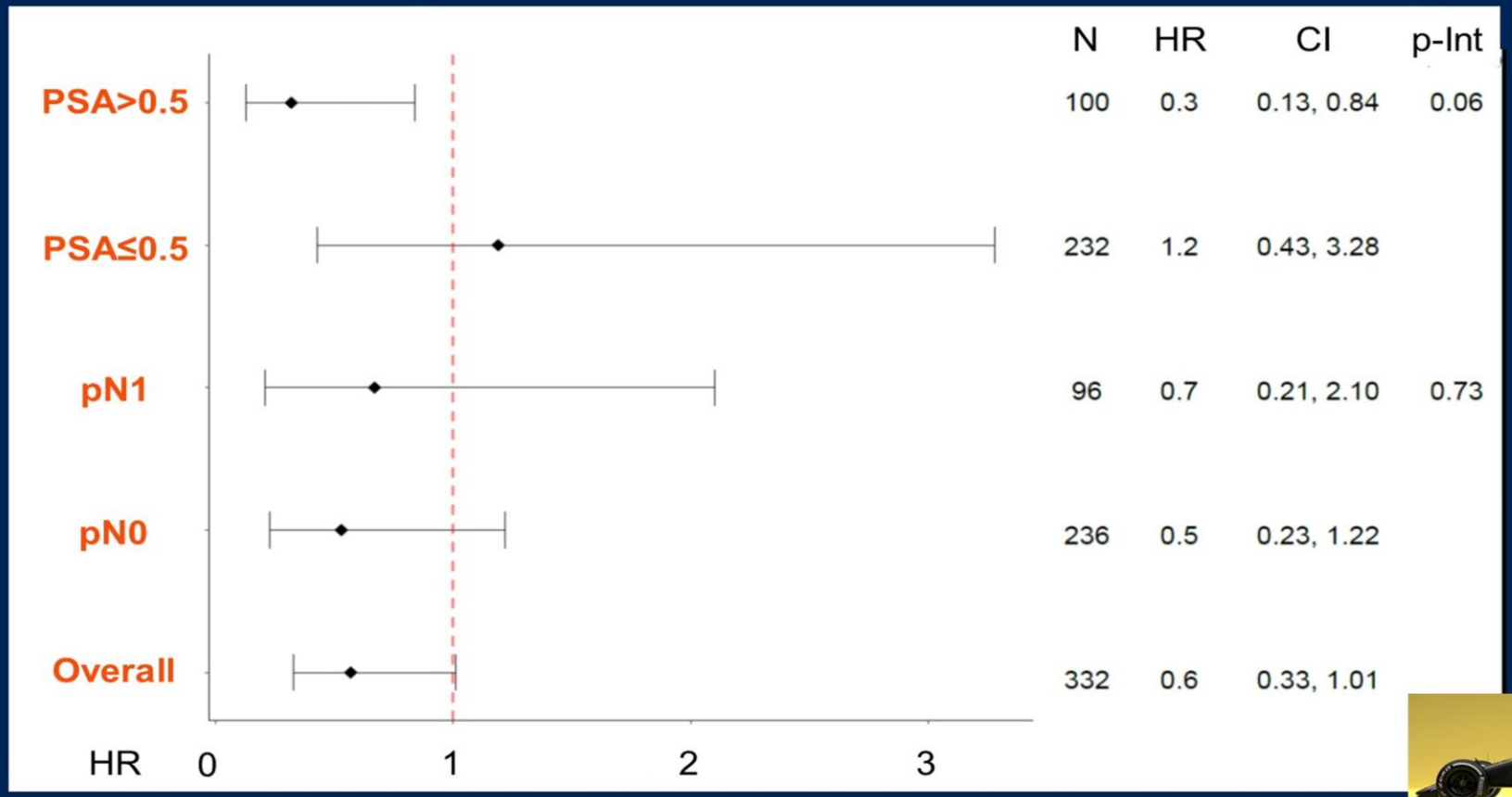
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

MFS Results by Pre-Planned Stratified Subgroups

13



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Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

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

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Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

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
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Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

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

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Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

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

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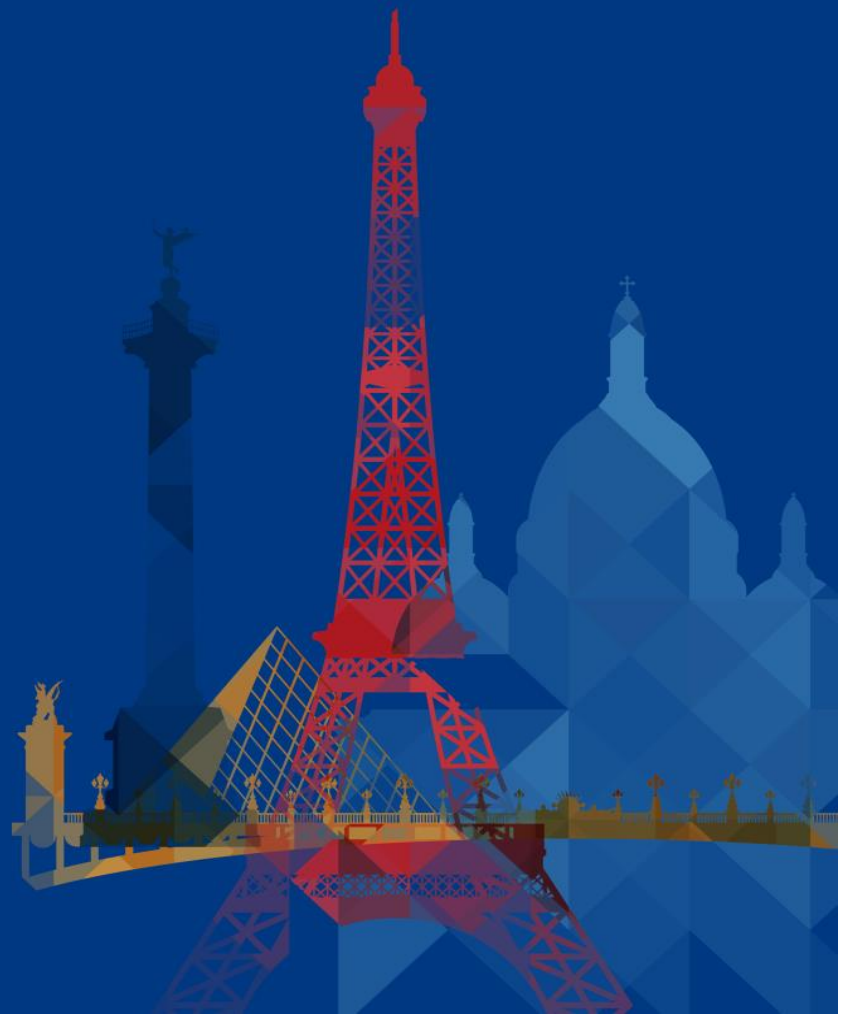
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PARIS 2022 ESMO congress

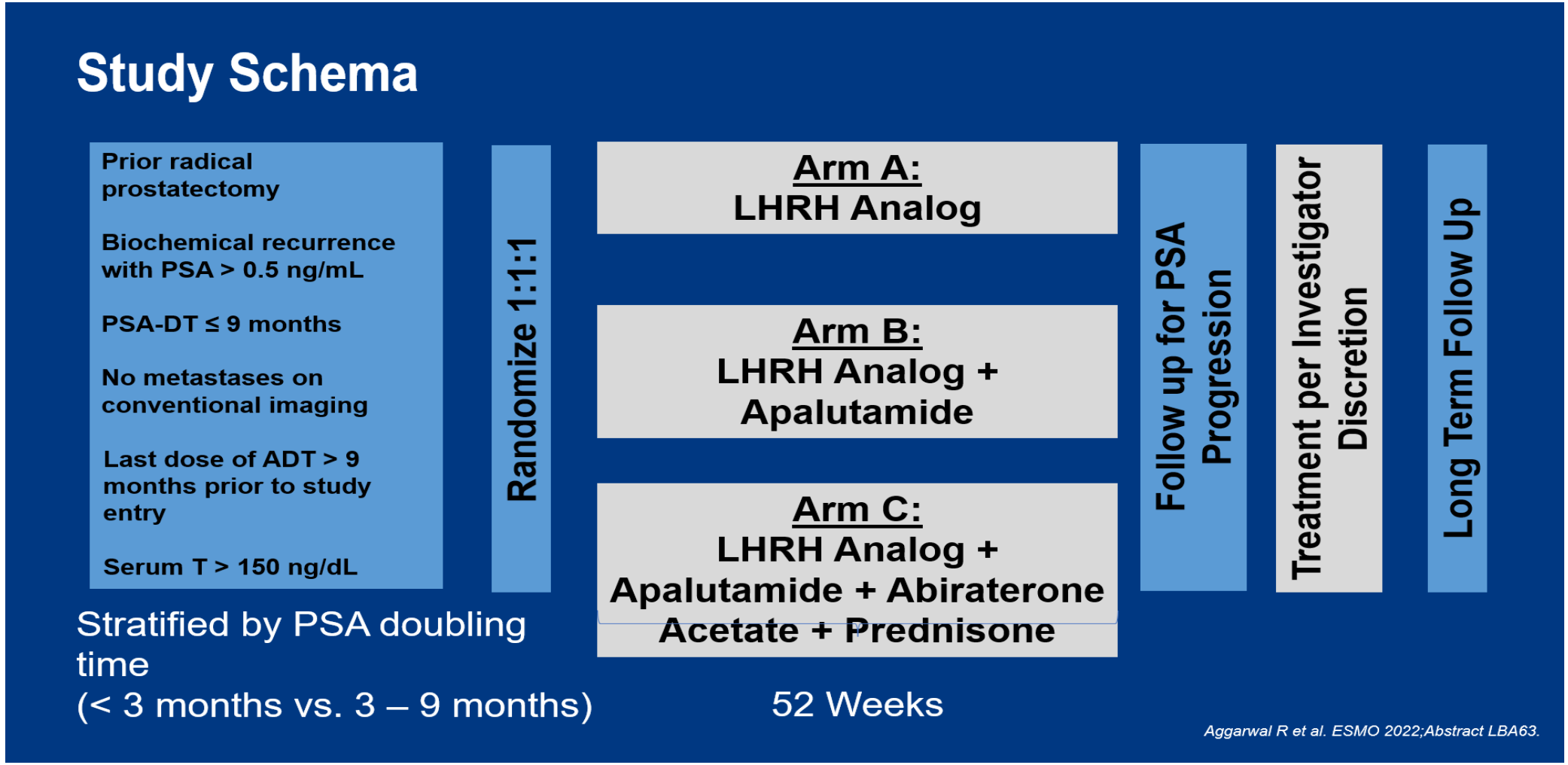
PRESTO: A Phase 3 Open-Label Study of Androgen Annihilation in Patients with High-Risk Biochemically Relapsed Prostate Cancer (AFT-19)

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

Paris, France
11 SEP 2022



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi



Aggarwal R et al. ESMO 2022;Abstract LBA63.

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

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

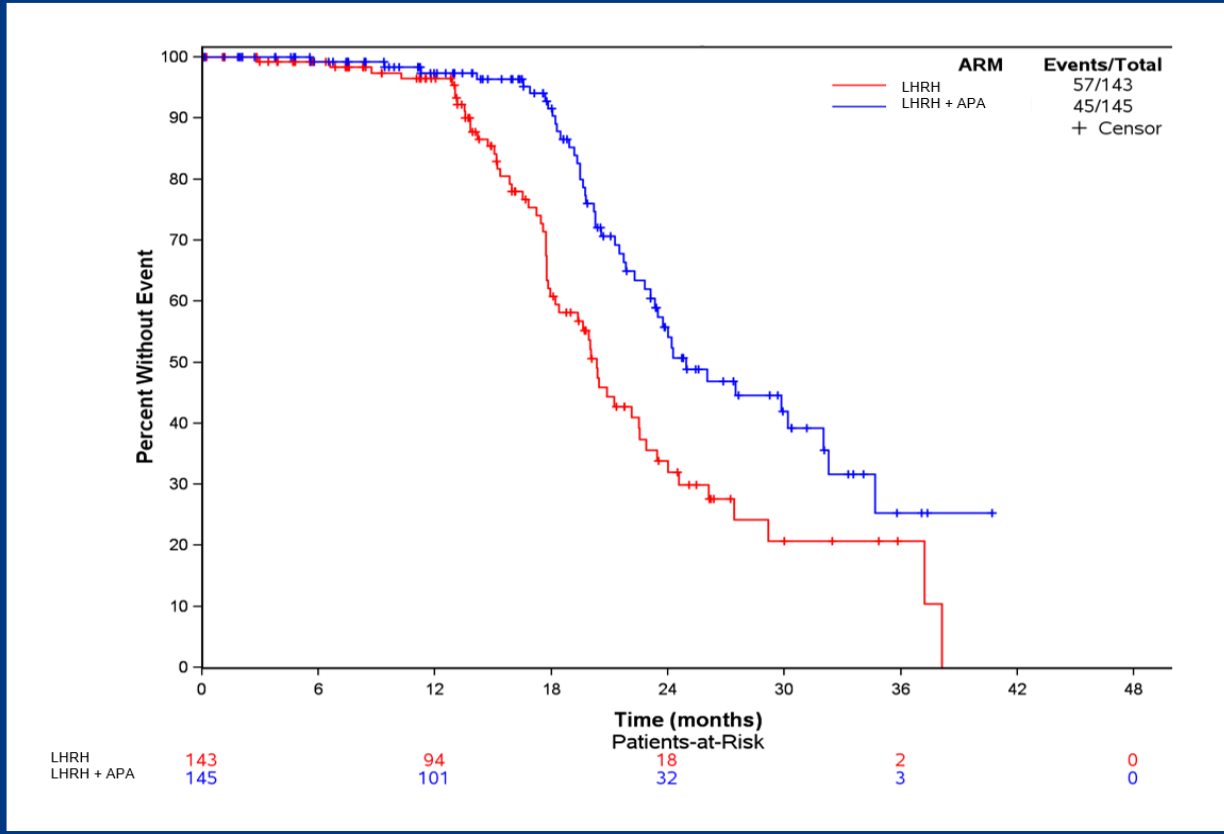
Baseline Characteristics, cont.

	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 3 – 9 months	 43 (25.9) 123 (74.1)	 43 (25.6) 125 (74.4)	 44 (26.0) 125 (74.0)	 130 (25.8) 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.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Arm B: ADT + apalutamide vs. ADT monotherapy

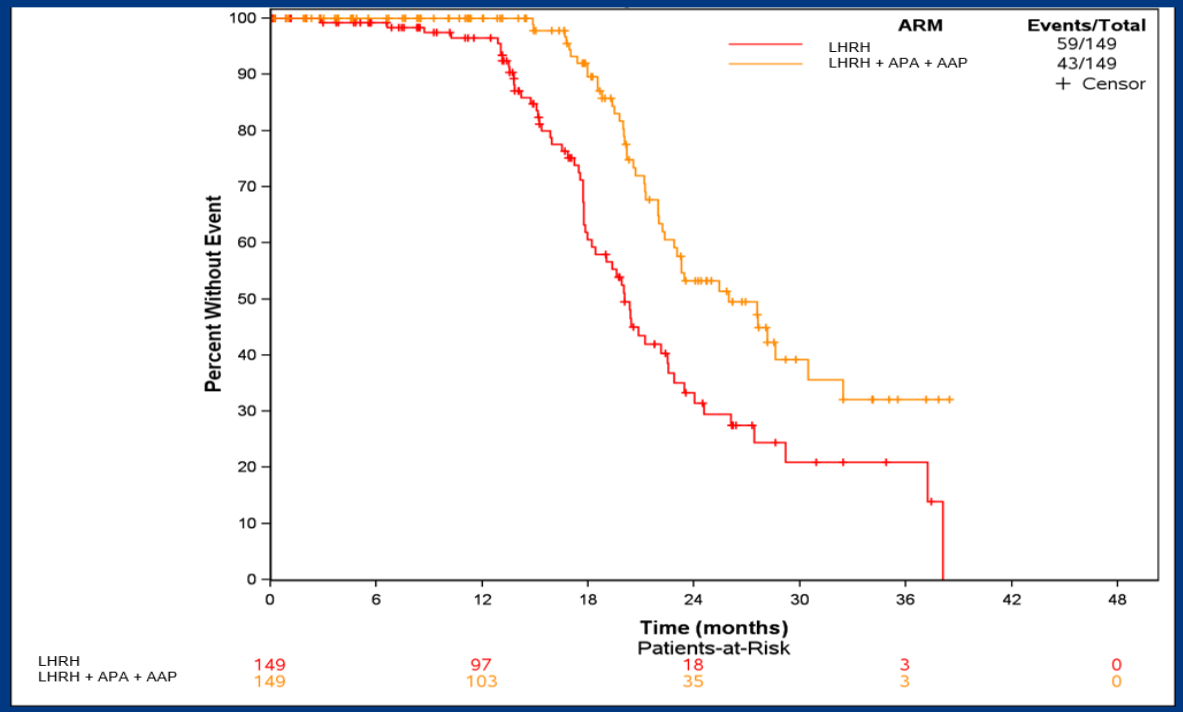


- Median follow up 21.5 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA = 24.9 months (95% CI: 23.3 – 32.3)
  - ADT alone = 20.3 months (95% CI: 18.2 – 22.9)
  - **Hazard ratio 0.52 (95% CI: 0.35 – 0.77)**
  - One-sided p-value = 0.00047)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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

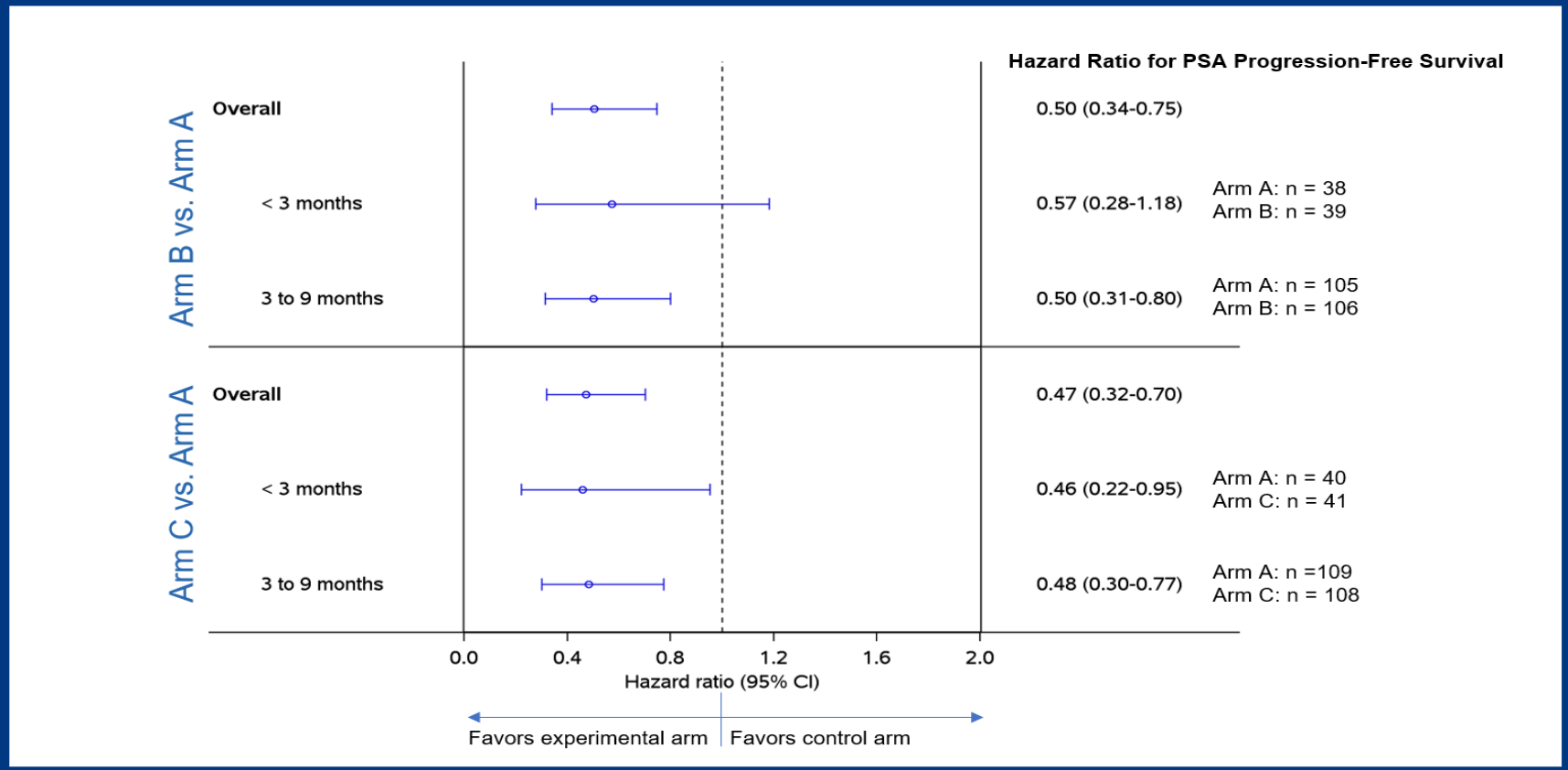


- Median follow up 21.3 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA + AAP = 26.0 months (95% CI: 22.9 – 32.5)
  - ADT alone = 20.0 months (95% CI: 18.2 – 22.5)
  - **Hazard ratio = 0.48 (95% CI: 0.32 – 0.71)**
  - One-sided p-value = 0.00008

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PSA Progression-Free Survival by PSA Doubling Time



Aggarwal R et al. ESMO 2022;Abstract LBA63.

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

Aggarwal R et al. ESMO 2022;Abstract LBA63.

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

Aggarwal R et al. ESMO 2022;Abstract LBA63.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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.

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

Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi

AUA 2023
CHICAGO ✶ APR 28-MAY 1

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.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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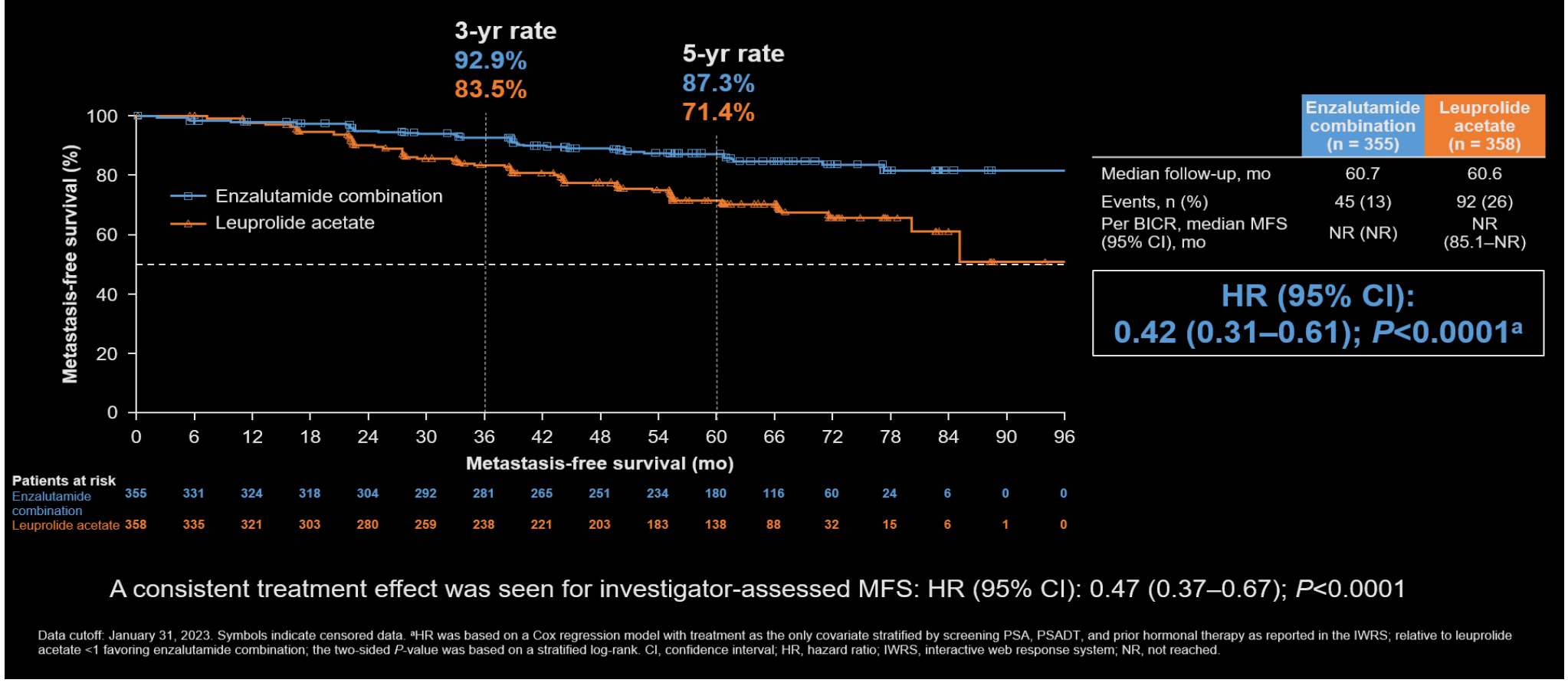
Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



	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

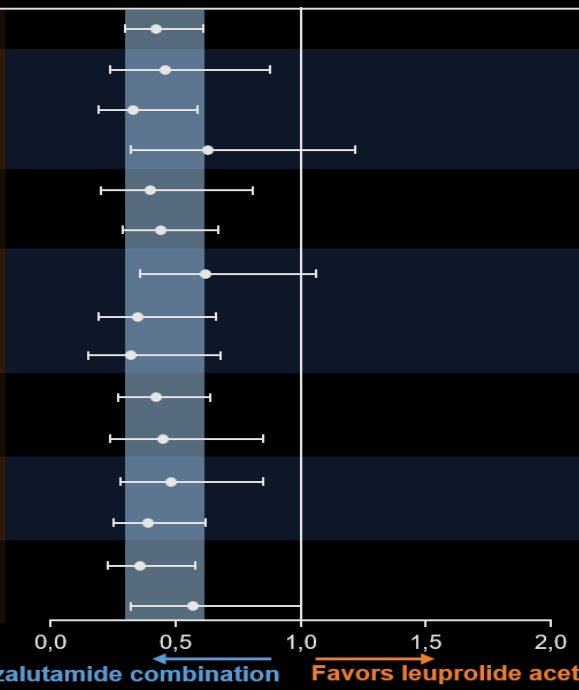
Data cutoff: January 31, 2023. Symbols indicate censored data. [a]HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide combination; the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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023
CHICAGO ✶ APR 28-MAY 1

Subgroup analysis of MFS for enzalutamide combination vs. leuprolide acetate

Subgroup		Enzalutamide combination Events, n	Leuprolide acetate /patients, n	MFS HR (95% CI)
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.

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023
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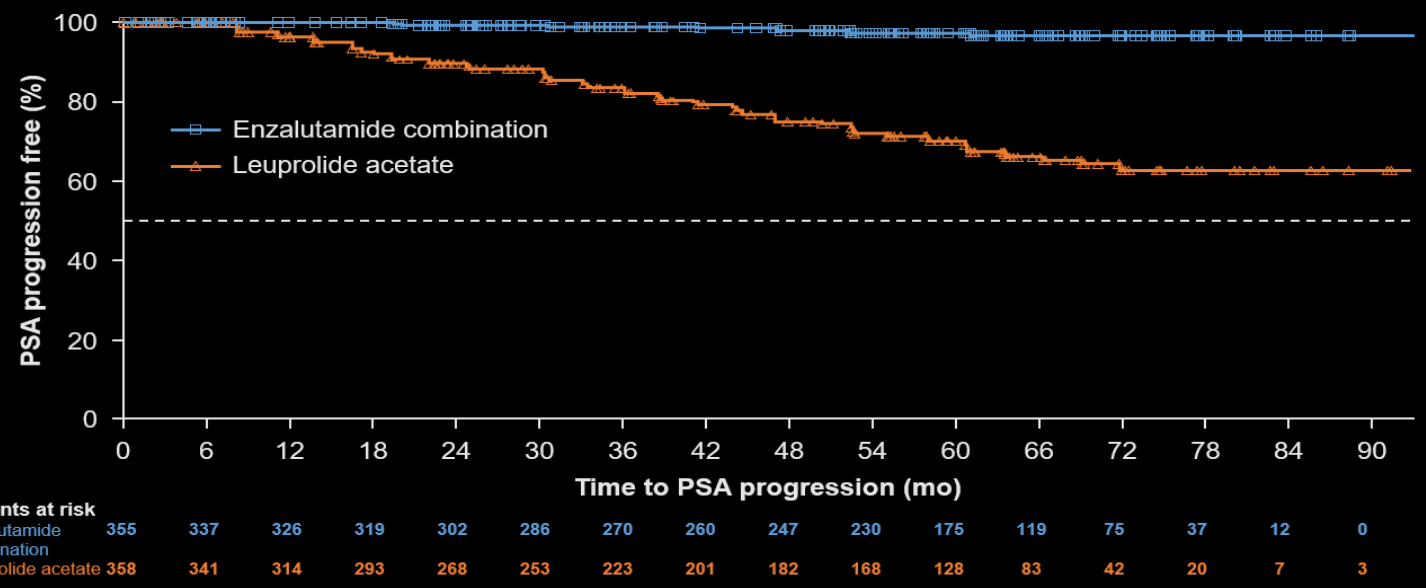
Key secondary endpoint — Time to PSA progression for enzalutamide combination vs. leuprolide acetate



	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]

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.

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023
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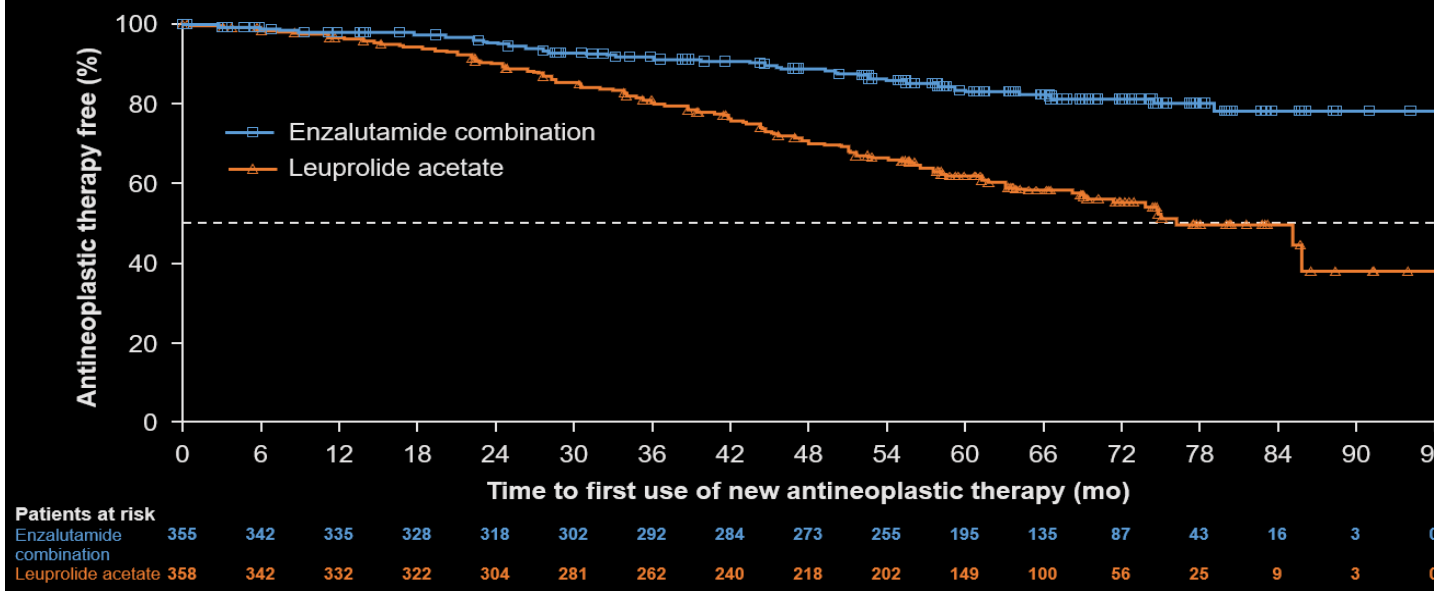
Key secondary endpoint — Time to first use of new antineoplastic therapy for enzalutamide combination vs. leuprolide acetate



	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]

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.

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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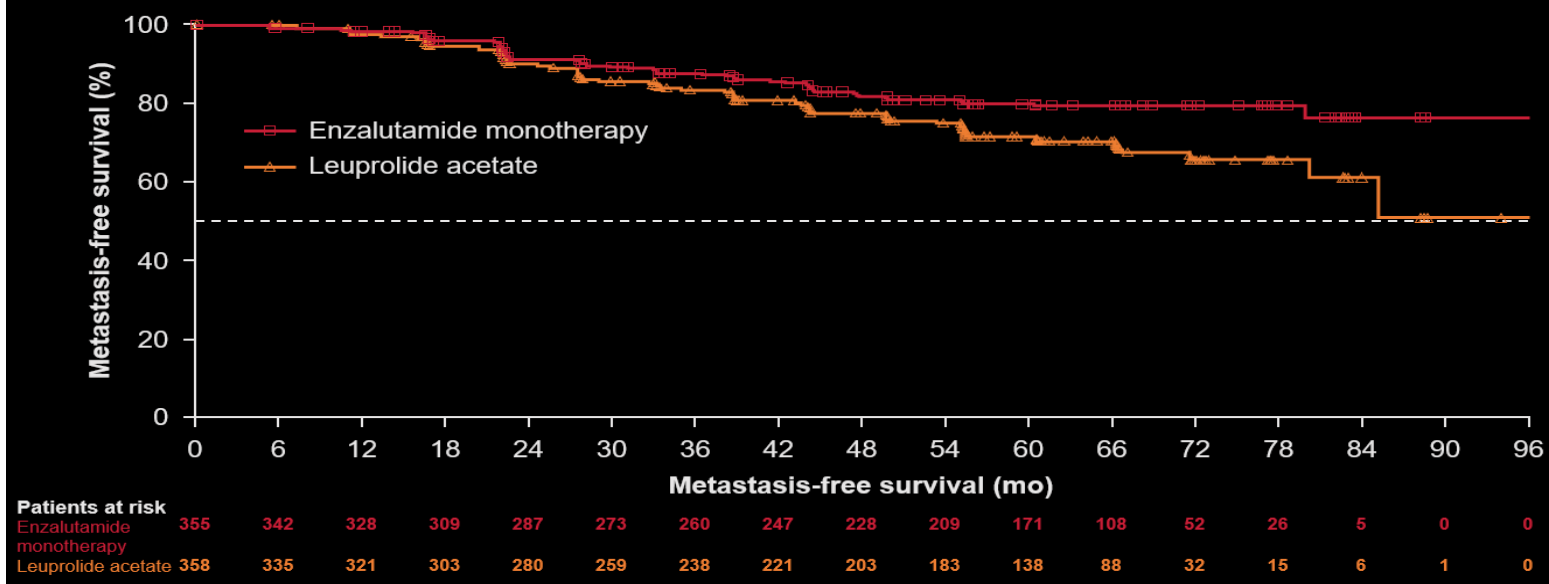
Key secondary endpoint — MFS for enzalutamide monotherapy vs. leuprolide acetate



	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]

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

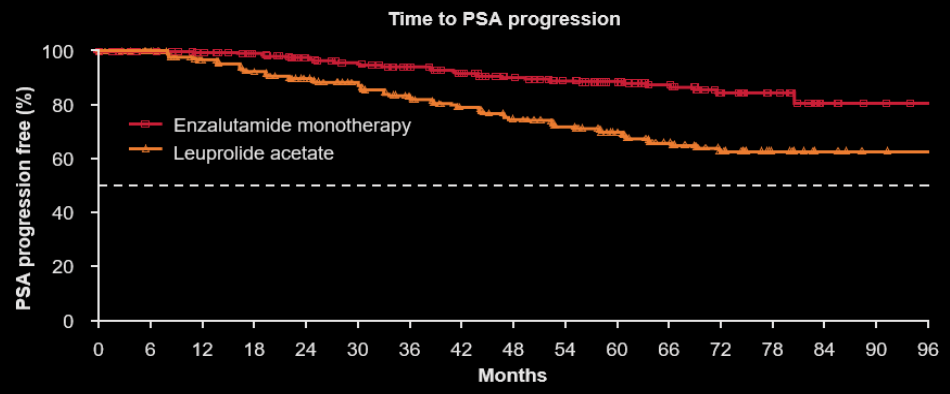
Data cutoff: January 31, 2023. Symbols indicate censored data. [a]The HR was based on a Cox regression model with treatment as the only covariate stratified by screening PSA, PSADT, and prior hormonal therapy as reported in the IWRS; relative to leuprolide acetate <1 favoring enzalutamide monotherapy;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

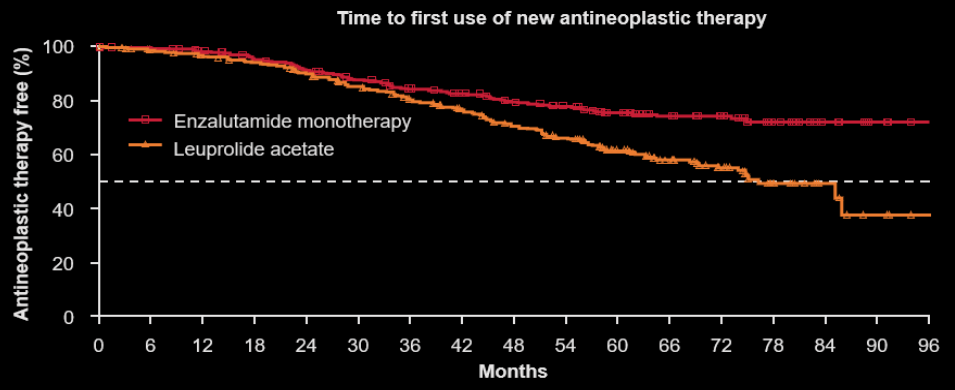
Shore N et al. AUA 2023;Abstract LBA02-09.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023
CHICAGO ★ APR 28-MAY 1

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

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 (%)	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]

	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.

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

Biyokimyasal Rekürens ve PSA Persistansı
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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.

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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Selected TEAEs of special interest

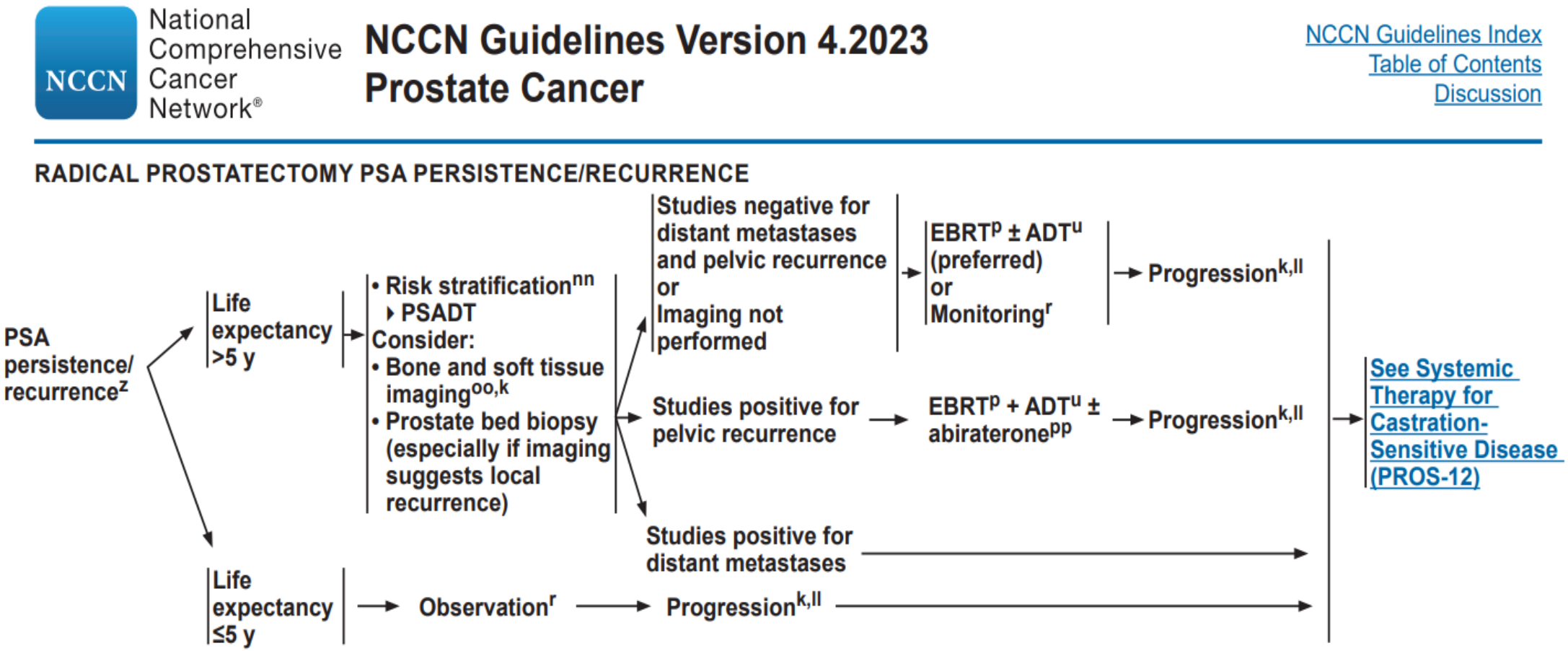
Clustered TEAEs of special interest, n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue[b]	178 (50.4)[c]	14 (4.0)	134 (37.9)[c]	6 (1.7)	191 (54.0)[c]	17 (4.8)
Musculoskeletal 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.

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

Sonuç 1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Prostate Cancer
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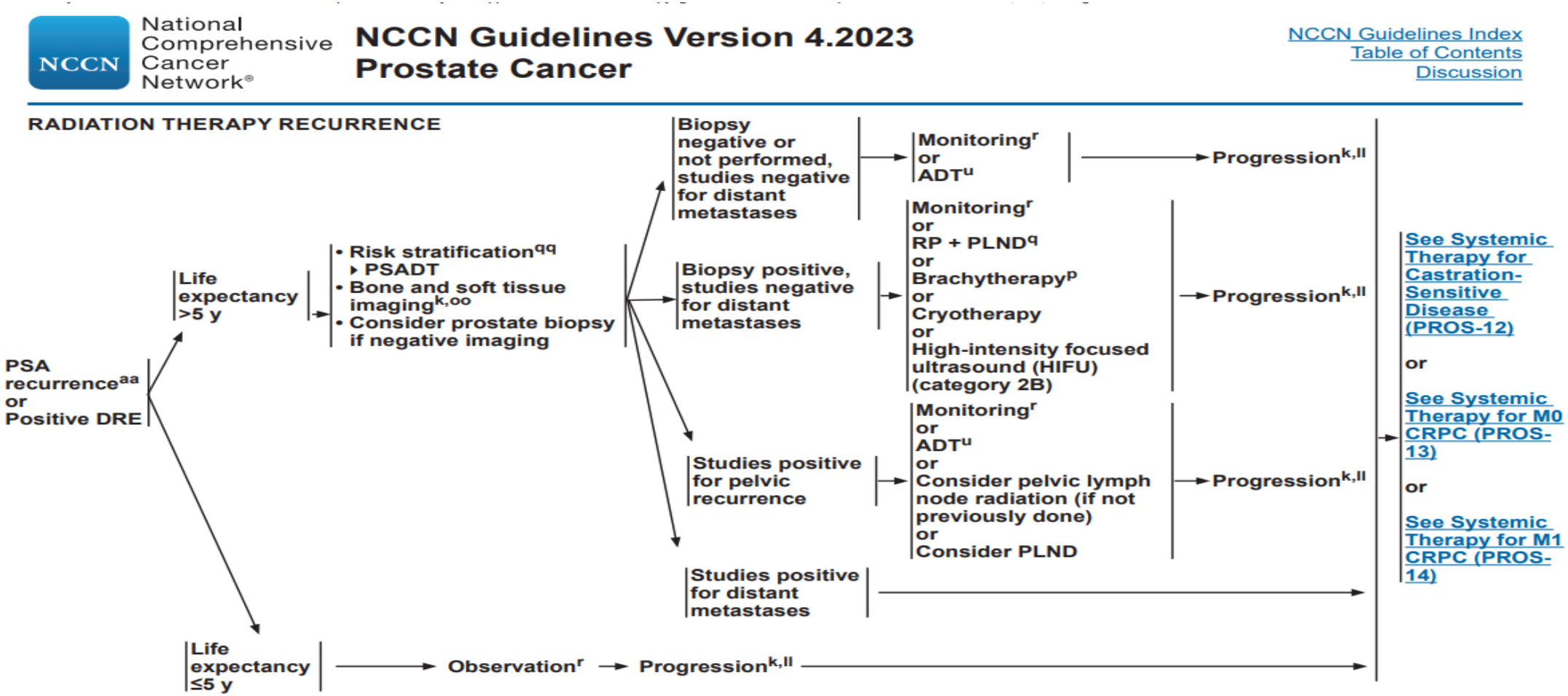
Discussion
RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE
PSA persistence/ recurrence[z]
Life expectancy >5 y
• Risk stratification[nn] ▸ PSADT
Consider:
• Bone and soft tissue imaging[oo,k]
• Prostate bed biopsy (especially if imaging suggests local recurrence)
Studies negative for distant metastases and pelvic recurrence or Imaging not performed
EBRT[p] ± ADT[u] (preferred) or Monitoring[r]
Progression[k,ll]
Studies positive for pelvic recurrence
EBRT[p] + ADT[u] ± abiraterone[pp]
Progression[k,ll]
Studies positive for distant metastases
Life expectancy ≤5 y
Observation[r]
Progression[k,ll]
See Systemic Therapy for Castration-Sensitive Disease (PROS-12)

Sonuç 2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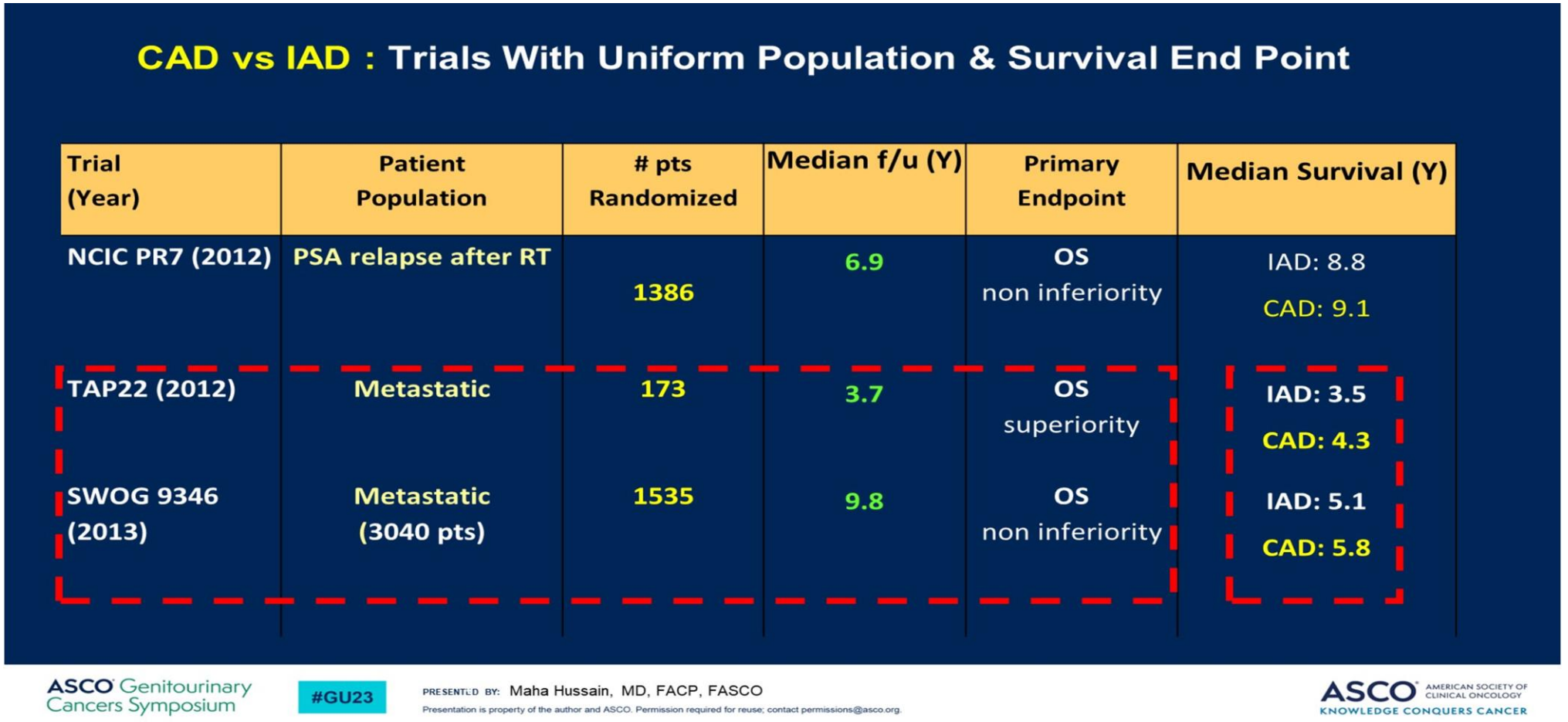
Discussion
RADIATION THERAPY RECURRENCE
PSA recurrence[aa] or Positive DRE
Life expectancy >5 y
• Risk stratification[qq] ▸ PSADT
• Bone and soft tissue imaging[k,oo]
• Consider prostate biopsy if negative imaging
Biopsy negative or not performed, studies negative for distant metastases
Monitoring[r] or ADT[u]
Progression[k,ll]
Biopsy positive, studies negative for distant metastases
Monitoring[r] or RP + PLND[q] or Brachytherapy[p] or Cryotherapy or High-intensity focused ultrasound (HIFU) (category 2B)
Progression[k,ll]
Studies positive for pelvic recurrence
Monitoring[r] or ADT[u] or Consider pelvic lymph node radiation (if not previously done) or Consider PLND
Progression[k,ll]
Studies positive for distant metastases
Life expectancy ≤5 y
Observation[r]
Progression[k,ll]
See Systemic Therapy for Castration-Sensitive Disease (PROS-12)
or
See Systemic Therapy for M0 CRPC (PROS-13)
or
See Systemic Therapy for M1 CRPC (PROS-14)

RT sonrası Biyokimyasal Rekürens



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

Table 1 – Trials comparing iADT to cADT

Trial	Patient population	mFU (yr)	Primary endpoint	Median (yr)		Trial design	HR for primary endpoint (iADT vs cADT) [a]		NI or SUP achieved?
				cADT	iADT		PST	HR (95% CI)	
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 ($p = 0.75$)
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.

PRESENTED BY: Maha Hussain, MD, FACP, FASCO

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Serritella, AV, Fenton SE, Hussain M:. European Urology Focus, 2023

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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 (±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 (±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

Sonuç 4

	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 (±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)

Sonuç 5

Please cite this article as: S. Gillessen, A. Bossi, I.D. Davis et al., Management of Patients with Advanced Prostate Cancer. Part I: Intermediate-/High-risk and Locally Advanced Disease, Biochemical Relapse, and Side Effects of Hormonal Treatment: Report of the Advanced Prostate Cancer Consensus Conference 2022, Eur Urol (2022), https://doi.org/10.1016/j.eururo.2022.11.002

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 12ay ≤ 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≥ ve gleason skoru ≥8)?
- Pelvik RT nüks riski yüksek hastalarda düşünülebilir(Gleason≥8, ≥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