Lokal İleri Prostat Kanserinde Sistemik Tedavi

Dr. Deniz Tural

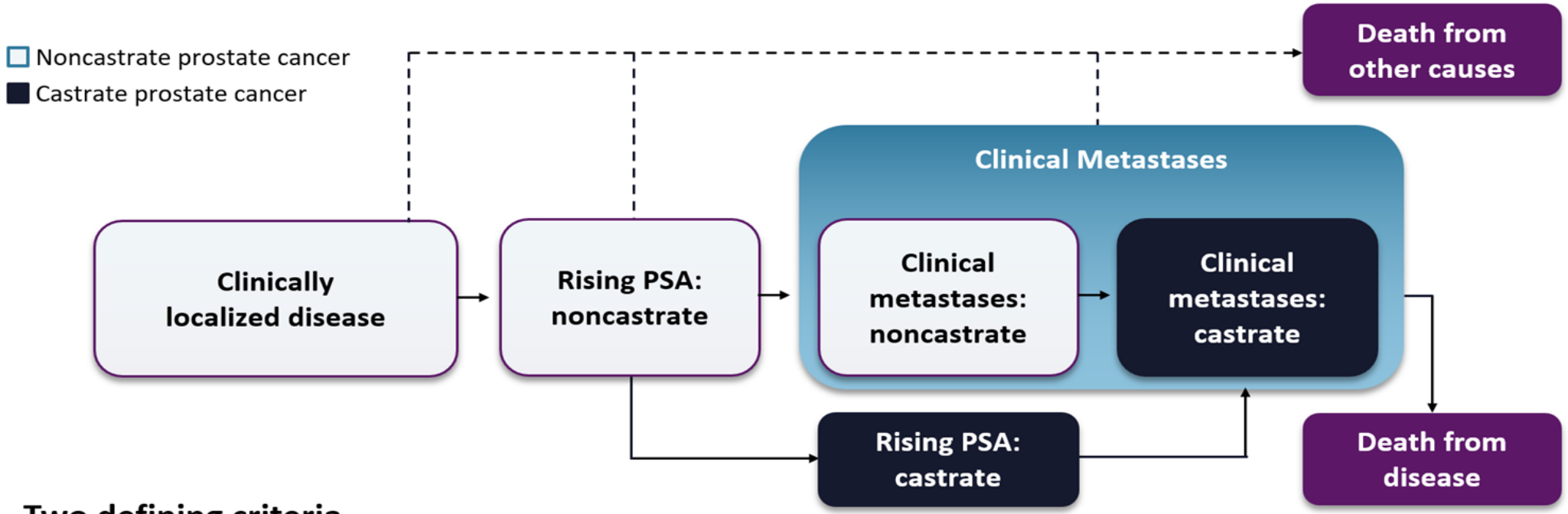
Koç Üniversitesi Hastanesi Tıbbi Onkoloji

Ders Planı

- ❑Neoadjuvan sistemik tedaviler
- ❑PSA persistent ve nüksü
- ❑Adjuvan tedaviler
- ❑Kombinasyon tedavileri
- ❑Sonuç

Prostat kanserinin seyri

Clinical Disease States Model of Prostate Cancer[1]



Two defining criteria

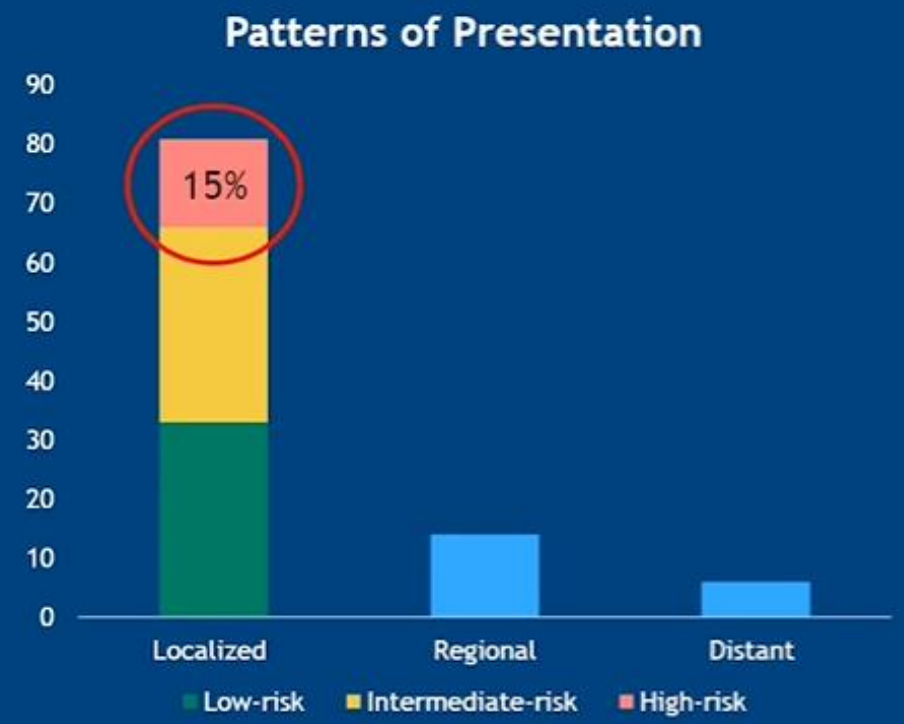
- Rising PSA in the setting of castrate testosterone levels (<50 ng/dL)
- No radiographically identifiable metastasis

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

Courtesy of Matthew R Smith, MD, PhD

Lokalize Yüksek Riskli Prostat Kanseri

Localized High-Risk Prostate Cancer



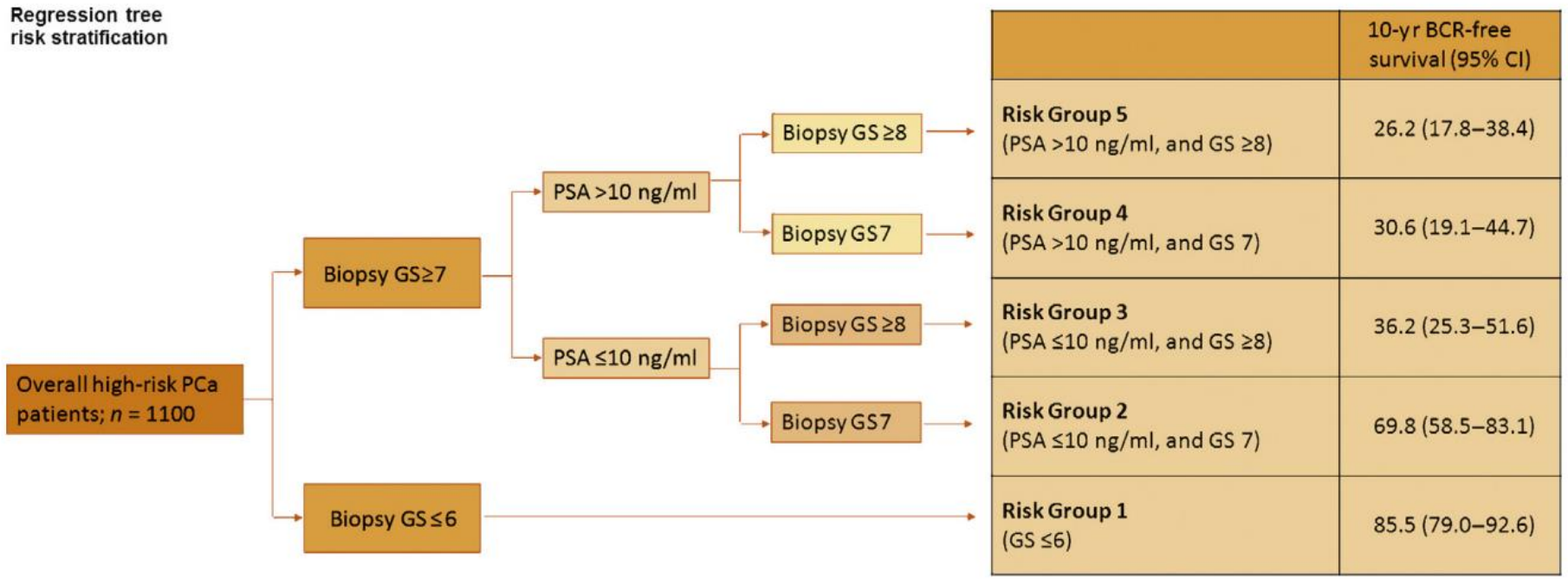
Increased Mortality in High-Risk Prostate Cancer

High-Risk Feature	15-Year PCSM
PSA > 20 ng/mL	22%
Gleason 8-10	34%
cT3	38%
High-risk Disease*	19%

PCSM=Prostate cancer specific mortality; PSA=Prostate specific antigen. *Defined by D'Amico criteria: PSA > 20 ng/mL, Gleason 8-10, or cT2c-T3.

Cooperberg, JCO, 2010; Eggener, J Urol, 2011

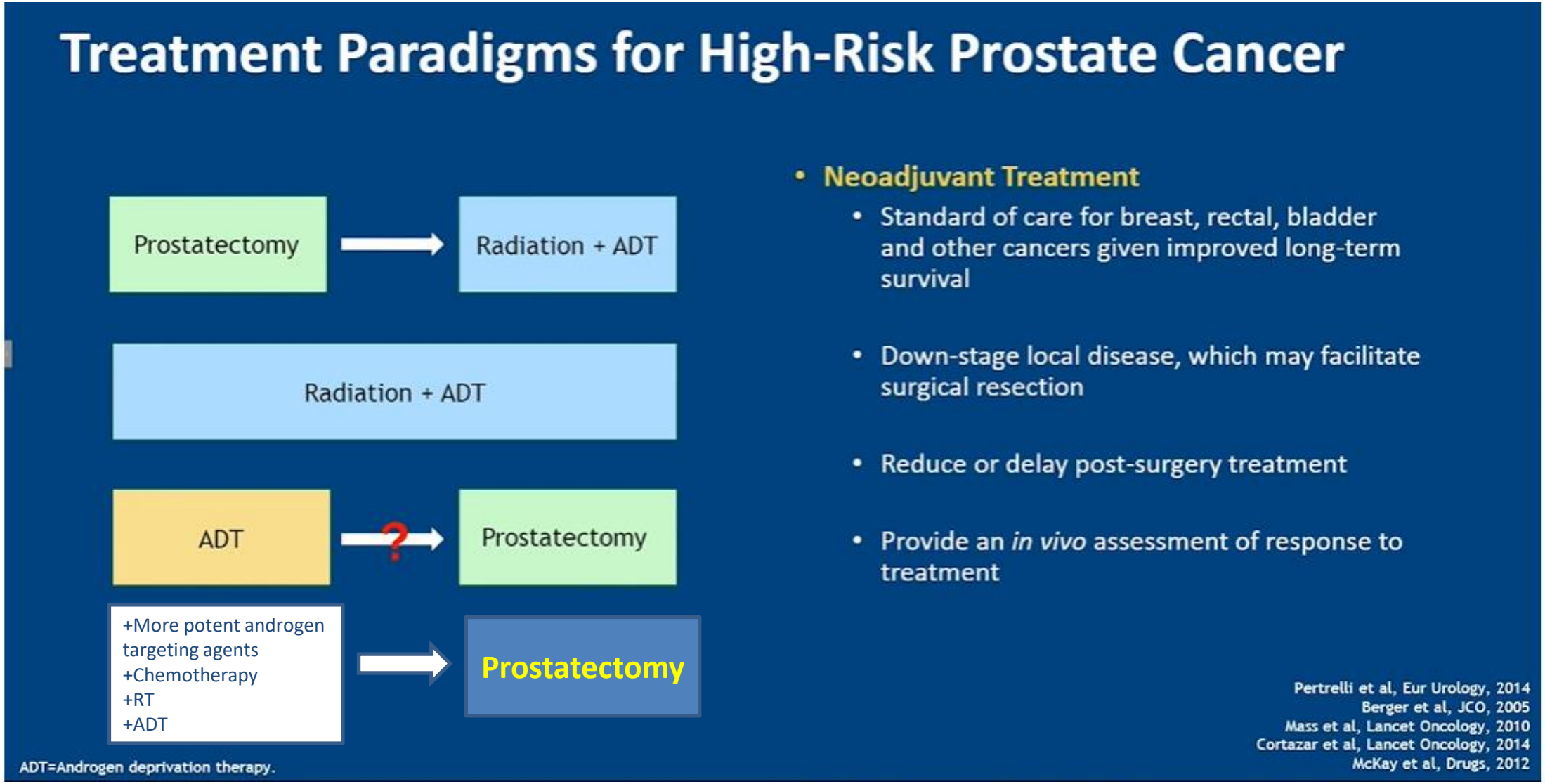
Lokalize Yüksek Riskli Prostat Kanseri



	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.

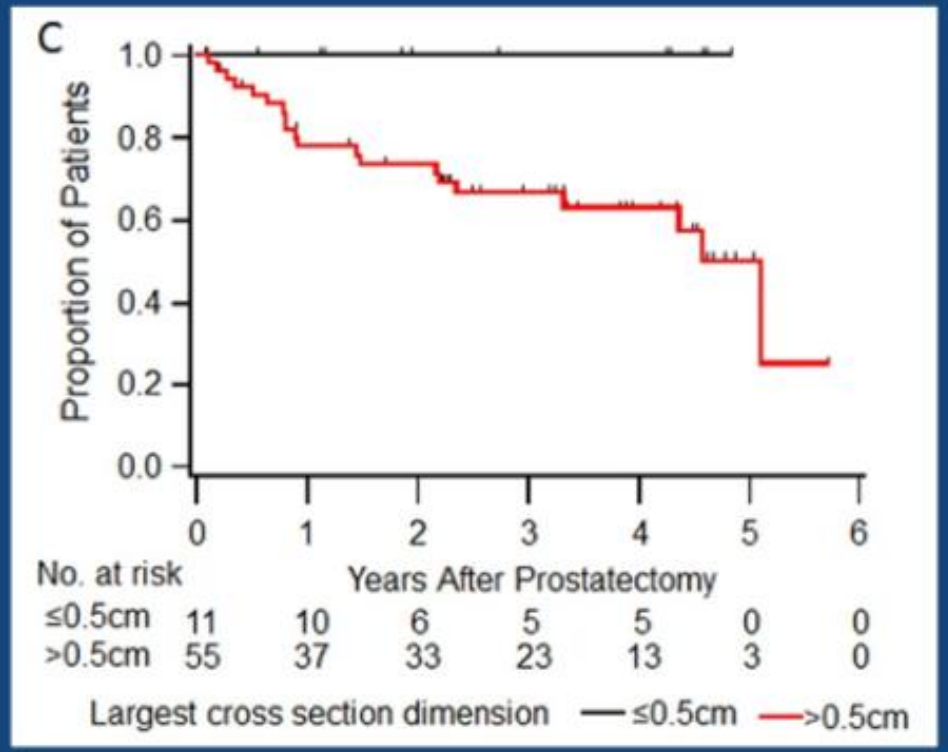
Neoadjuan Tedavi Gerekçesi



Neoadjuan Tedavi Gerekçesi

Correlation of Pathologic Response with PSA Recurrence

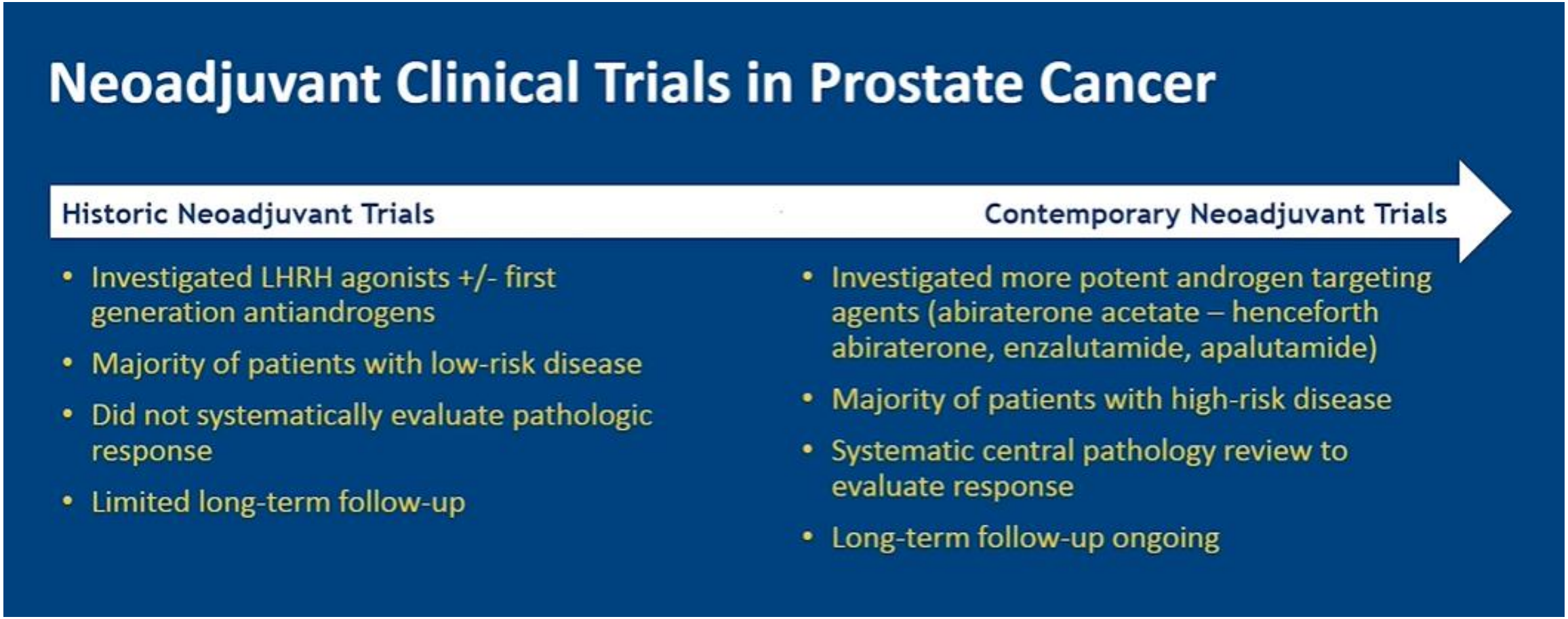
- Pooled analysis of three contemporary neoadjuvant studies (n=72)
- Median follow-up 3.4 years
- No recurrences observed in patients with a pCR or MRD at radical prostatectomy



pCR=Pathologic complete response; MRD=Minimum residual disease.

McKay et al, PCPD, 2018

Neoadjuan Tedavi Gerekçesi



ADT ile Neoadjuan Tedavi

Neoadjuvant therapy with Convention Androgen Deprivation therapy agents

Author	Year	Location	n	Abbreviated inclusion criteria	Agent (Duration)	Primary endpoint results
Labrie (26)	1993	Québec, Canada	77	Early stage prostate cancer	Leuprolide + Flutamide (3 Months)	Cancer-positive margins were reduced from 38.5% in control patients to 13.0% in men who received neoadjuvant combination (p = 0.006).
Debruyne (27)	1994	Nijmegen, Netherlands.	65	cT2-3, N0, M0 stages of prostate cancer	Goserelin + Flutamide (3 Months)	Serum PSA levels and prostatic volume decreased from a mean of 12.8 ng/ml and 42.8 cm3 to a mean of 0.8 ng/ml and 29.5 cm3, respectively.
Van Poppel	1995	Leuven,	65	Stages T2b and T3 prostate cancer	Estramustine +	For T2b tumors, a significant decrease in
		Canada			months *vs* 8 months)	group (0.052 *vs* 0.12mc/L, P<0.001). Surgical margins favored 8 month ADT group (12% *vs* 23%, p=0.01).
Selli (34)	2002	Pisa, Italy	265	Surgically resectable clinical stage (T2–T3, N0, M0) prostatic cancer	Goserelin, Bicalutamide (3/6 Months)	PSA progression: significant differences between treatment groups.
Prezioso (35)	2004	Naples, Italy	91	Prostatic cancer clinical stage T2b or less	Leuprolide, Cyproterone (3 Months)	Neoadjuvant group: 31% of patients had a decrease in tumor and prostate volume.
Gravina (36)	2007	L'Aquila, Italy	61	Prostate cancer clinical Stage T2-T3a	Bicalutamide (4 Months)	Neoadjuvant treatment had a reduction of positive surgical margins (13.1% versus 34.5%, $P = 0.011$).

ADT ile daha iyi cerrahi sınır, down staging

BPFS ve OS katkısı yok

Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Pathologic Responses from Potent Neoadjuvant Therapy

Conducted a series of neoadjuvant trials over the last 10 years

Phase 2 biomarker integrated trials evaluating potent neoadjuvant hormone therapy

	NeoAbi (n=58)	NeoEnza (n=40)	NeoAbiEnza (n=75)
Arms	12wAbi vs. 24wAbi	Enza vs. EDL	EL vs. APEL
CR	4% vs. 10%	0% vs. 4%	8 vs. 12%
MRD*	0% vs. 14%	0% vs. 13%	11% vs. 18%
CR + MRD	4% vs. 24%	0% vs. 17%	19% vs. 30%

Abi=Abiraterone; Enza=Enzalutamide; EDL=Enzalutamide, dutasteride, leuprolide; APEL=Abiraterone, prednisone, enzalutamide, leuprolide; EL=Enzalutamide, leuprolide; CR=Complete response; MRD=Minimum residual disease. *Defined as residual tumor with largest cross section dimension ≤ 0.3-0.5 cm.

Taplin et al, JCO, 2014
Montgomery et al, CCR, 2016
McKay et al, JCO, 2019

Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Pathologic Responses from Potent Neoadjuvant Therapy

Conducted a series of neoadjuvant trials over the last 10 years

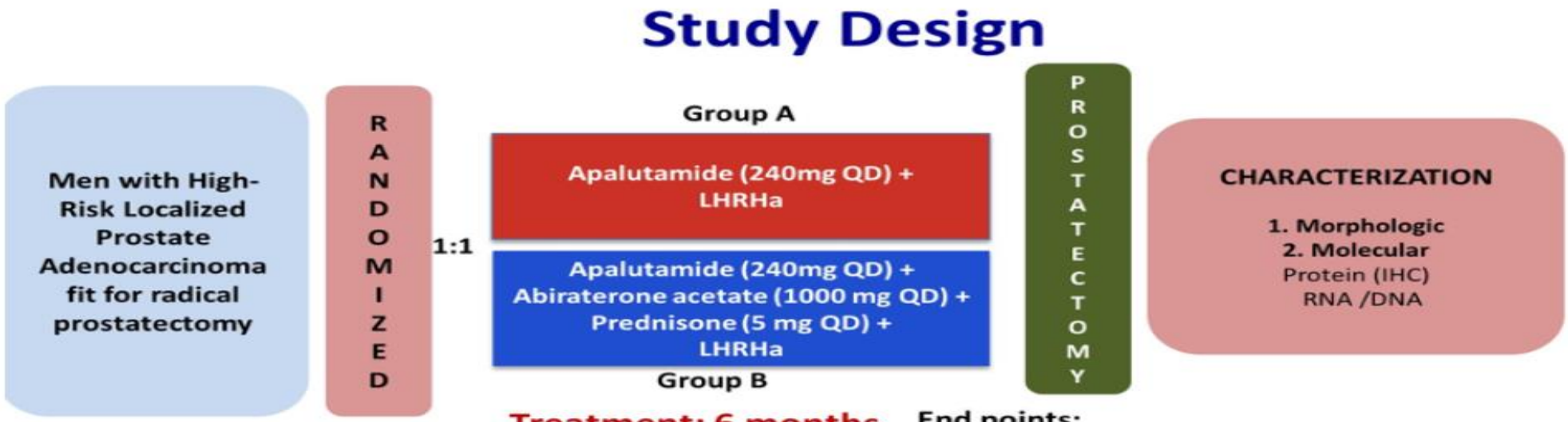
Phase 2 biomarker integrated trials evaluating potent neoadjuvant hormone therapy

	NeoAbi (n=58)	NeoEnza (n=40)	NeoAbiEnza (n=75)
Arms	12wAbi vs. 24wAbi	Enza vs. EDL	EL vs. APEL
CR	4% vs. 10%	0% vs. 4%	8 vs. 12%
MRD*	0% vs. 14%	0% vs. 13%	11% vs. 18%
CR + MRD	4% vs. 24%	0% vs. 17%	19% vs. 30%

Abi=Abiraterone; Enza=Enzalutamide; EDL=Enzalutamide, dutasteride, leuprolide; APEL=Abiraterone, prednisone, enzalutamide, leuprolide; EL=Enzalutamide, leuprolide; CR=Complete response; MRD=Minimum residual disease. *Defined as residual tumor with largest cross section dimension ≤ 0.3-0.5 cm.

Taplin et al, JCO, 2014
Montgomery et al, CCR, 2016
McKay et al, JCO, 2019

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri



Eligibility:

- Adenocarcinoma
- Gleason ≥ 8 *OR* Gleason 7 + ≥cT2b+PSA>10ng/ml
- Absent metastases by conventional imaging criteria

End points:

- Cytoreduction/Therapy effect
- Screen for univariate / multivariate links of pretreatment markers to outcome
- Residual cancer quantification, characterization
- PSA recurrence
- Safety

63 of 65 patients enrolled had RP. 98% of the patients had a PSA <0.1 and 40% of patients had the organ-confined disease at the time of surgery. Prostatectomy specimens revealed significant heterogeneity in tumor viability despite uniform PSA responses. 16% of patients receiving APL had a complete response and 10% of patients receiving APAL had a complete response – this was not a significant difference, consistent with the prior study.

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri

confined disease at the time of surgery. Prostatectomy specimens revealed significant heterogeneity in tumor viability despite uniform PSA responses. 16% of patients receiving APL had a complete response and 10% of patients receiving APAL had a complete response – this was not a significant difference, consistent with the prior study.

Radical Prostatectomy Findings

Surgery	Group A APA+LHRHa	Group B APA+AA+LHRHa	
N*(Robotic-assisted radical prostatectomy)	32	31	
Lymph nodes, mean (range)	20 (9-33)	22 (7-39)	
Perioperative serious AE	1 abdominal hematoma, 1 anemia, 1 vasovagal reaction	1 dehydration	
Blood loss, mL, median (range)	100 (20-550)	100 (25-550)	
Pathology			*P* value
≤ ypT2N0, n (%)	13 (41)	12 (39)	ns
ypT0N0	5 (16)	3 (10)	
Surgical margin negative, n (%)	29 (91)	25 (81)	ns
Lymph nodes negative, n (%)	22 (69)	21 (68)	
PSA nadir			
PSA ≤ 0.1 ng/mL, n (%)	32 (100)	30 (97)	ns

**Two pts did not have RP due to withdrawal of consent*

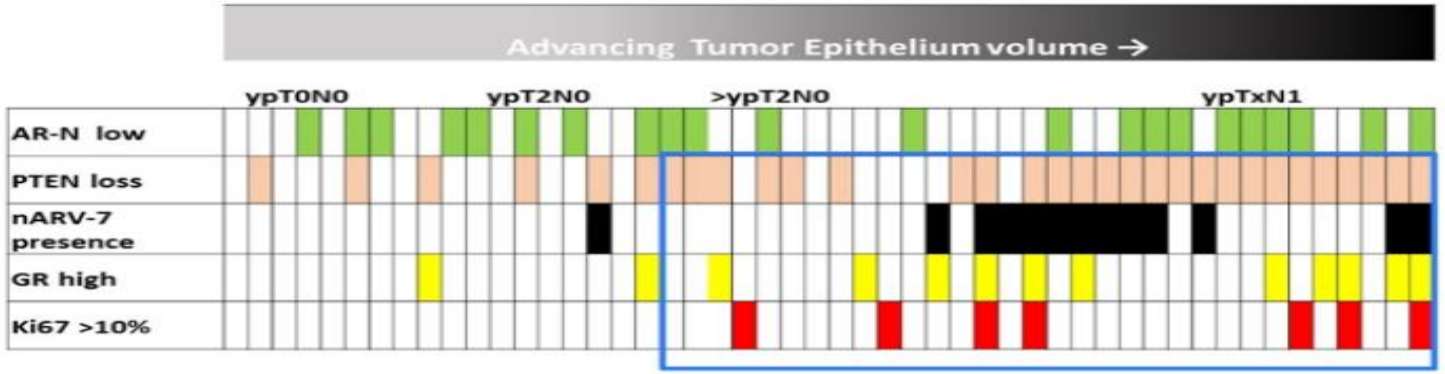
Tumor volume and tumor cellularity varied significantly. The finding of ≤ypT2N0 did not correlate with Gleason score, but did correlate with a pre-specified molecular signature, PTEN expression, and absence of cribriform/intraductal spread.

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri

Tumor volume and tumor cellularity varied significantly. The finding of ≤ypT2N0 did not correlate with Gleason score, but did correlate with a pre-specified molecular signature, PTEN expression, and absence of cribriform/intraductal spread.

A 4-marker candidate signature (PTEN loss, nARV-7 presence, Glucocorticoid receptor (GR) high, or Ki67>10%) was predictive of resistance.

Univariate Analyses for association of pretreatment tumor characteristics with therapy effect



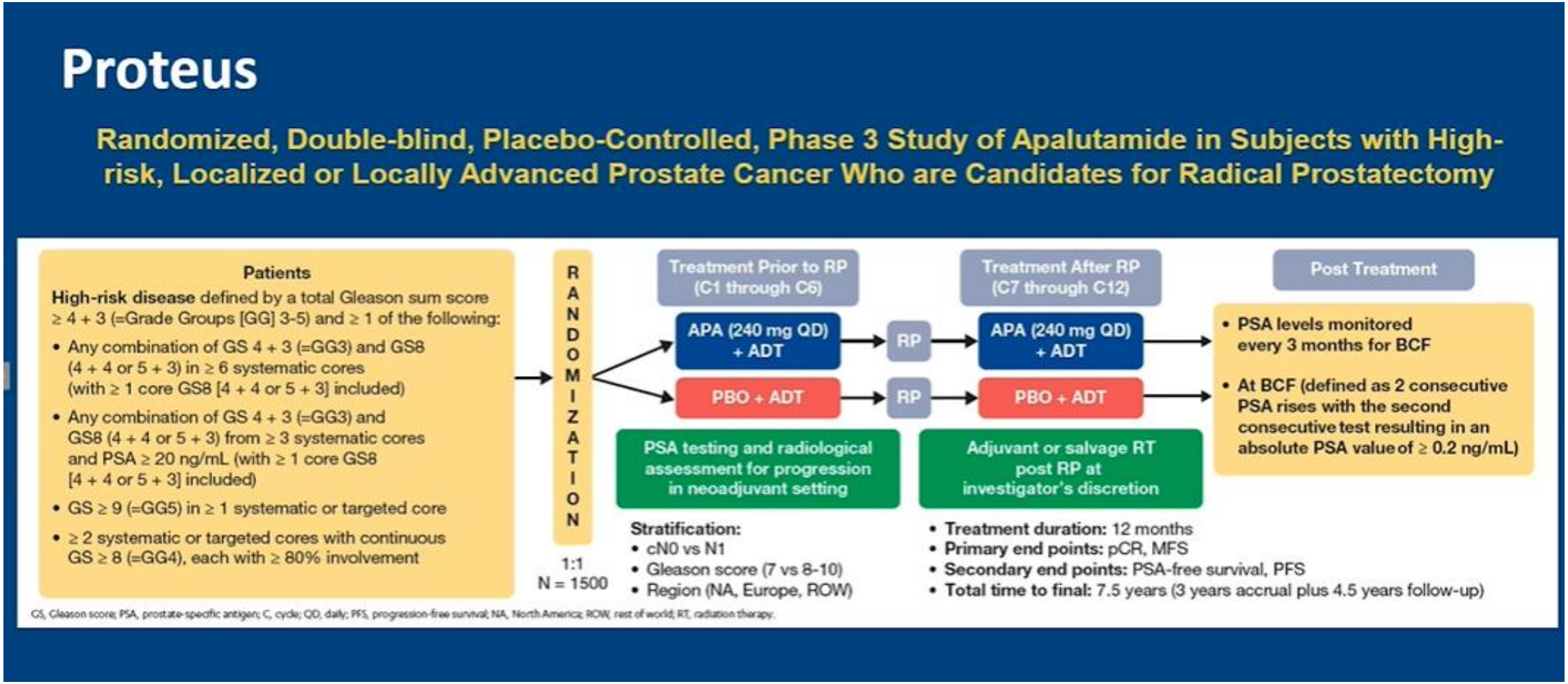
Marker		Pathology Stage >ypT2N0 N(%)	Pathology Stage ≤ypT2N0 N(%)	Fisher exact test p-value
AR-N	Low	13(42)	9(47)	0.77
	High	18(58)	10(53)	
PTEN	Loss	**24(77)**	**7(37)**	**0.007**
	Intact	**7(23)**	**12(63)**	
ARV7 nuclear	absence	**19(61)**	**18(95)**	**0.009**
	presence	**12(39)**	**1(5)**	
GR	Low	20(65)	17(89)	**0.091**
	High	11(35)	**2(11)**	
Ki67	≤10%	24(77)	19(100)	**0.035**
	>10%	7(23)	**0(0)**	
Clinical Stage	cT2	6(16)	**11(44)**	**0.02**
	cT3/4	**32(84)**	14(56)	
Biopsy Gleason	7	10(26)	8(32)	0.77
	8-10	28(73)	17(68)	
Diagnostic PSA >10ng/ml		26 (68)	16 964)	0.23

Diagnostic Biopsy Markers:

- ✓ **PTEN loss** enriched in persistent cancers
- ✓ **Nuclear ARV7 presence, GR high (>10%), Ki67 >10%,**

correlate with persistent cancers

Devam Eden Çalışmalar



Neoadjuvan Kemoterapi+ADT

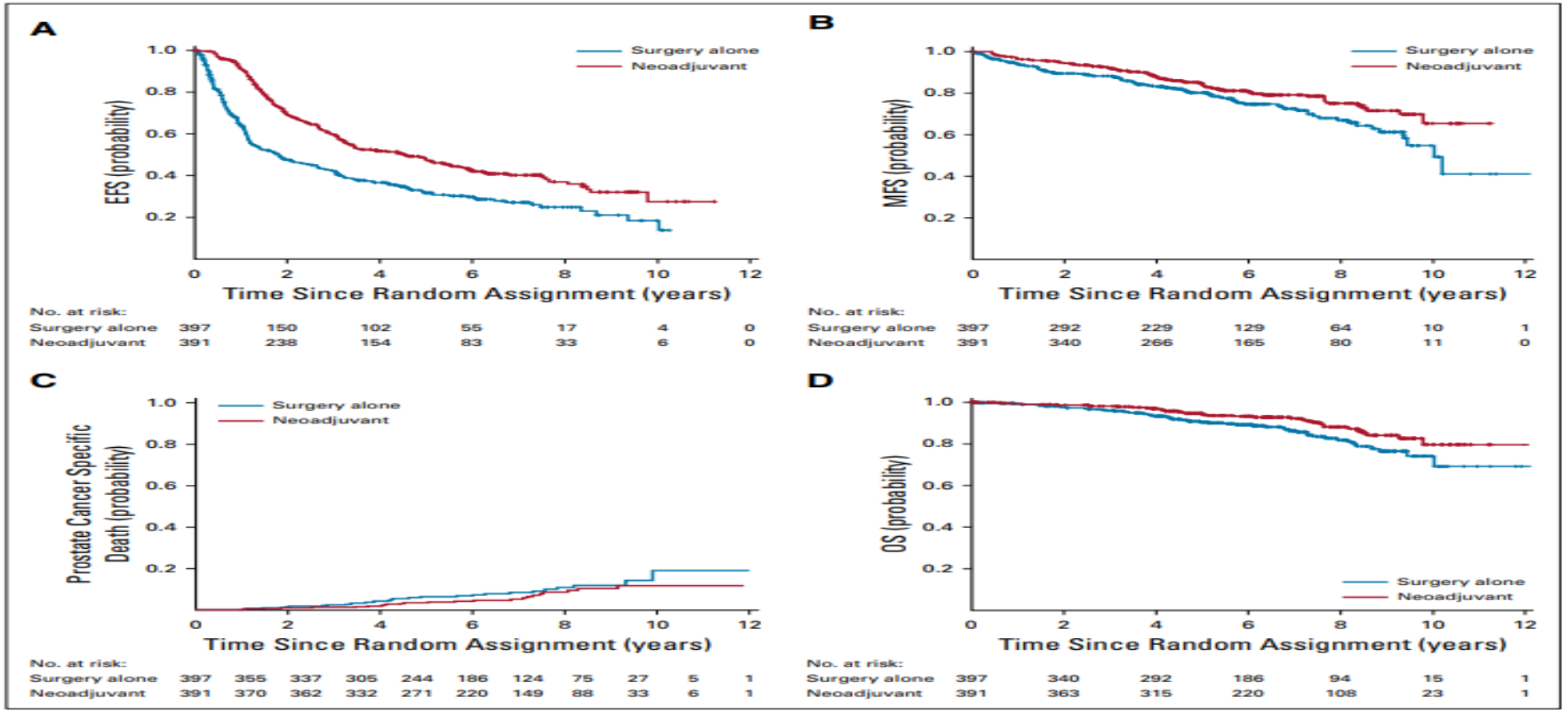


FIG 3. (A) Event-free survival (EFS) or the likelihood of not requiring additional treatment after radical prostatectomy in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy (designated neoadjuvant) versus radical prostatectomy alone (designated surgery alone). An event is defined as death, prostate-specific antigen progression, local or distant progression, initiation of androgen-deprivation therapy, and/or radiation therapy > 6 months after surgery. (B) Metastasis-free survival (MFS; the time from randomization to metastasis) in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy versus radical prostatectomy alone. (C) Prostate cancer–specific survival (the time from randomization to death from prostate cancer) in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy versus radical prostatectomy alone. Cause of death was assigned by the treating physician. (D) Overall survival (OS; the time from randomization to death) in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy versus radical prostatectomy alone.

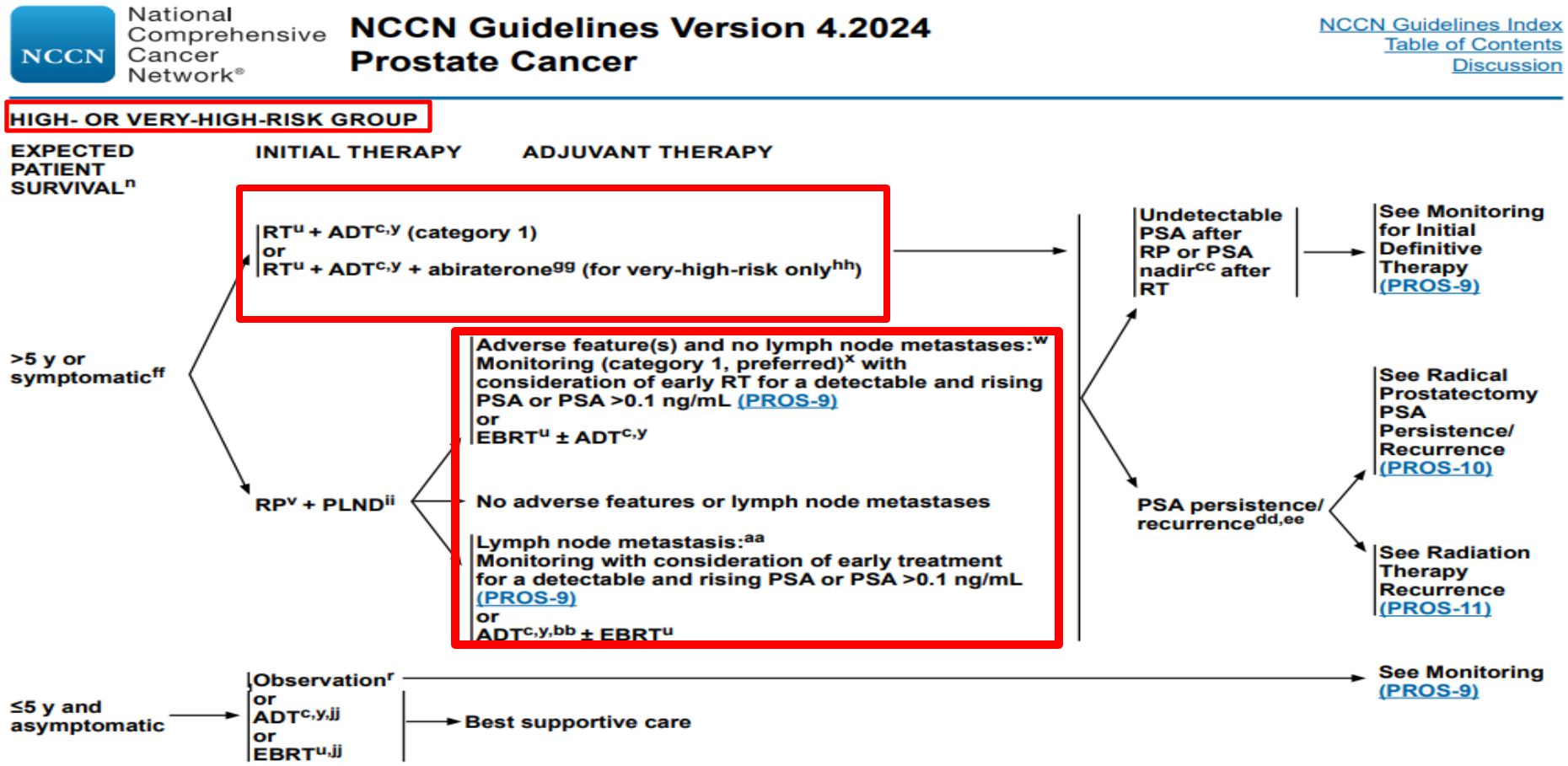
Lokal ileri yüksek risk(endokrin diferansiasyon yok) ve PSA düşük(PSA≤3 ng/ml)

In the majority of patients with high-risk localised/locally advanced prostate cancer cT3, Gleason 8– 10 (no evidence of small cell carcinoma) and low PSA (eg,≤3 ng/ml) what do you recommend?

- ❑ **Radiation plus long-term ADT alone: 14% (15 votes)**
- ❑ **Radiation plus long-term ADT plus abiraterone for 2 years: 50% (52 votes)**
- ❑ **Radiation plus ADT plus 4–6 cycles of docetaxel: 4% (4 votes)**
- ❑ **Surgery, recognising that it may be part of a multimodality approach: 32% (34 votes)**
- ❑ **Abstain/unqualified to answer (1 vote)**

Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC), Eur Urol (2024).

ADJUVAN TEDAVİ



Abireteron+ADT+RT

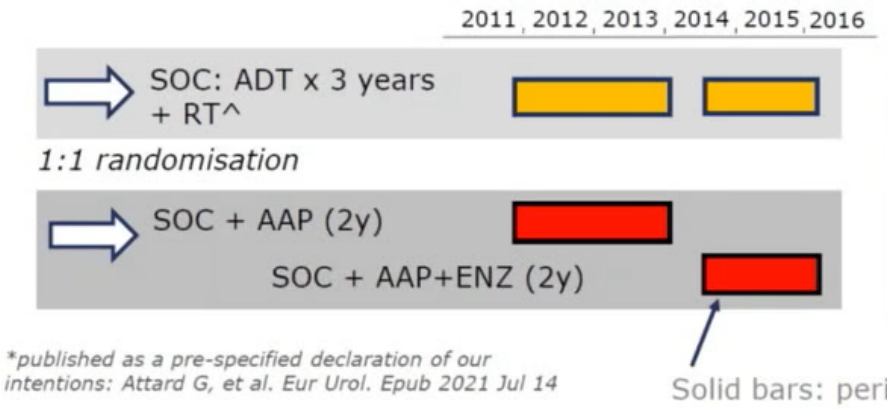
Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

In 2019, the reporting plan was amended to
- Split M1 and nonmetastatic patients, power the **primary endpoint on MFS**
- **Meta-analyze data** from the AAP ± enzalutamide + ADT vs ADT comparisons

Newly diagnosed
1. cN1
2. High risk cN0
≥ 2 of T3/4
GS 8-10
PSA ≥40

M0 with conventional imaging

Relapsing disease (Prior RT/RP)
Any of the following
cN1
PSA ≥20
PSA ≥4 & DT <6m



*published as a pre-specified declaration of our intentions: Attard G, et al. Eur Urol. Epub 2021 Jul 14

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

RT was mandated in N0M0 and suggested in N+ disease

Attard al. Lancet. 2022 Jan

Abiraterone+ADT+RT

Patient characteristics

- Randomised groups were well balanced (**N=1974**)

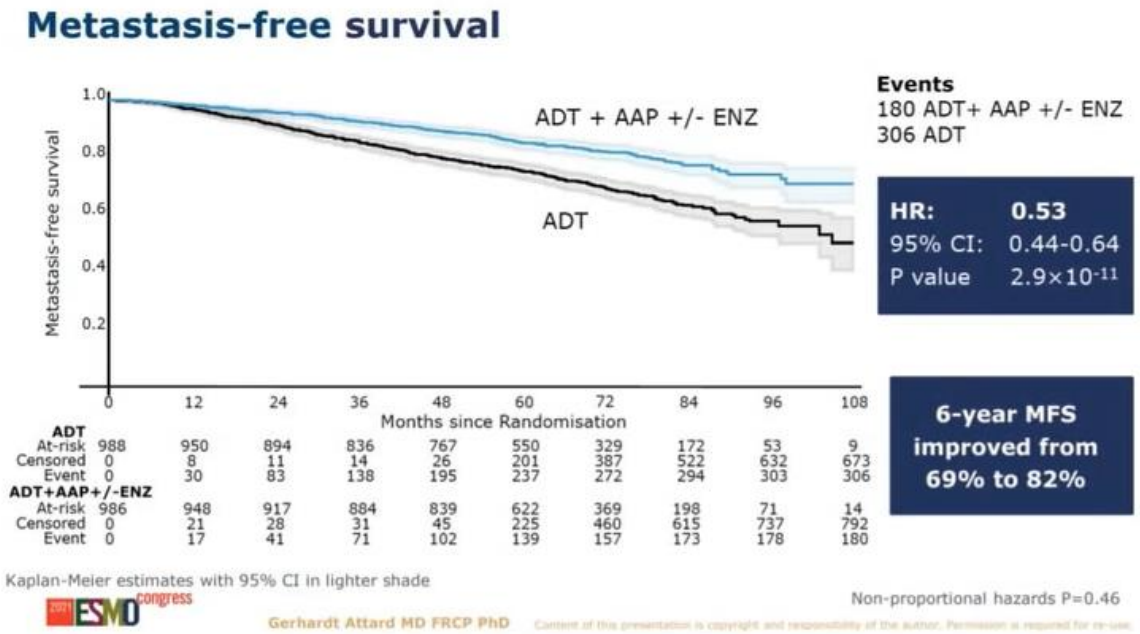
- Median age = 68 years
- Median PSA = 34 ng/ml
- N1 = 39%
- 3% relapsing after prior treatment

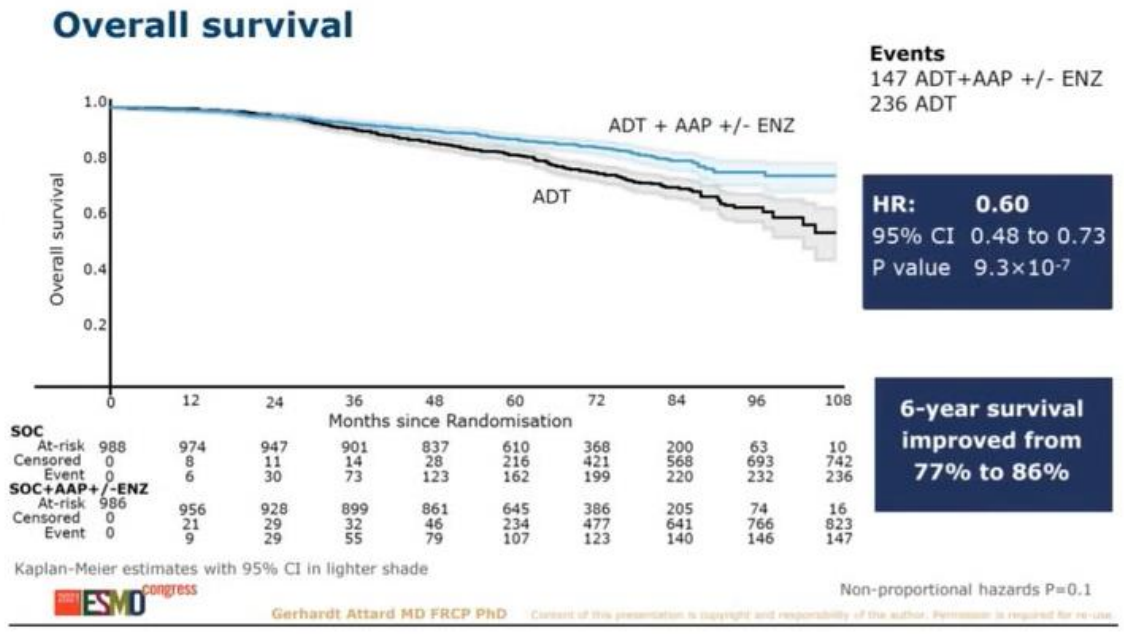
- Planned for local radiotherapy: - 99% newly-diagnosed, N0
  - 71% newly-diagnosed, N1
  - 7% previously-treated patients

- Median follow-up = 72 months
  (85 months AAP comparison & 60 months AAP+ENZ comparison)

Attard al. Lancet. 2022 Jan

Abiraterone+ADT+RT

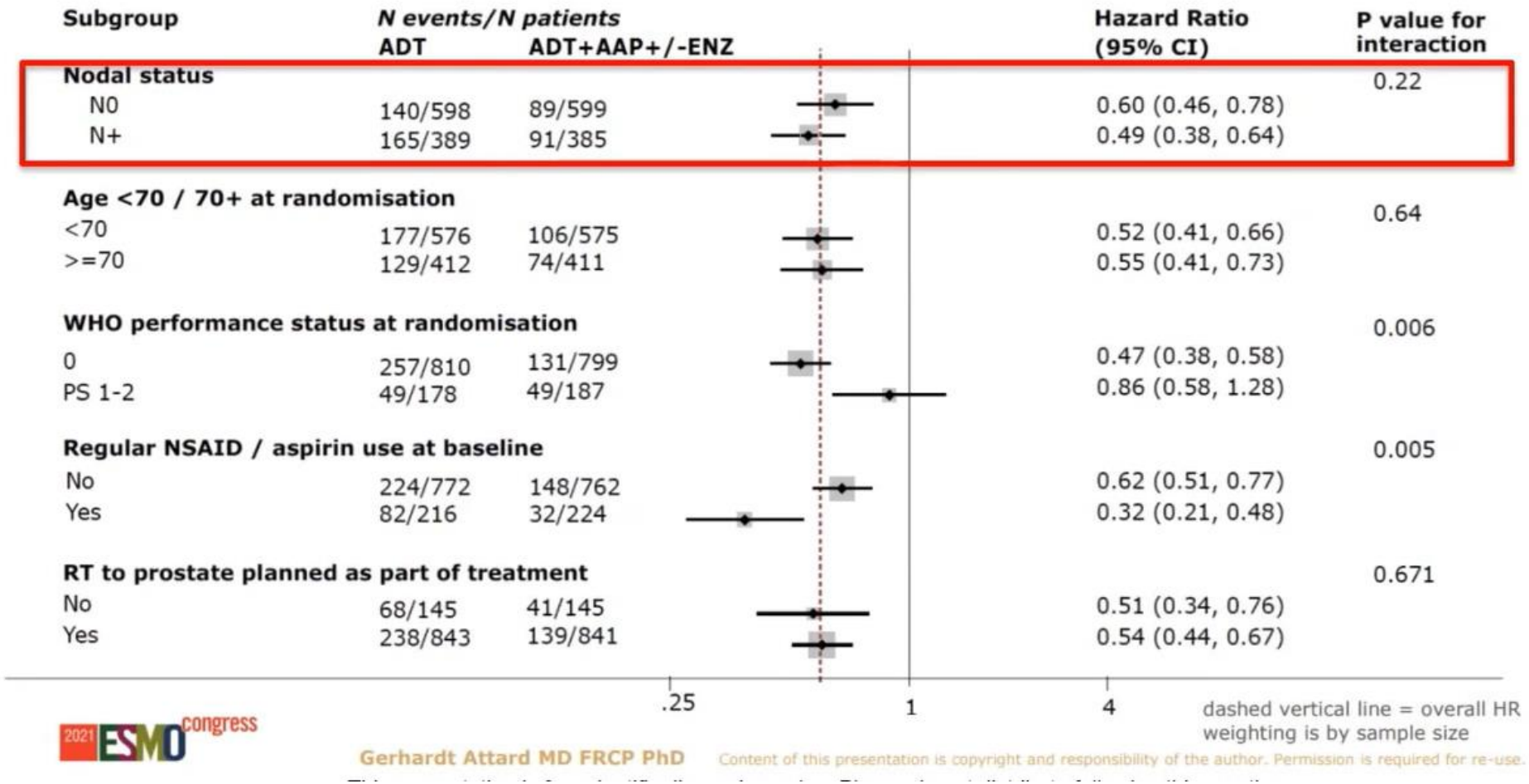




Attard al. Lancet. 2022 Jan

Abiraterone+ADT+RT

Metastasis-free survival: Subgroup analysis



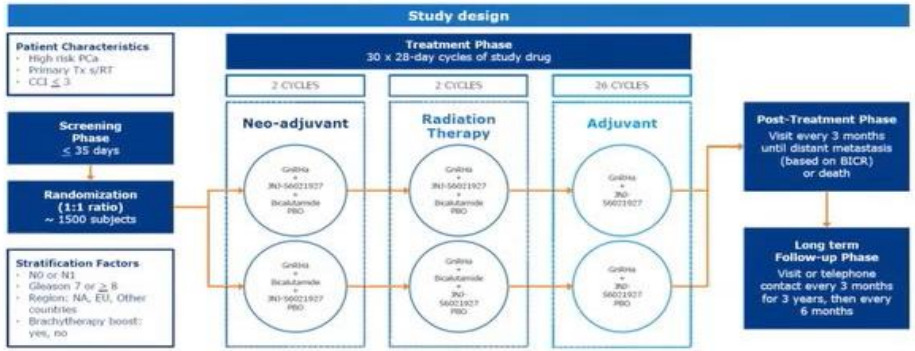
2021 ESMO congress

Gerhardt Attard MD FRCP PhD

Definitif RT+ADT+ Yeni Nesil AR-yolağı İnhibitörleri

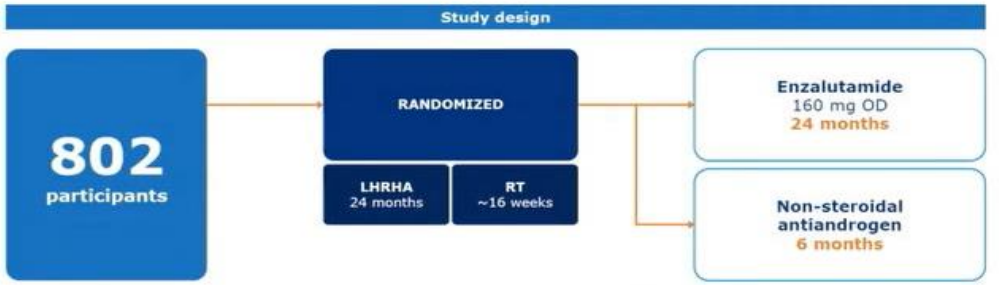
Apalutamide

ATLAS: Apalutamide in high-risk, localized or locally advanced PC patients receiving primary RT



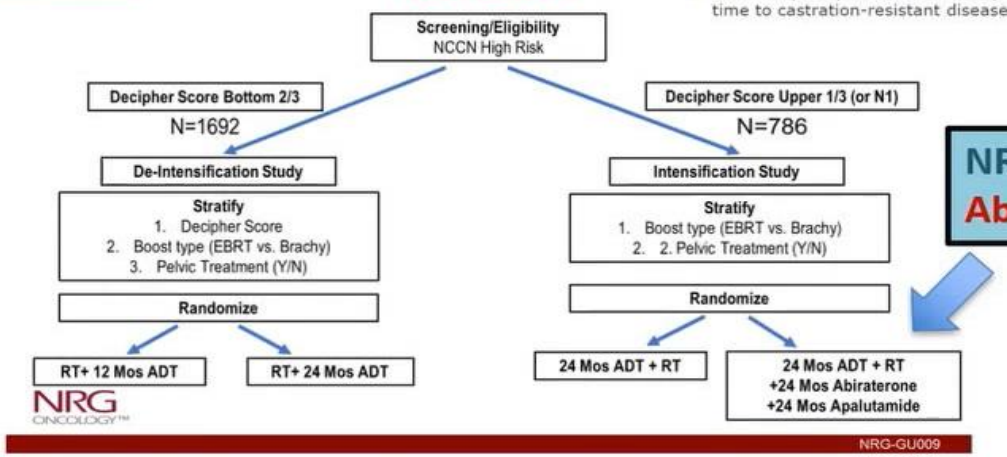
Enzalutamide

ENZARAD: Enzalutamide in ADT with RT for high-risk, clinically localized PC



- Primary endpoint is OS
- Secondary endpoints include CSS, PSA PFS, clinical PFS, time to subsequent hormonal therapy, time to castration-resistant disease (PCWG2 criteria), MFS, AEs and HRQOL

SCHEMA



NRG GU009
Abiraterone + Apalutamide

Clinical Trial Information:
NCT02531516; NCT02446444; NCT04513717

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%.

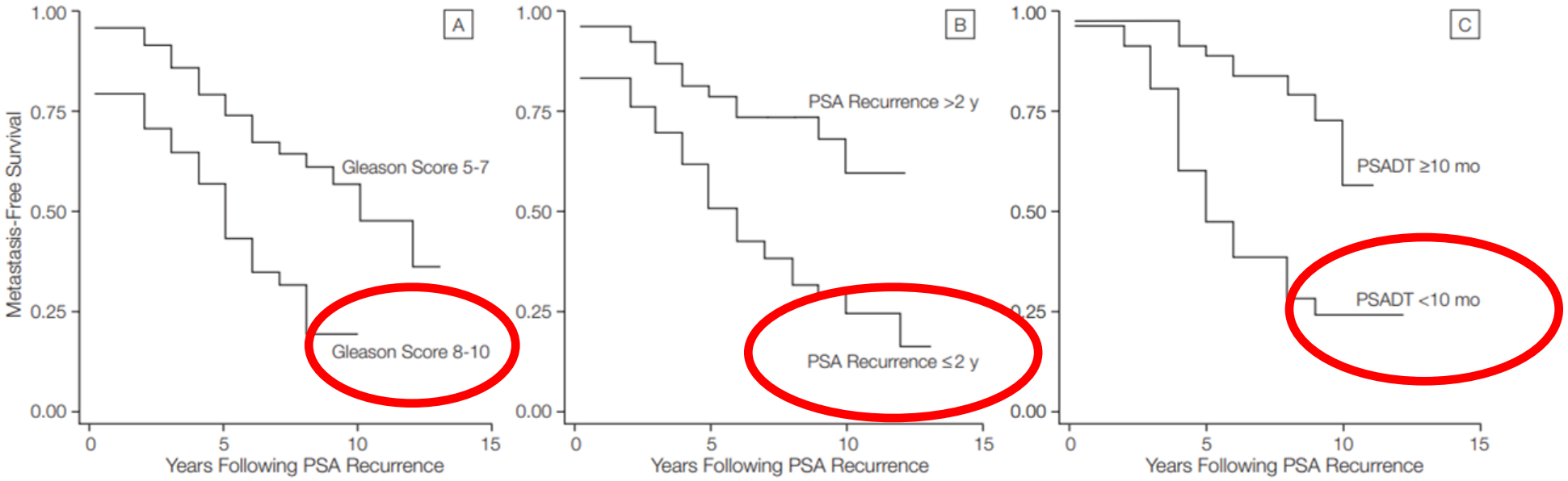
- Biyokimyasal Rekürens olan hastaların hepsinde metastaz görülmez. Bu nedenle risk skorlamasına göre yüksek grupta olanlar erken ya da salvage tedavi almalıdır.

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

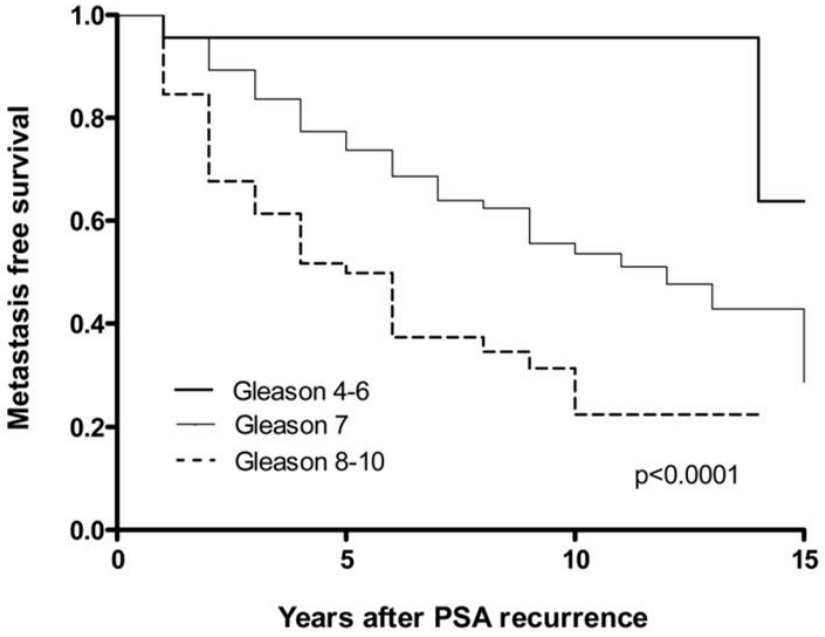
Biyokimyasal Rekürens ve PSA Persistansı Metastaz riski

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

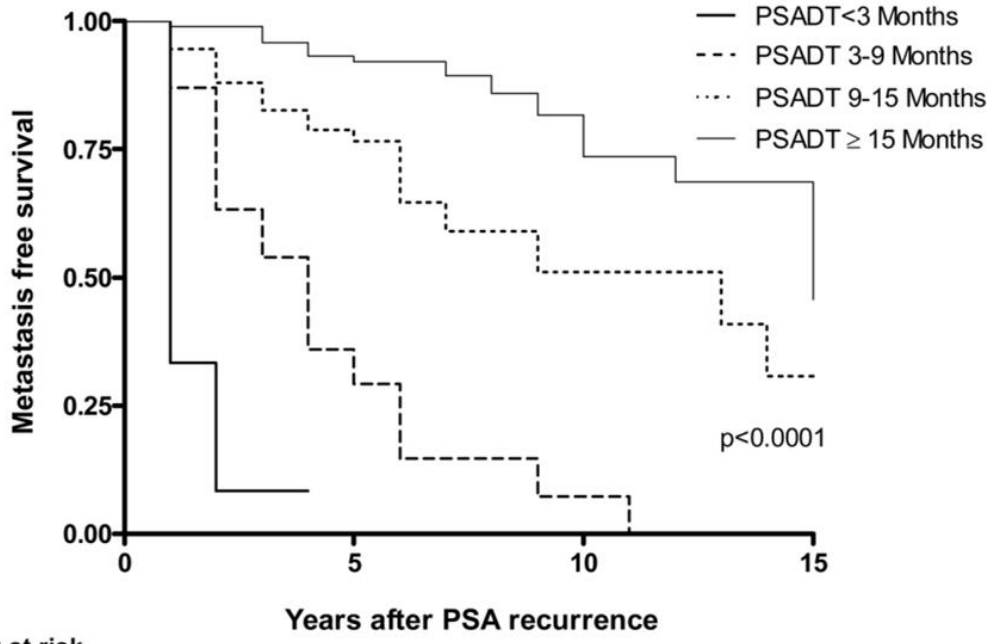


A, Based on Gleason scores in the radical prostatectomy specimen ($P<.001$). B, Based on years until initial biochemical recurrence ($P<.001$). C, Based on prostate-specific antigen doubling time (PSADT) ($P<.001$).

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

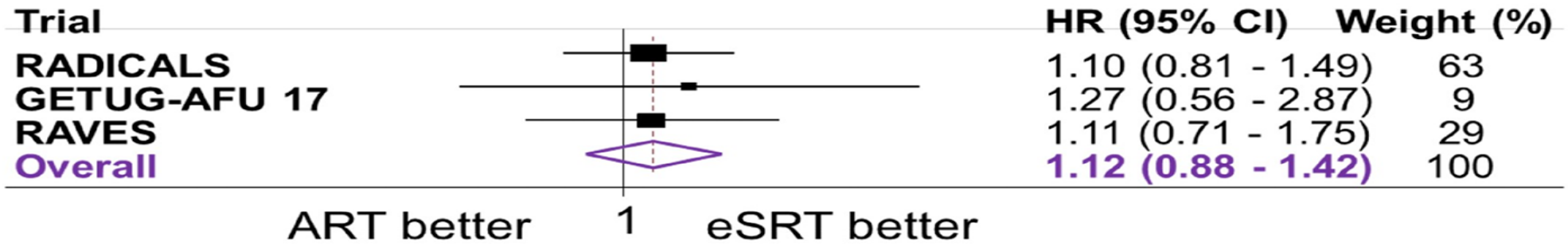
Cerrahi sonrası mediyan 8 yıl takip süresinde, 450 biyokimyasal nüks gelişen ve herhangi bir salvage tedavi almayan hastanın 134'de metastaz görüldü(%29.8).

Emmanuel S. Antonarakis, BJU Int. 2012

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> 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 Lokal ileri yüksek risk ve PSA nadir Adjuvan tedavi

For the majority of patients with pT3b pN0 following radical prostatectomy with extended PLND and ISUP grade group 4–5 and R1 and with undetectable postoperative PSA, what is your recommendation provided the patient has regained continence

- ❑ **Monitoring and early salvage therapy (RT or systemic therapy or both) in case of a confirmed PSA rise: 73% (75 votes)**
- ❑ **Adjuvant therapy (RT or systemic therapy or both): 27% (28 votes)**
- ❑ **Abstain/unqualified to answer (3 votes)**

Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC), Eur Urol (2024).

Radikal Prostatektomi sonrası Adjuvan RT> Salvage RT

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

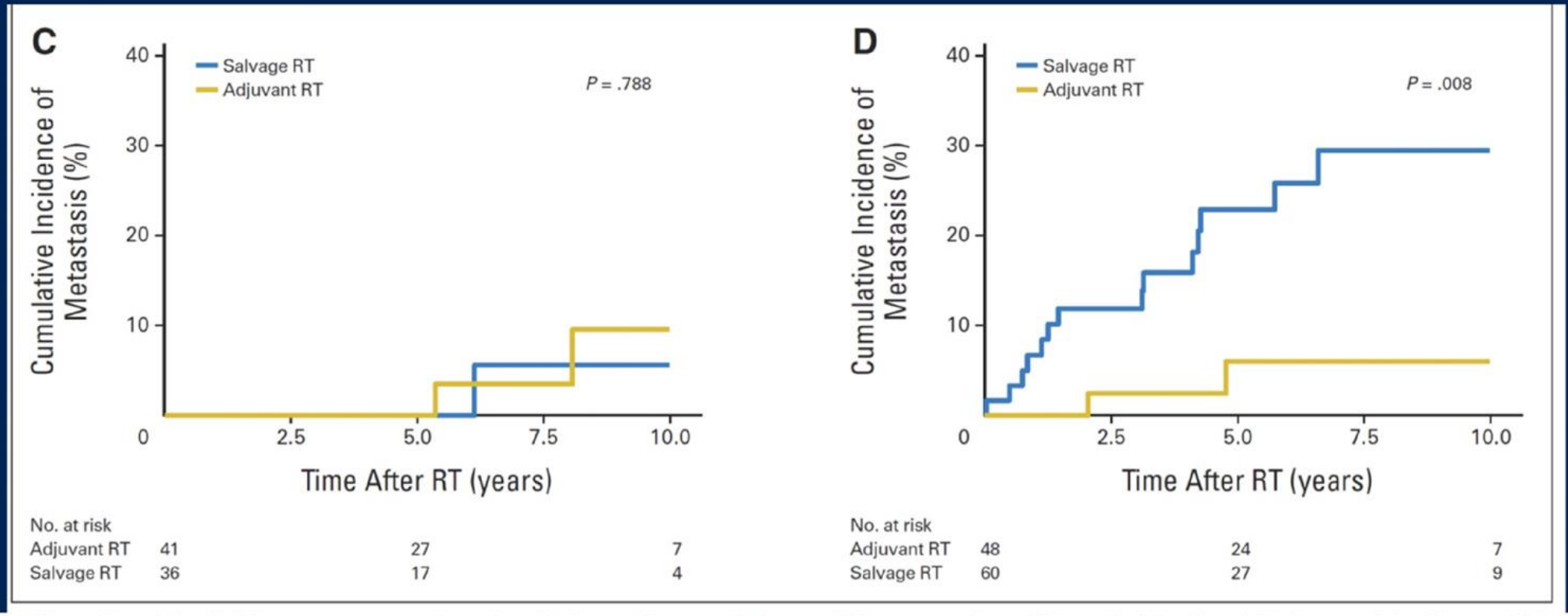
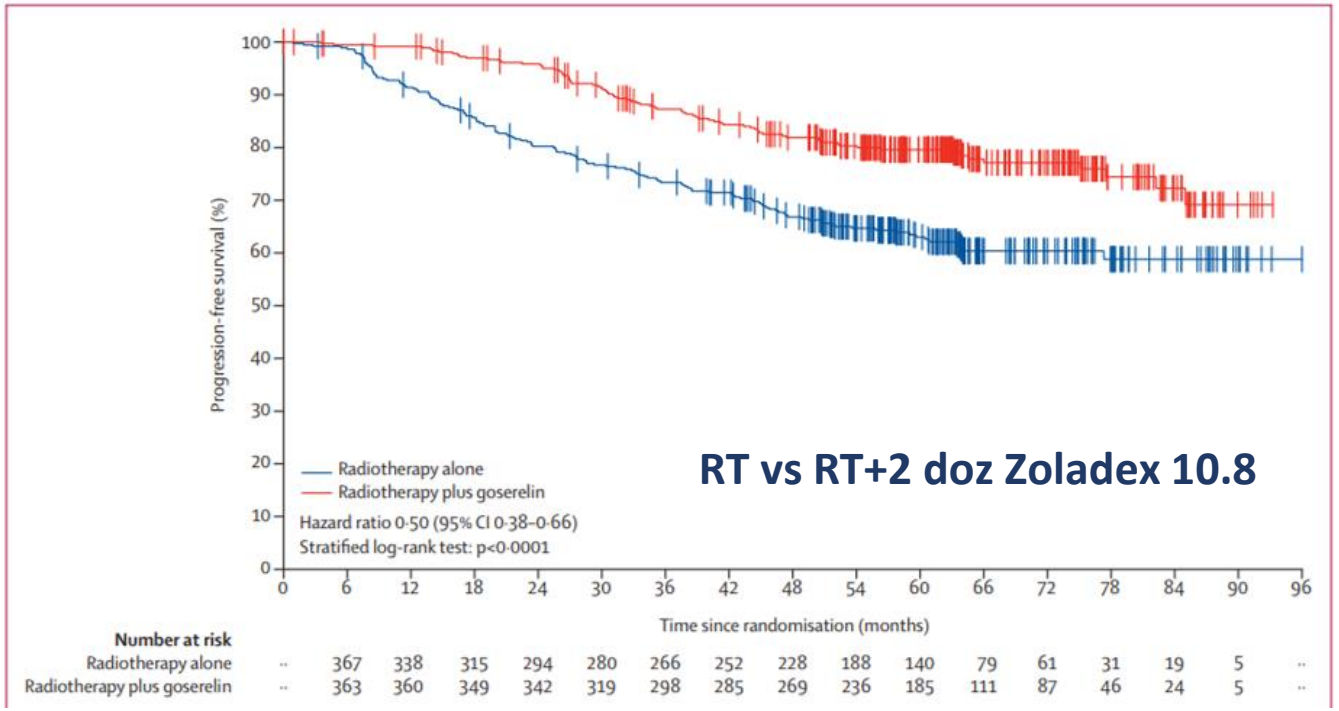


Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (C and D) genomic classifier (GC).

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)

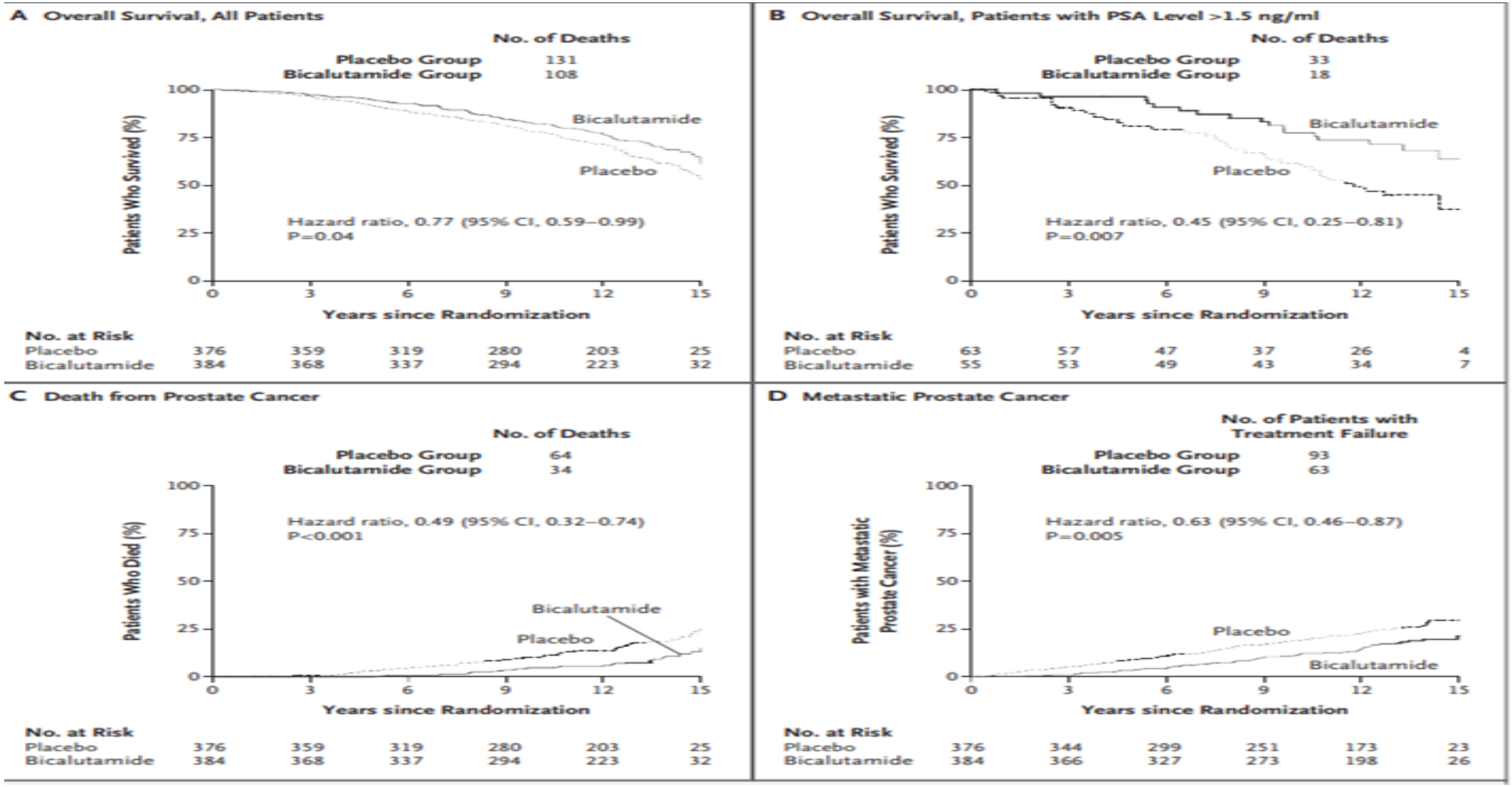


RT vs RT+2 doz Zoladex 10.8

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

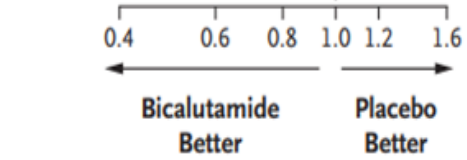
Biyokimyasal Rekürens ve PSA Persistansı
RT+2 yıl bicalutamide 150 mg/gün(RTOG 9601)



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

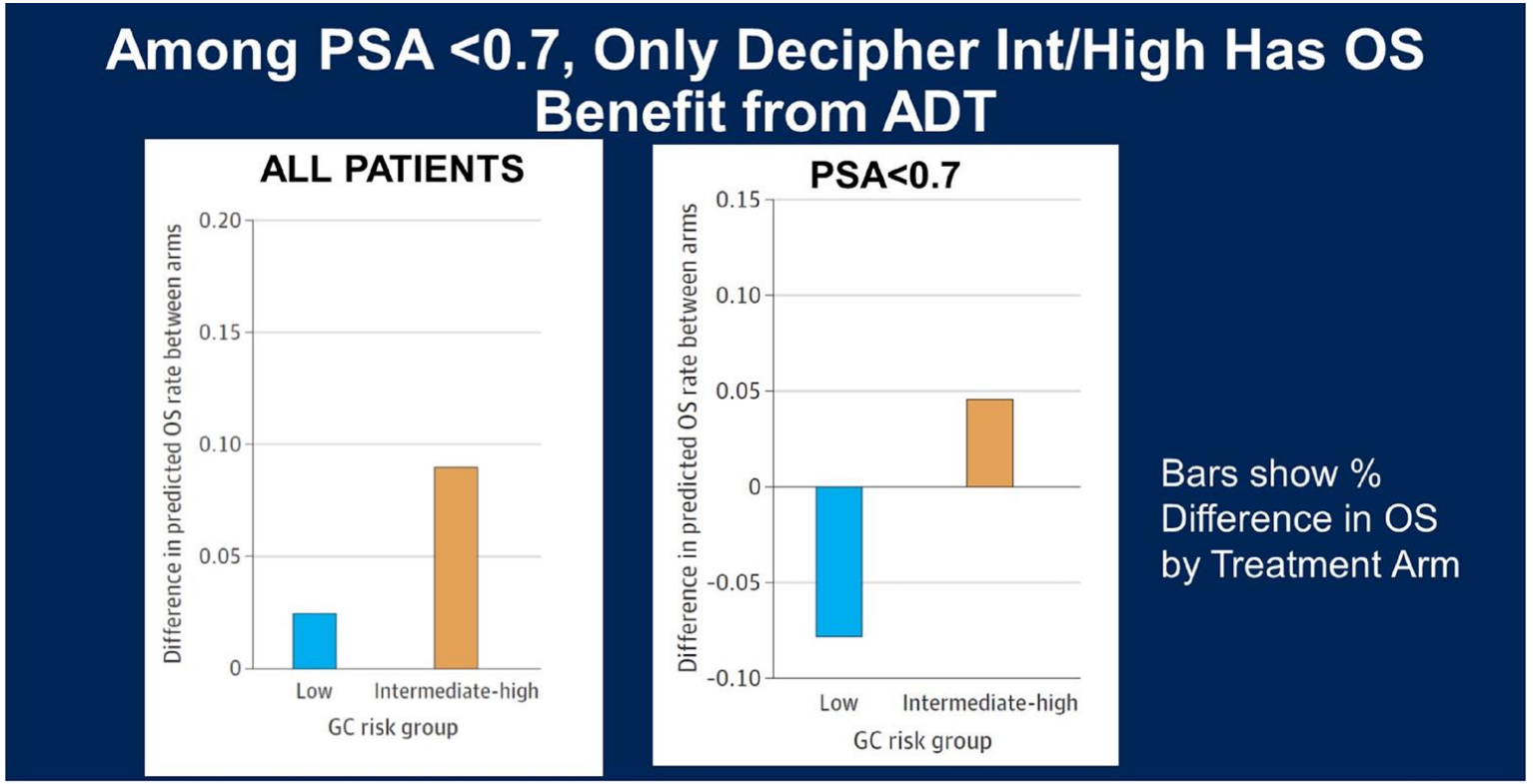


Resulting in 69.7% of the patients in the bicalutamide group having gynecomastia

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)



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

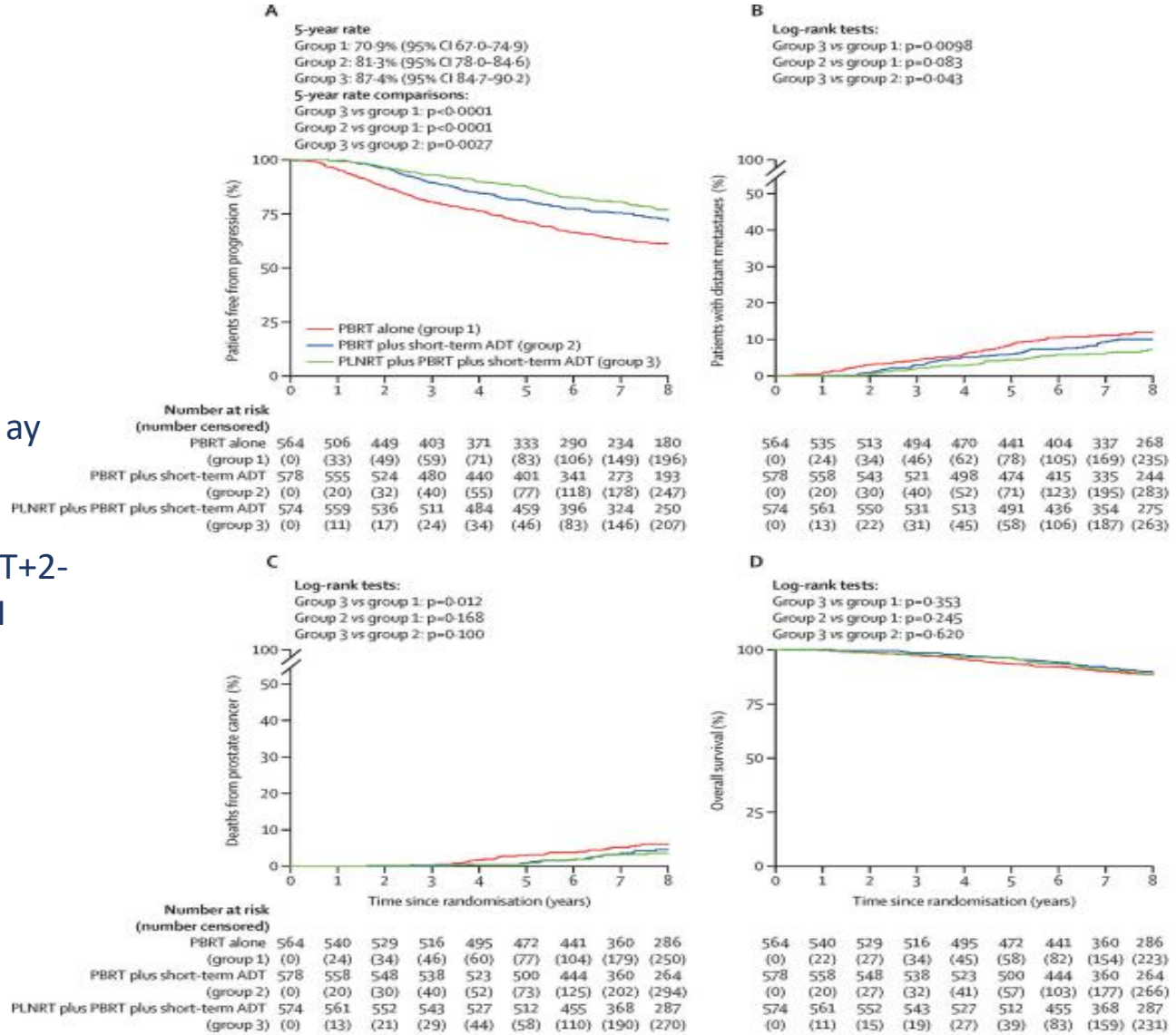


Figure 2:
Kaplan-Meier estimates and cumulative incidence curves: (A) Freedom from progression,

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

PSMA PET-CT negatif yüksek riskli hastalarda pelvik RT

In patients with high-risk localised/locally advanced prostate cancer undergoing RT to the prostate, who have had a PSMA PET and are cN0, do you recommend radiation therapy to the pelvic nodes

- ❑ **Yes, in the majority of patients: 56% (50 votes)**
- ❑ Yes, but only in selected patients based on risk factors: 21% (19 votes)
- ❑ No: 23% (21 votes)
- ❑ Abstain/unqualified to answer (16 votes)

Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC), Eur Urol (2024).

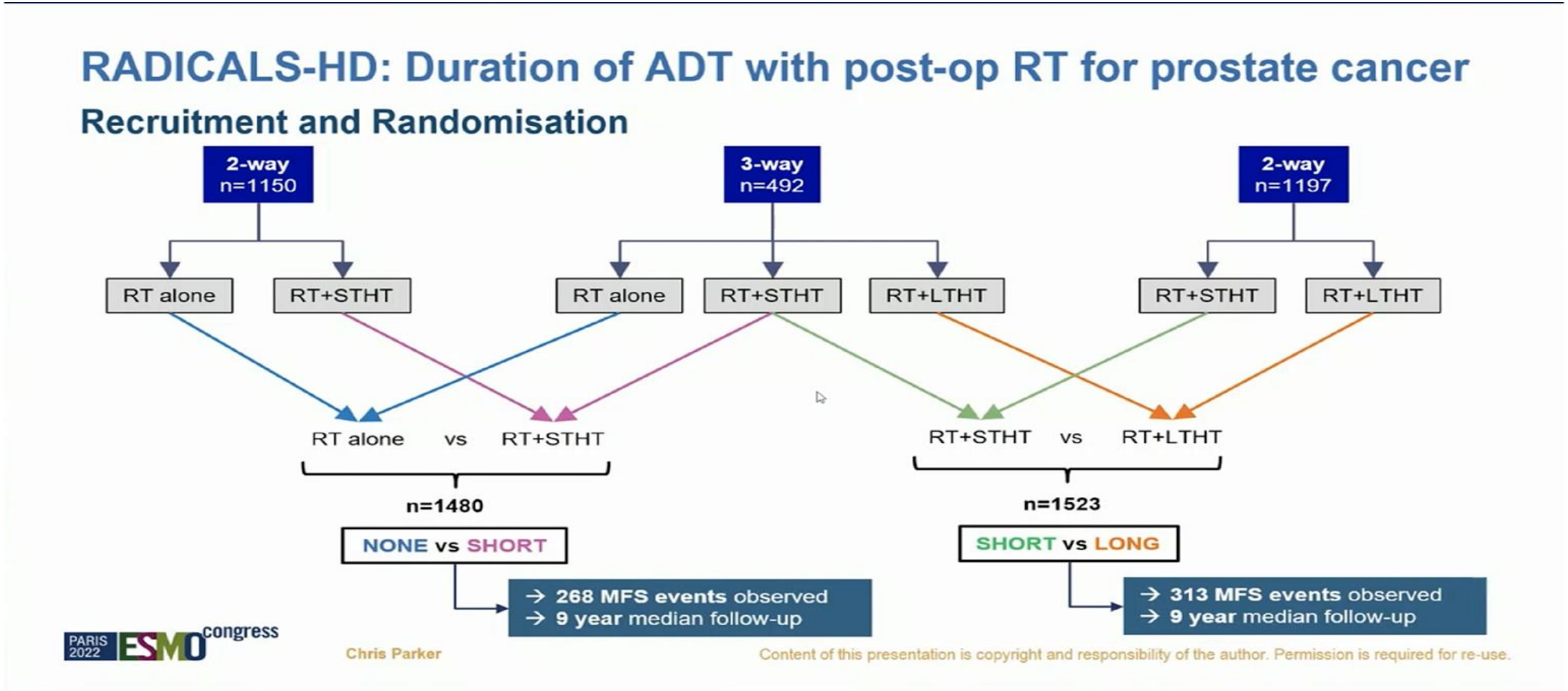
PSA Persistansı adjuvan tedavi

For patients with PSA persistence post RP, pN0 on extended PLND and 2 or more risk factors (risk factors: R1, pT3, ISUP grade group 4–5) and a negative postoperative PSMA PET that you treat with immediate therapy, what do you recommend?

- ❑ **Radiation therapy prostate bed alone: 6% (6 votes)**
- ❑ **Radiation therapy prostate bed plus pelvis: 4% (4 votes)**
- ❑ **Radiation therapy prostate bed plus short-term systemic therapy: 15% (15 votes)**
- ❑ **Radiation therapy prostate bed plus pelvis plus shortterm systemic therapy: 38% (37 votes)**
- ❑ **Radiation therapy prostate bed plus long-term systemic therapy: 8% (8 votes)**
- ❑ **Radiation therapy prostate bed plus pelvis plus longterm systemic therapy: 29% (28 votes)**
- ❑ **Systemic therapy alone: 0% (0 votes)**
- ❑ **Abstain/unqualified to answer (including I do not recommend immediate therapy) (8 votes)**

Management of Patients with Advanced Prostate Cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC), Eur Urol (2024).

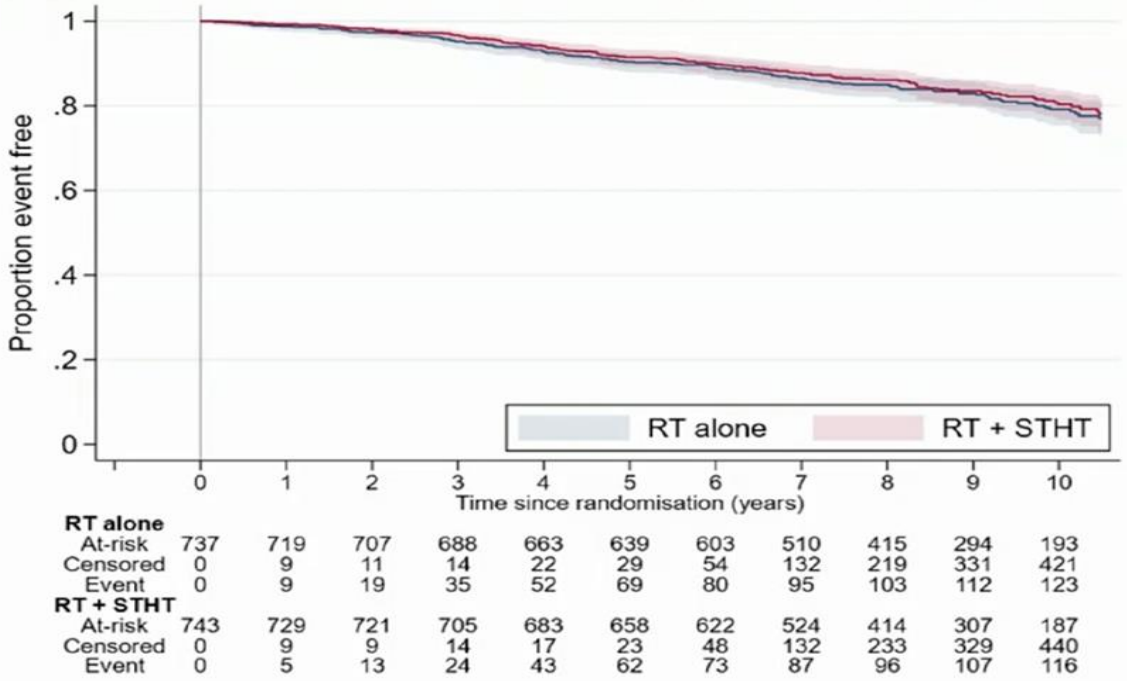
Biyokimyasal Rekürens ve PSA Persistansı RT+uzun dönem ADT



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

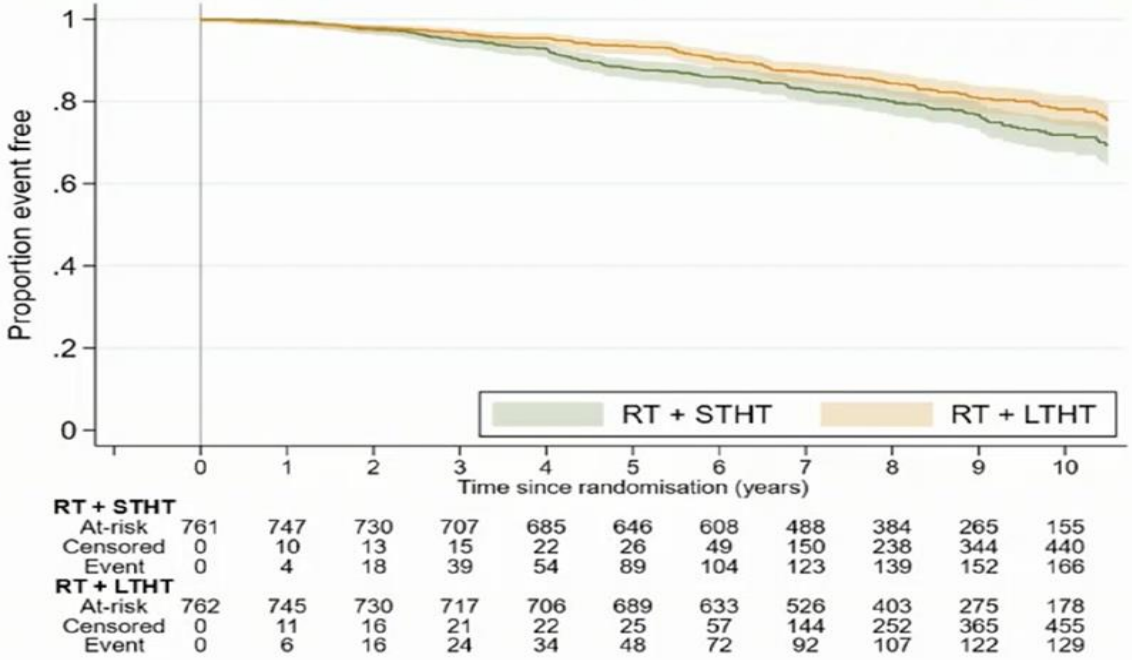
PARIS 2022 ESMO congress

Chris Parker

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%

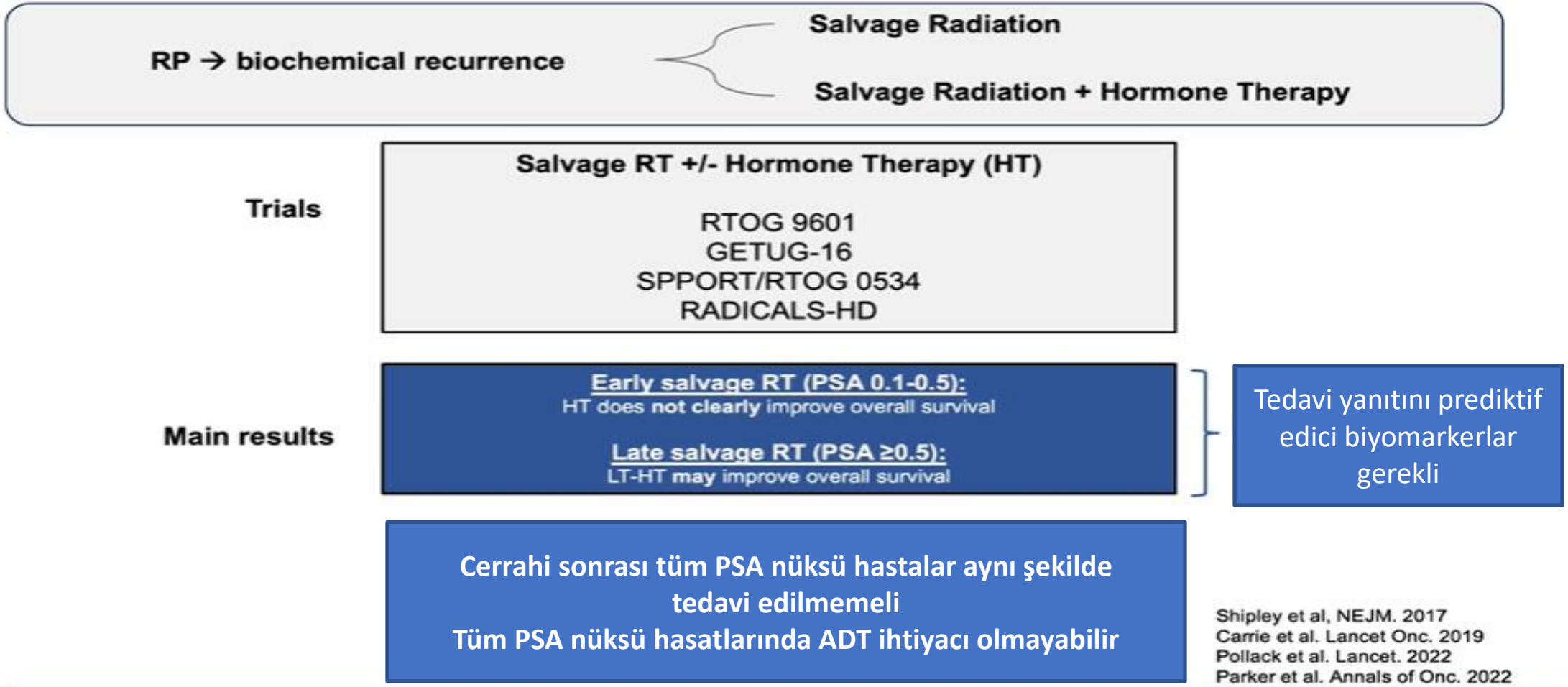
43% Received *Adjuvant RT*

28% Gleason 8-10

PARIS 2022 ESMO congress

Chris Parker

Biyokimyasal Rekürens ve PSA Persistansı

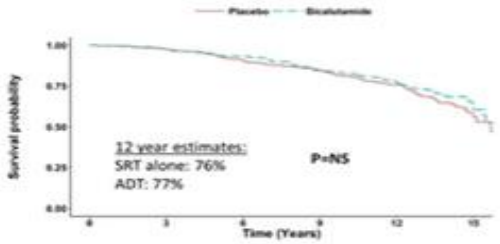


ADT+RT ile artmış MFS , Tüm popülasyonda OS faydası yok

Consistent Results in >5,000 patients: Lack of Overall Survival Benefit

RTOG 9601

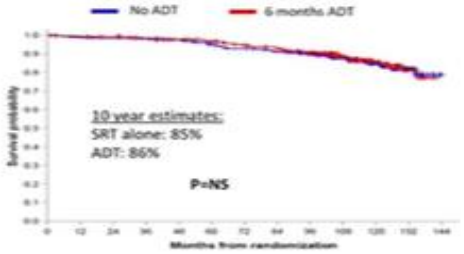
PSA 0.2-1.5 ng/mL stratum



Median follow-up: 13 years

GETUG-16

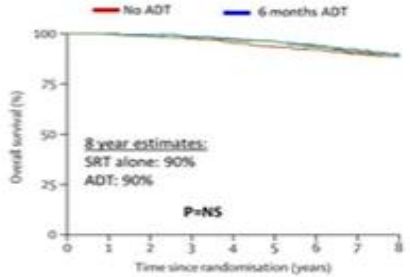
PSA 0.2-2.0 ng/mL



Median follow-up: 9 years

SPPORT

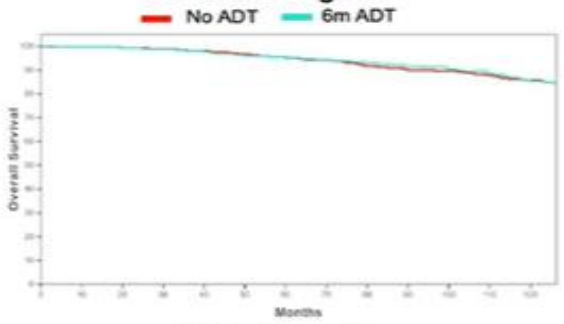
PSA 0.1-2.0 ng/mL



Median follow-up: 8 years

RADICALS-HD 0 vs 6m ADT

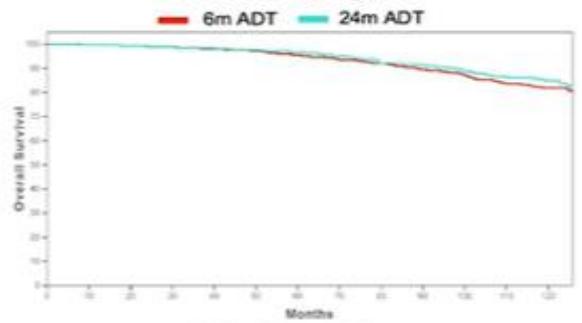
PSA 0.0-4.2 ng/mL



Median follow-up: 9 years

RADICALS-HD 6 vs 24m ADT

PSA 0.0-5.0 ng/mL

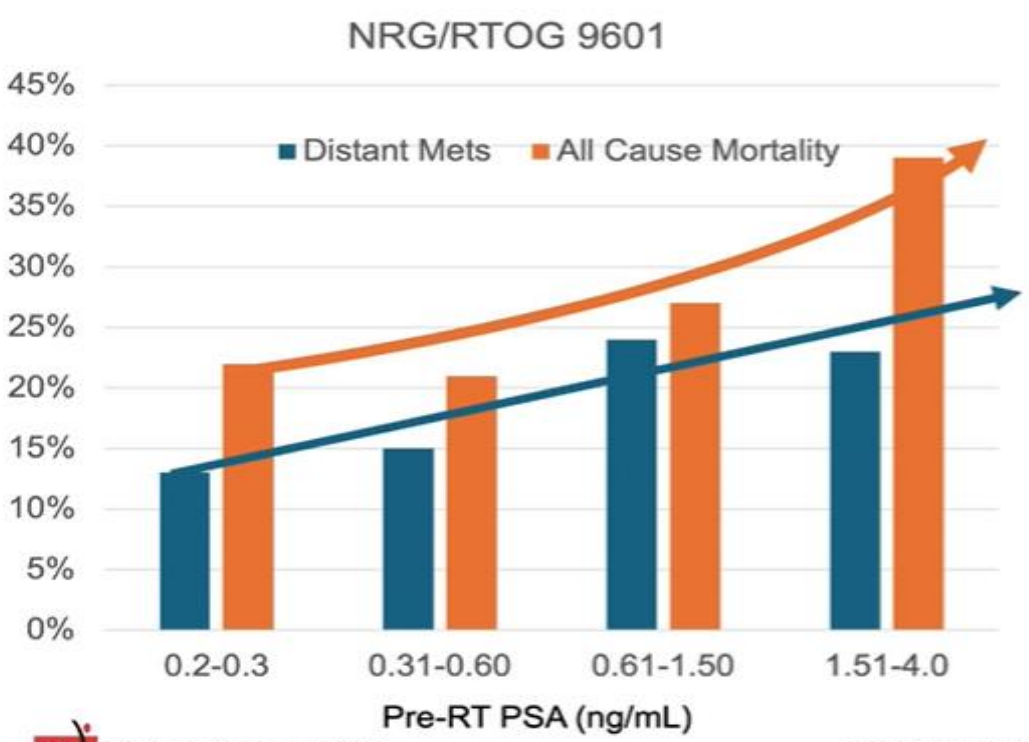


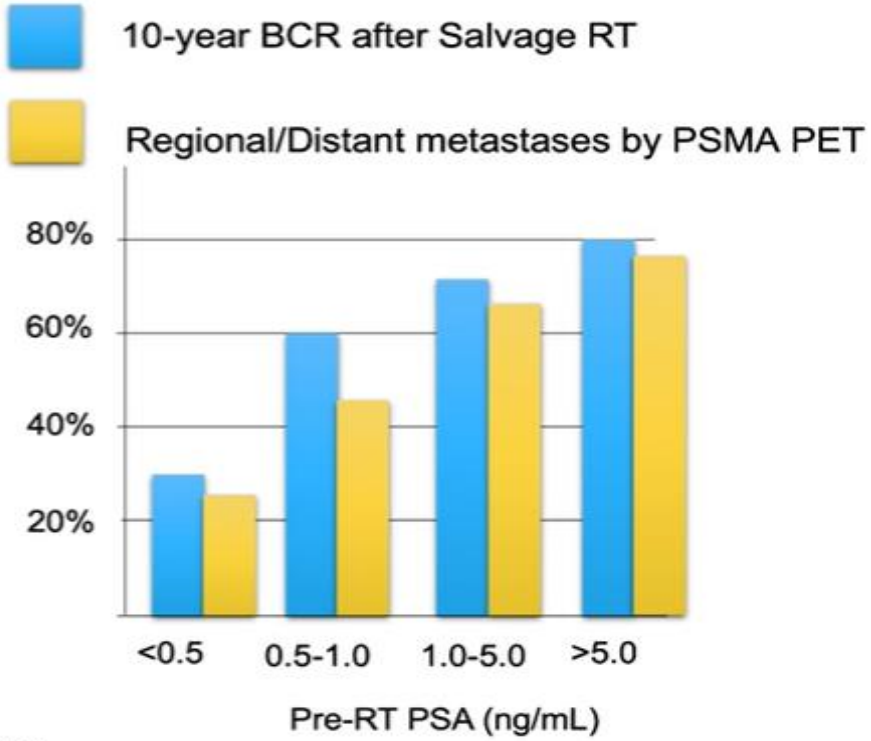
Median follow-up: 9 years

Shipley et al, NEJM. 2017
Carrie et al. Lancet Onc. 2019
Pollack et al. Lancet. 2022
Parker et al. Annals of Onc. 2022

Tedavi öncesi PSA metastaz için güçlü prognostik marker

Pre-SRT PSA Consistently Most Prognostic Variable

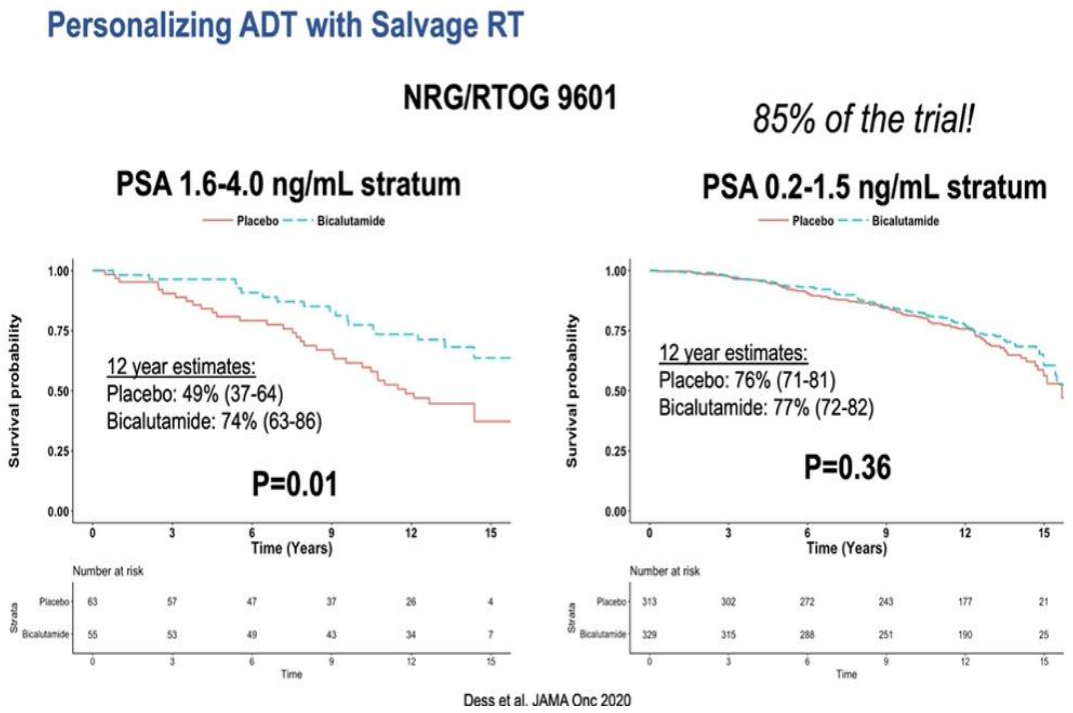


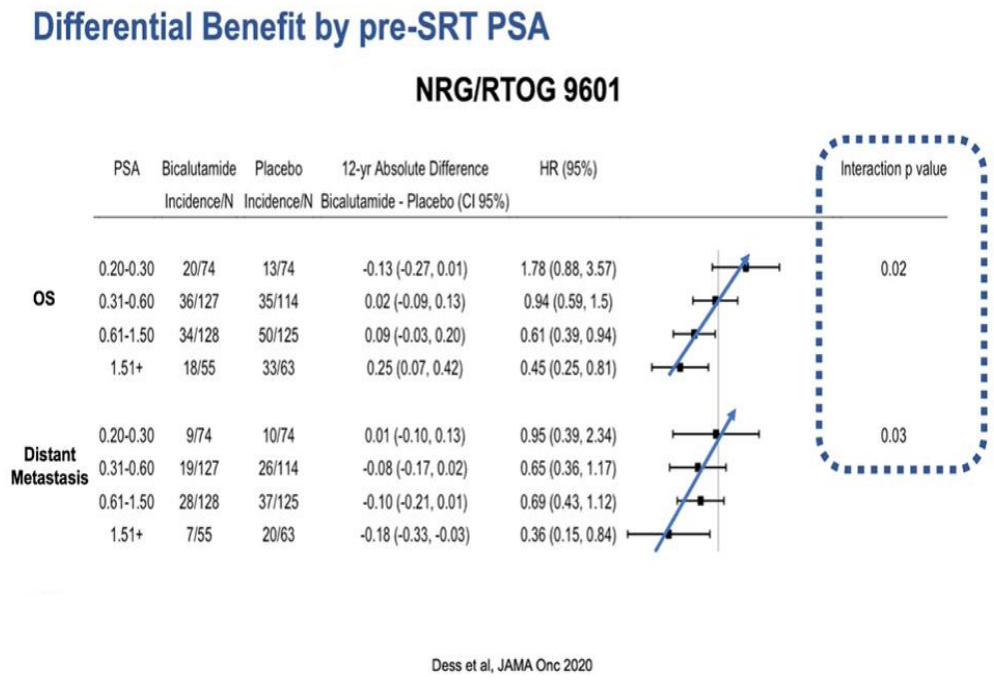


University Hospitals
Seidman Cancer Center

Dess et al. JAMA Onc. 2020
Tendulkar R, et al, JCO 2016
Fendler WP, et al, JAMA Onc 2019

Tedavi öncesi PSA tedavi için güçlü prediktif marker

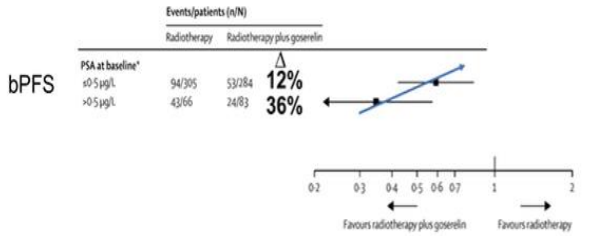




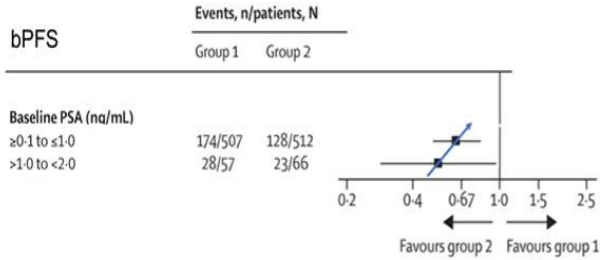
Tedavi öncesi PSA metastaz için güçlü prognostik marker

Differential Benefit by pre-SRT PSA

GETUG-AFU-16



SPPORT/RTOG 0534



RADICALS-HD

0 vs 6m ADT

Randomisation stratification factors

Element		HR	95%CI	p*
Gleason	≤7	0.89	0.68, 1.16	0.93
	≥8	0.79	0.45, 1.38	
Margins	Negative	1.13	0.77, 1.67	0.12
	Positive	0.76	0.56, 1.03	
RT schedule	52.5Gy in 20f	0.93	0.61, 1.41	0.93
	66Gy in 33f	0.86	0.64, 1.16	
RT timing	Adjuvant	1.07	0.66, 1.74	0.06
	Early salvage	0.82	0.62, 1.08	
Long-term HT	LHRH agonist	0.92	0.72, 1.19	0.22
	Bicalutamide	0.56	0.27, 1.18	

* Interaction test

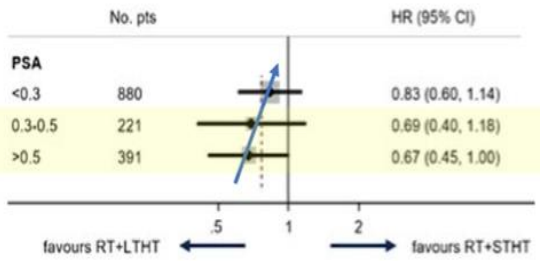
Carrie C, et al, Lancet Onc, 2016
Pollack A, et al. Lancet 2022
Parker C et al, ESMO. 2022

Differential Benefit by pre-SRT PSA

RADICALS-HD

6m vs 24m ADT

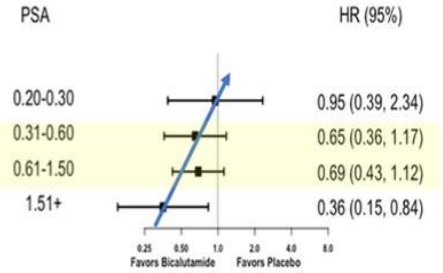
MFS



NRG/RTOG 9601

0 vs 24m HT

Distant Metastasis



Parker C et al, ESMO. 2022
Dess R et al. JAMA Onc. 2020

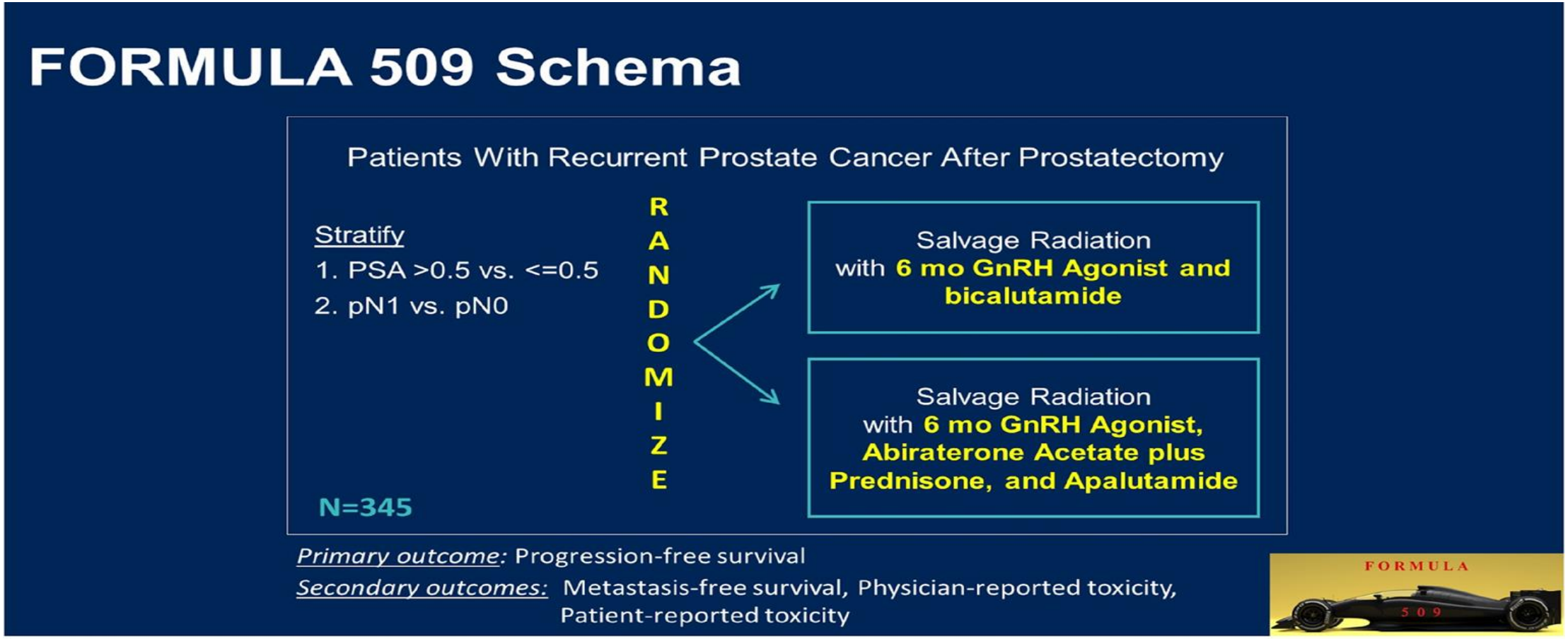
İzole PSA nüksünde hangi hastalara sistemik tedavi

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.

+Tedavi öncesi PSA(≥0.5 ng/dl

Biyokimyasal Rekürens ve PSA Persistansı
Doz Yoğun Tedavi



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

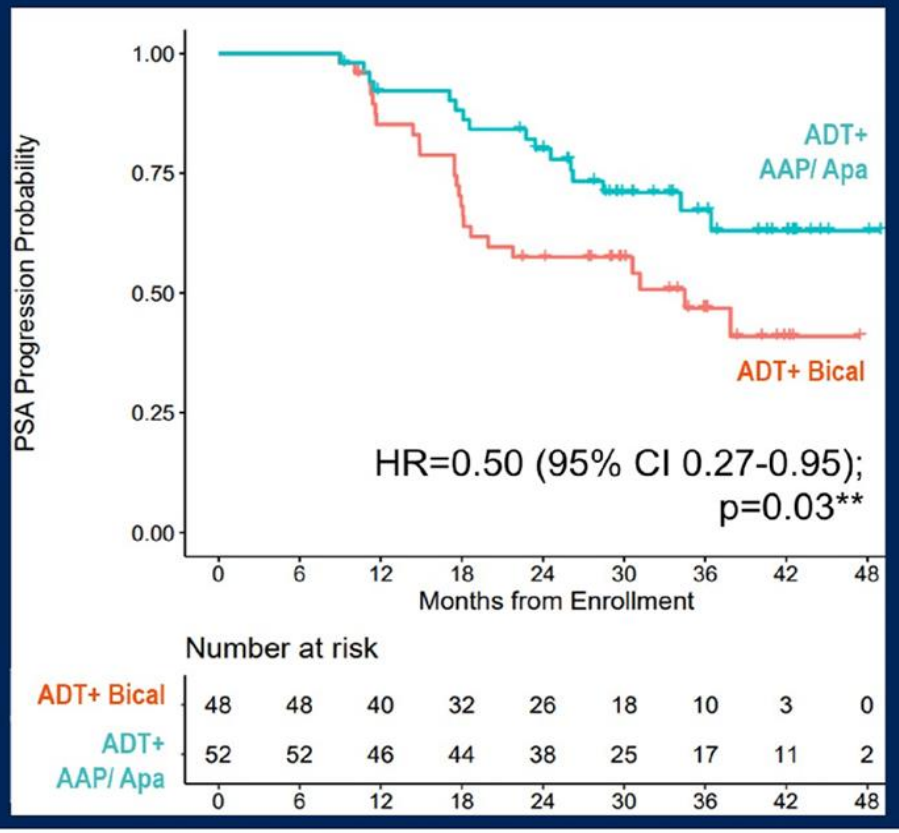
Patient Characteristics

	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

PFS Benefit Among PSA >0.5 (n=100)



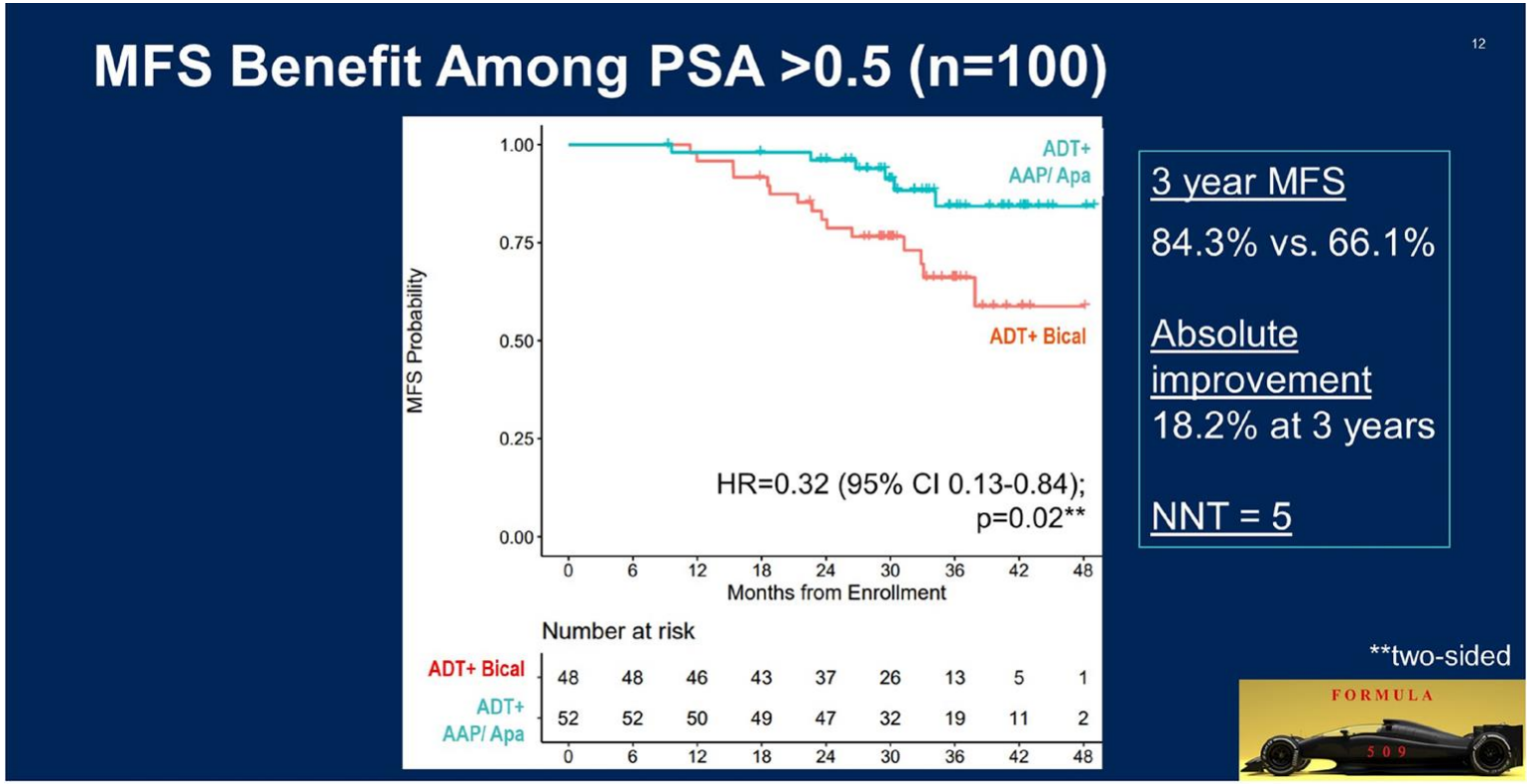
3 year PFS

67.2% vs. 46.8%

**two-sided

PRESENTED BY: Paul Nguyen, MD, MBA; FORMULA 509 Trial

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi



Tedavi öncesi PSA düzeyi kombine tedaviler için prediktif

Differential Benefit by pre-SRT PSA

Formula-509

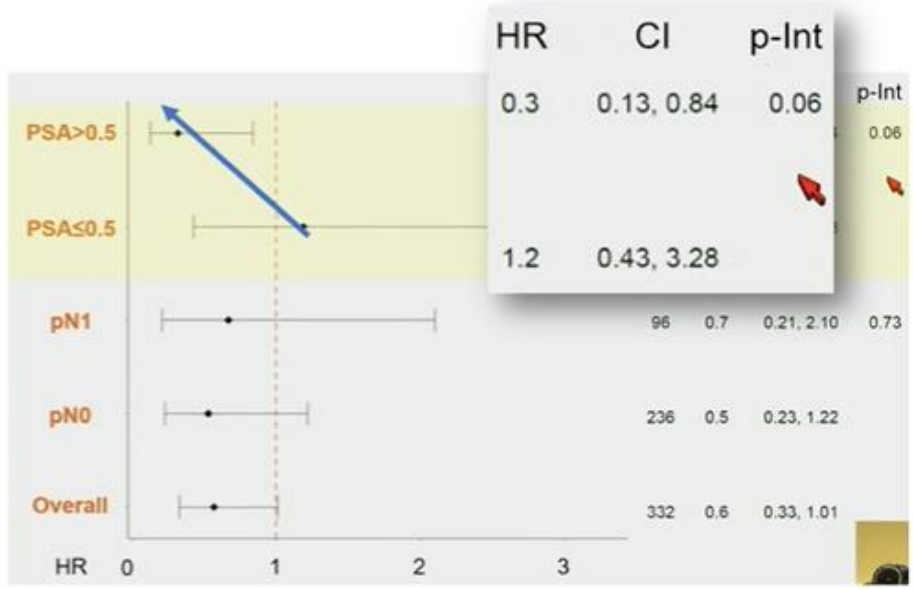
Patients With Recurrent Prostate Cancer After Prostatectomy

Stratify
1. PSA >0.5 vs. <=0.5
2. pN1 vs. pN0

RANDOMIZE

- Salvage Radiation with **6 mo GnRH Agonist and bicalutamide**
- Salvage Radiation with **6 mo GnRH Agonist, Abiraterone Acetate plus Prednisone, and Apalutamide**

N=345



Nguyen P et al. ASCO GU 2023

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
  - PIs Karen Hoffman (MDACC) & Marisa Kollmeier (MSKCC) & Paul Nguyen

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)

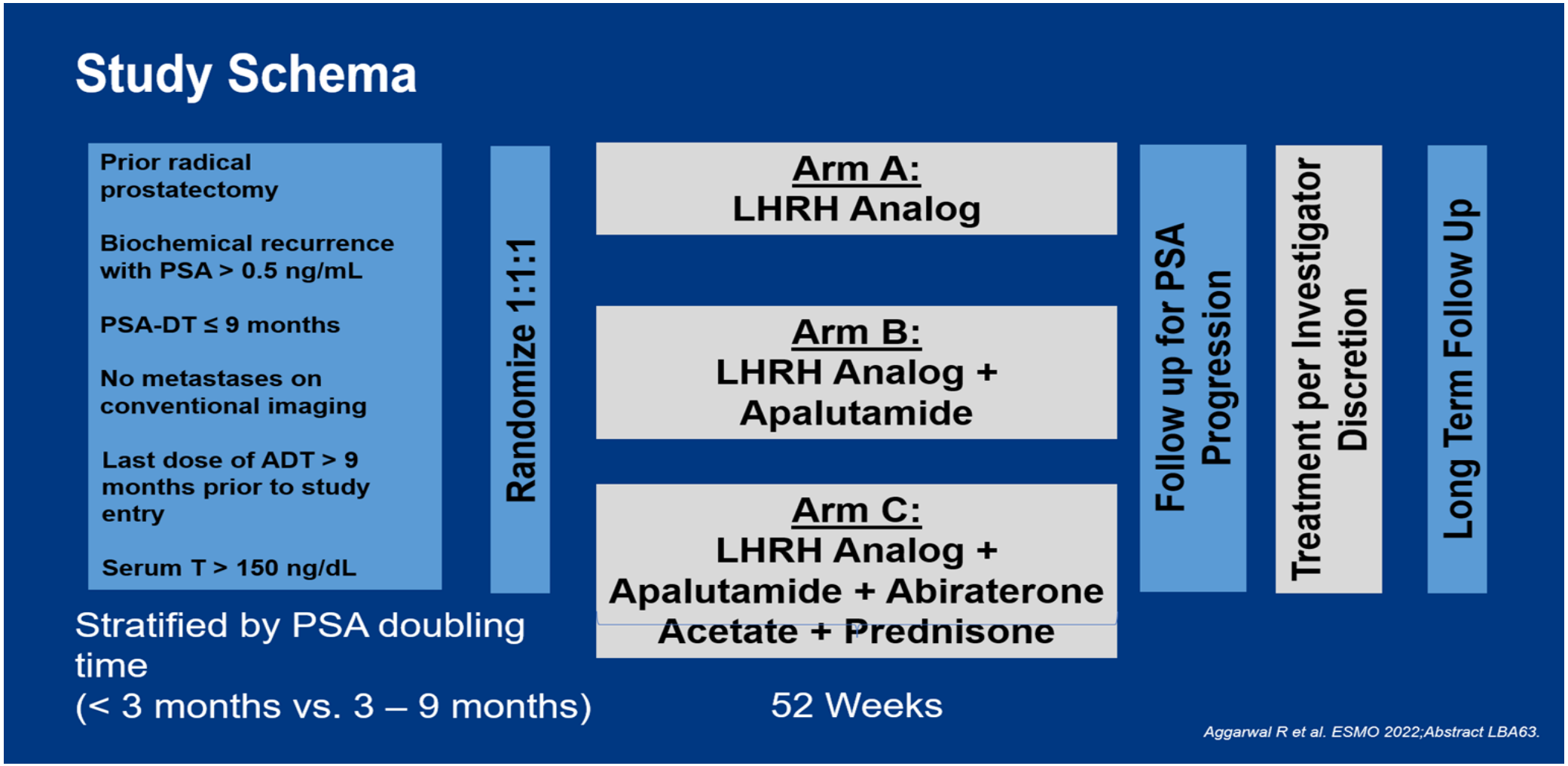
	LOW RISK	INTERMEDIATE RISK	HIGH RISK
INTACT PROSTATE	NO ADT	Short Term ADT	Long Term ADT
POST-OP PROSTATE	NO ADT	Short Term ADT	Long Term ADT

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

RISK CUTPOINTS WILL BE DIFFERENT FOR INTACT VS POST-OP

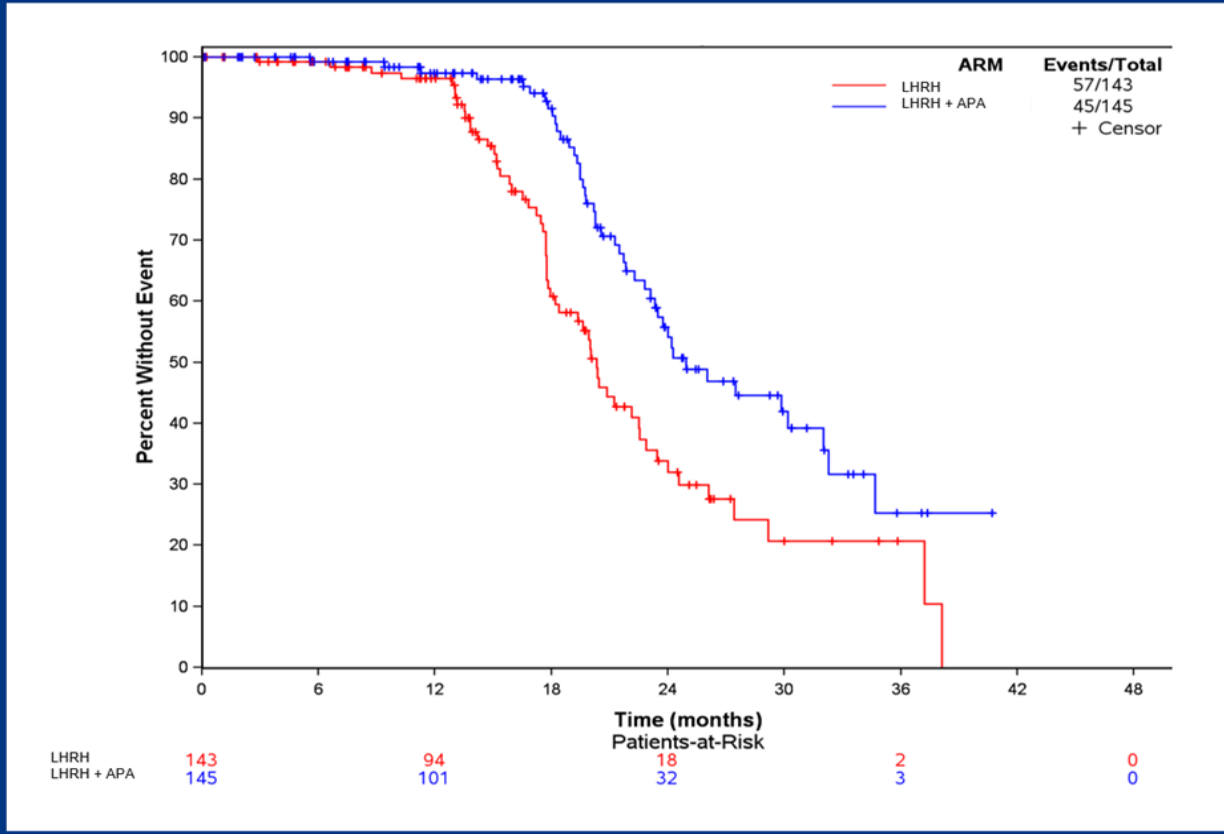
Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Arm B: ADT + apalutamide vs. ADT monotherapy



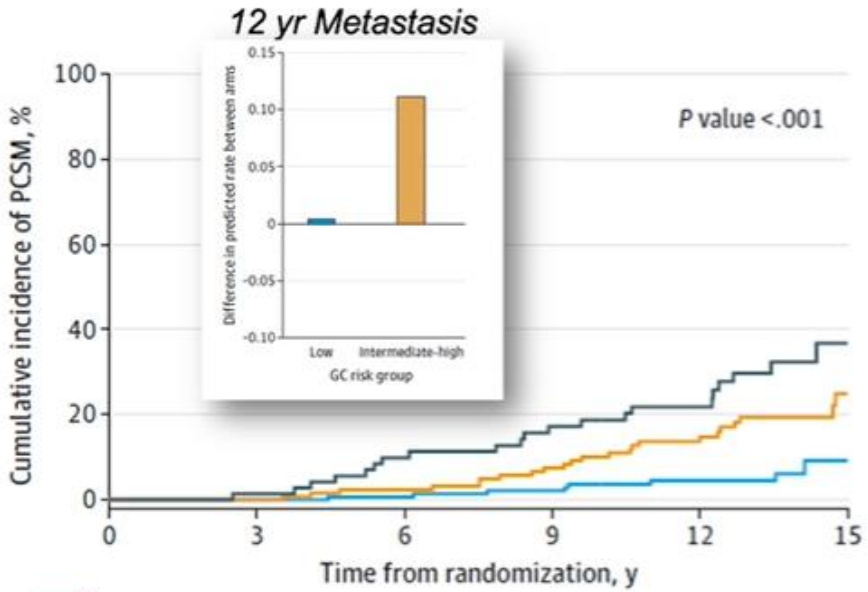
- Median follow up 21.5 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA = 24.9 months (95% CI: 23.3 – 32.3)
  - ADT alone = 20.3 months (95% CI: 18.2 – 22.9)
  - **Hazard ratio 0.52 (95% CI: 0.35 – 0.77)**
  - One-sided p-value = 0.00047)

Aggarwal R et al. ESMO 2022;Abstract LBA63.

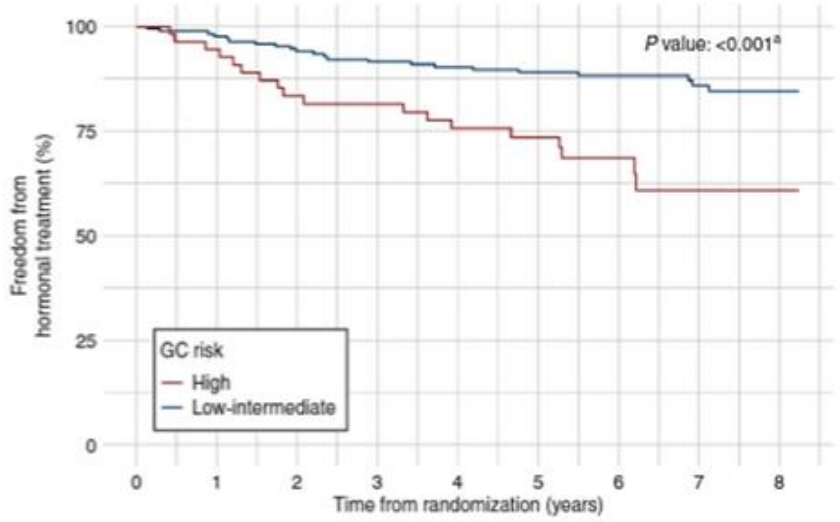
Sistemik tedaviler için yeni prediktif eden markerlar

22-Gene Genomic Classifier Post-RP

NRG/RTOG 9601



SAKK 09/10



University Hospitals
Seidman Cancer Center

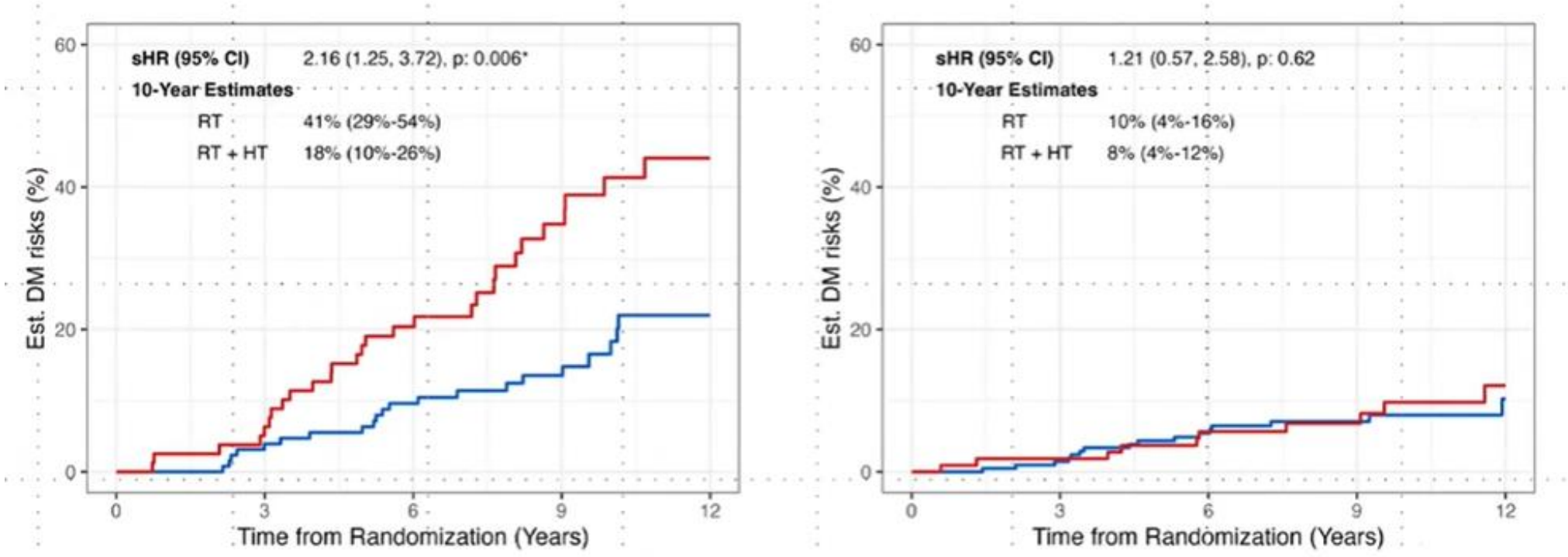
Feng FY et al. JAMA Onc 2021

Dal Pra A et al, Annals of Oncology. 2022

Sistemik tedaviler için yeni prediktif markerlar

Sistemik tedaviler için yeni prediktif markerlar

New Artera Multi-modal AI model:



University Hospitals
Seidman Cancer Center

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

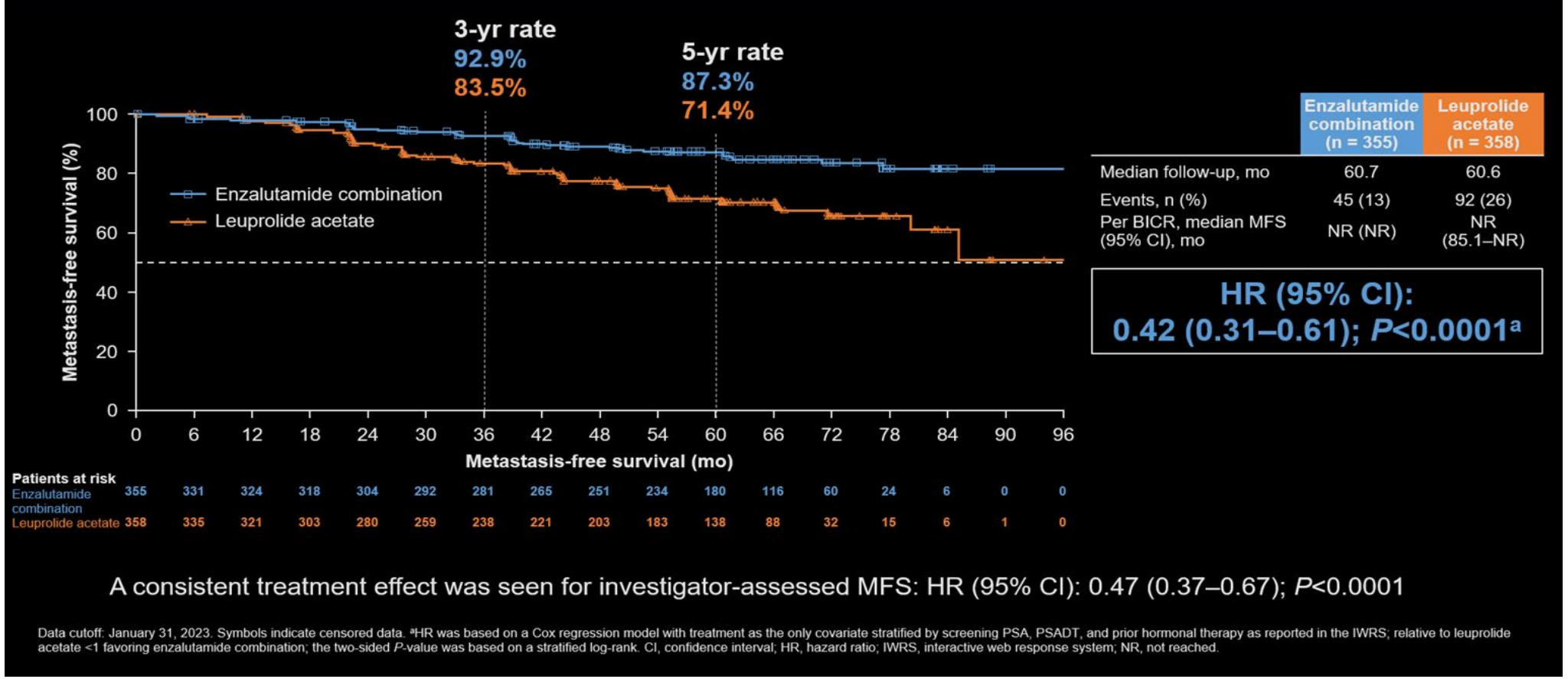
Characteristic	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)	Enzalutamide monotherapy (n = 355)
Age, median (range), yr	69 (51–87)	70 (50–92)	69 (49–93)
Race, n (%)[a]			
White	293 (82.5)	301 (84.1)	295 (83.1)
Asian	26 (7.3)	26 (7.3)	26 (7.3)
Black	16 (4.5)	16 (4.5)	15 (4.2)
Other[b]	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

AUA 2023
CHICAGO ★ APR 28-MAY 1

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]

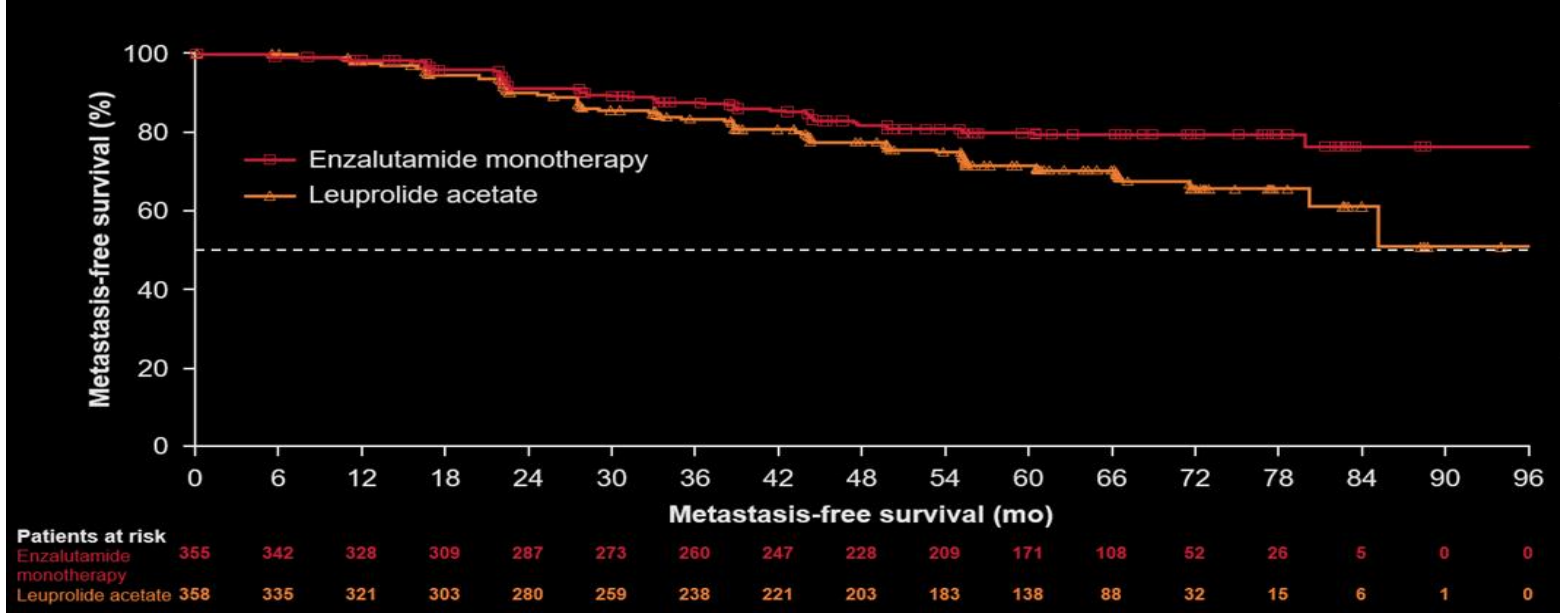
A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); *P*<0.0001

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

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.

Özet

- ❑ Neoadjuvan tedavi özel durumlar dışında rutin olarak önerilmez
- ❑ Yeni nesil AR-yolak inhibitörleriyle bir grup hastada iyi sonuçlar elde edilmiştir
- ❑ Özelikle lokalize yüksek riskli prostat kanserinde karşılanmamış bir tedavi ihtiyacı vardır
- ❑ Bu grup hastalarda sistemik tedavinin etkin olduğu adjuvan çalışmalarda gösterilmiştir
- ❑ Çok sayıda devam eden çalışmalar mevcuttur
- ❑ Neoadjuvan tedavi ilerleyen zamanlarda daha çok gündemimize girecek

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
- Salvage RT ve ADT (6ay)düşünülmelidir
- Uzun dönem 24 ay adjuvan ADT(pT3≥ ve gleason skoru ≥8) ve pelvik lenf nodu pozitif
- Pelvik RT nüks riski yüksek hastalarda düşünülebilir(Gleason≥8, ≥pT3, cerrahi sınır pozitifliği) ve pelvik lenf nodu+
- Enzalutamide , double time ≤ 9 ay, RP sonrası PSA>1 ng/ml ve Radyoterapi sonrası 2 ng/ml

Özet

- RT sonrası Biyokimyasal Rekürens olan hastalarda
- PSA değeri ≥2 ng/ml olan hastalar için, PSA double time ≤ 9 ay olanlarda enzalutamide önerilebilir
- Enzalutamide ulaşamıyorsa, intermittent ADT önerilir
- Sistemik tedavi(ADT ve yeni nesil AR yolağı inhibitörü); Tedavi öncesi PSA değeri, primer tümör gleason skoru, PSA double time, Decipher Skoru, AI risk skorlaması yol gösterici
- ADT 6 ay vs. 24 ay; pelvik lenf nodu pozitif hastalarda uzun dönem ADT