

Lokal İleri Prostat Kanserinde Sistemik Tedavi

Dr. Deniz Tural

Ko Üniversitesi Hastanesi Tıbbi Onkoloji

Ders Planı

☐ Neoadjuvan sistemik tedaviler

☐ PSA persistent ve nüksü

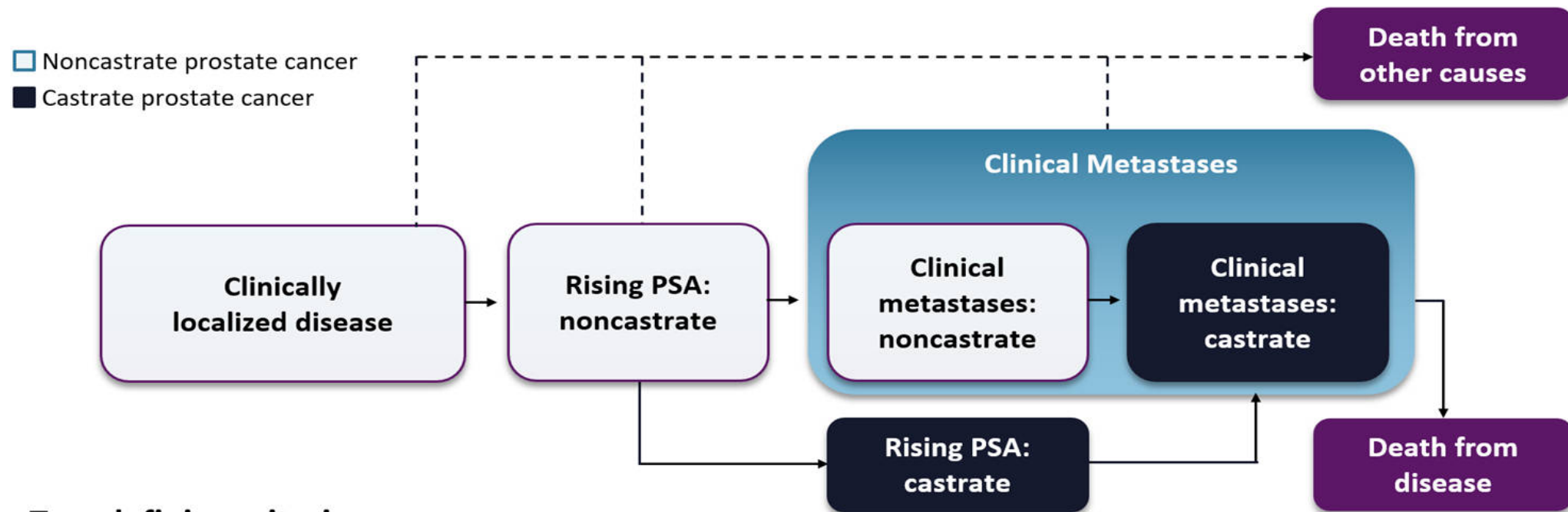
☐ Adjuvan tedaviler

☐ Kombinasyon tedavileri

☐ Sonuç

Prostat kanserinin seyri

Clinical Disease States Model of Prostate Cancer¹



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.

Lokalizasyon Yüksek Riskli Prostat Kanseri

Localized High-Risk Prostate Cancer

Patterns of Presentation



Increased Mortality in High-Risk Prostate Cancer

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

Lokalize Yüksek Riskli Prostat Kanseri

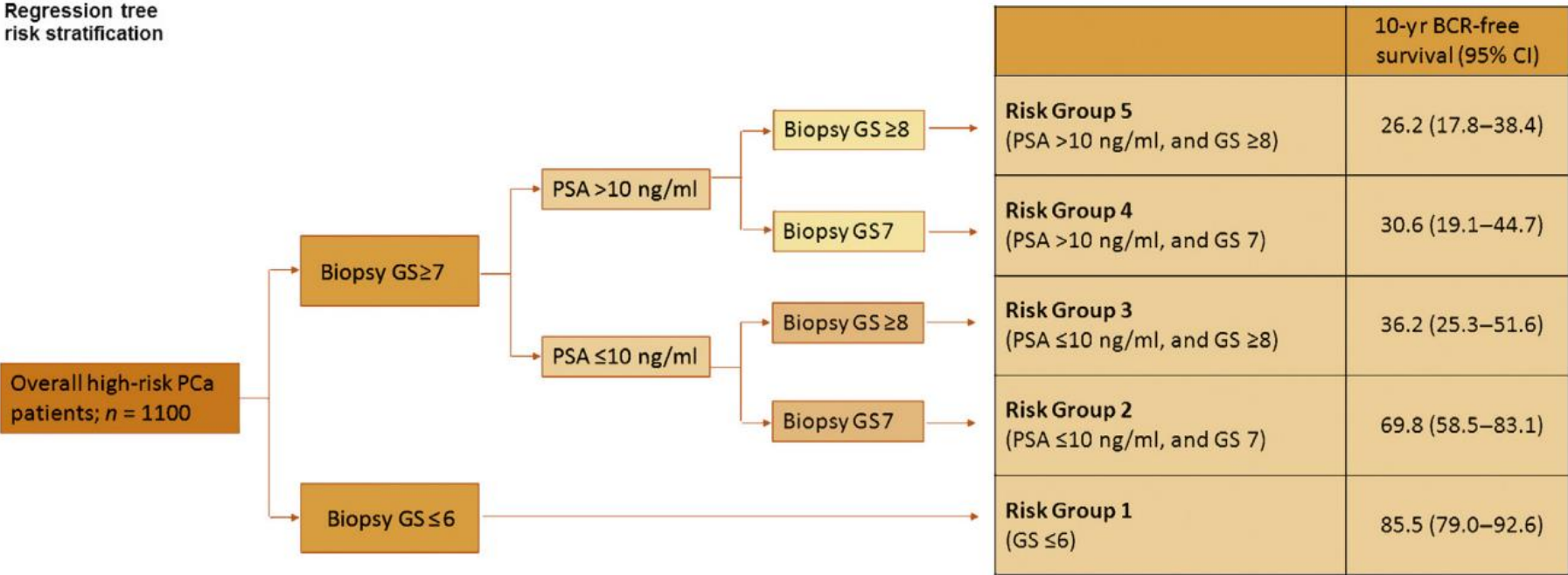
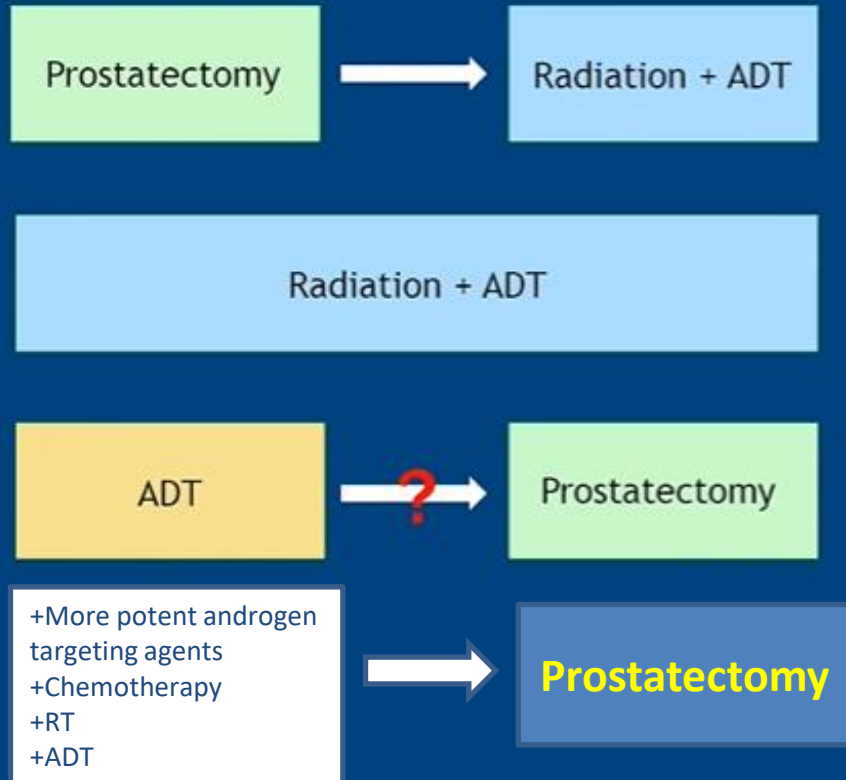


Fig. 1 – A novel biochemical recurrence risk stratification regression tree, based on the data of 1100 D’Amico high-risk prostate cancer patients treated with robot-assisted radical prostatectomy with and without lymph node dissection between 2002 and 2013 at three tertiary care centers.
BCR = biochemical recurrence; CI = confidence interval; GS = Gleason score; PCa = prostate cancer; PSA = prostate-specific antigen.

Neoadjuvan Tedavi Gerekçesi

Treatment Paradigms for High-Risk Prostate Cancer



• Neoadjuvant Treatment

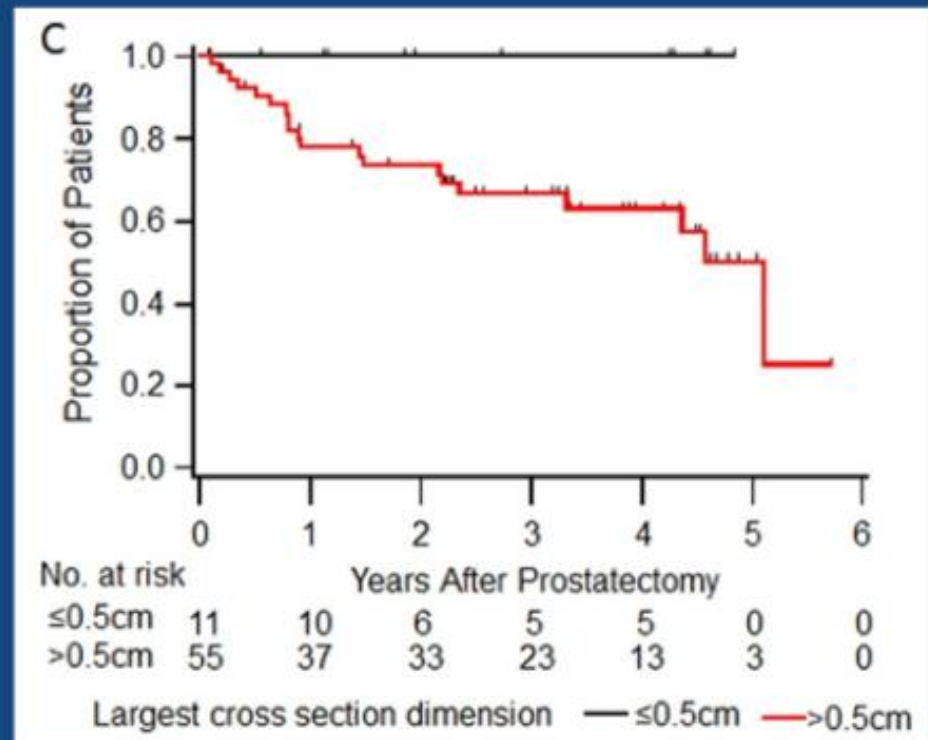
- Standard of care for breast, rectal, bladder and other cancers given improved long-term survival
- Down-stage local disease, which may facilitate surgical resection
- Reduce or delay post-surgery treatment
- Provide an *in vivo* assessment of response to treatment

Pertreli et al, Eur Urology, 2014
Berger et al, JCO, 2005
Mass et al, Lancet Oncology, 2010
Cortazar et al, Lancet Oncology, 2014
McKay et al, Drugs, 2012

Neoadjuvan 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



Neoadjuvan Tedavi Gerekçesi

Neoadjuvant Clinical Trials in Prostate Cancer

Historic Neoadjuvant Trials

- Investigated LHRH agonists +/- first generation antiandrogens
- Majority of patients with low-risk disease
- Did not systematically evaluate pathologic response
- Limited long-term follow-up

Contemporary Neoadjuvant Trials

- Investigated more potent androgen targeting agents (abiraterone acetate – henceforth abiraterone, enzalutamide, apalutamide)
- Majority of patients with high-risk disease
- Systematic central pathology review to evaluate response
- Long-term follow-up ongoing

ADT ile Neoadjuvan 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 cm ³ to a mean of 0.8 ng/ml and 29.5 cm ³ , respectively.
Van Poppel	1995	Leuven	65	Stages T2b and T3 prostate cancer	Estramustine +	For T2b tumors, a significant decrease in

ADT ile daha iyi cerrahi sınır, down staging
BPFS ve OS katkısı yok

		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%, $P = 0.011$).

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

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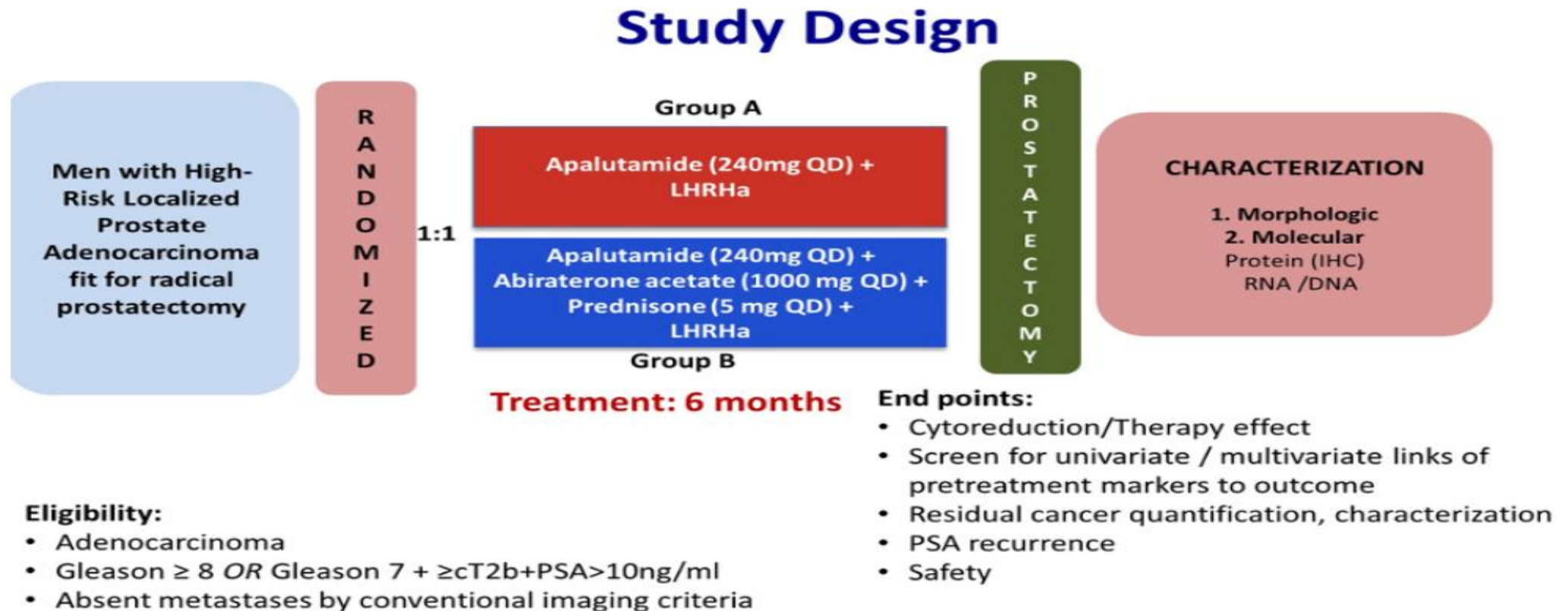
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Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri



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

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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*

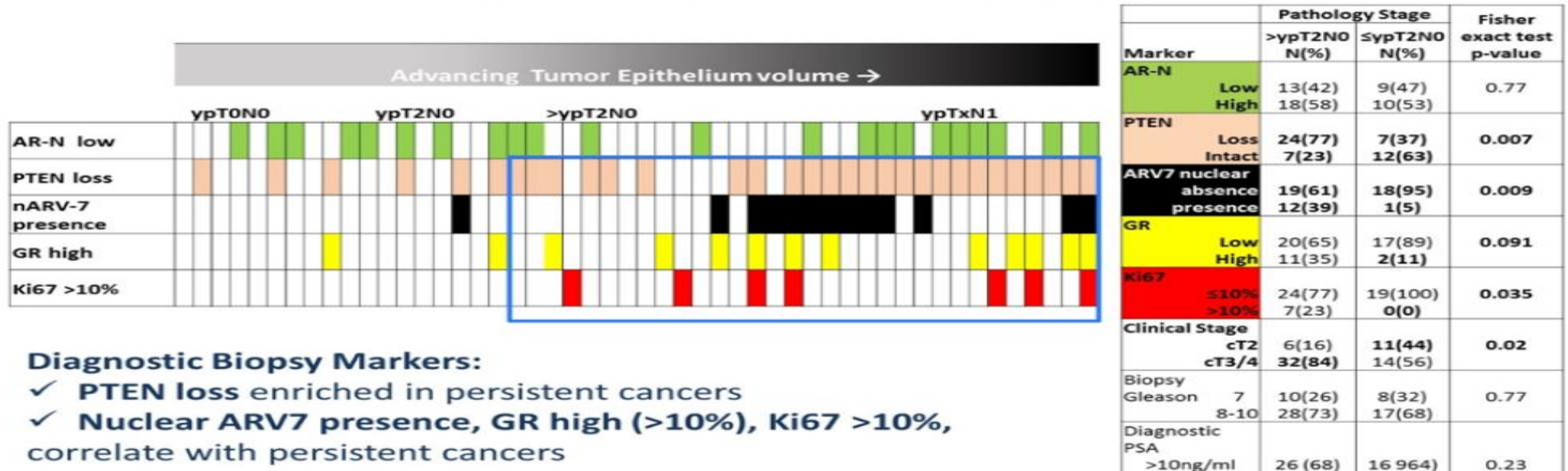
Tumor volume and tumor cellularity varied significantly. The finding of ≤ypT2N0 did not correlate with Gleason score, but did correlate with a pre-specified molecular signature, PTEN expression, and absence of cribriform/intraductal spread.

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri

Tumor volume and tumor cellularity varied significantly. The finding of $\leq$ 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.

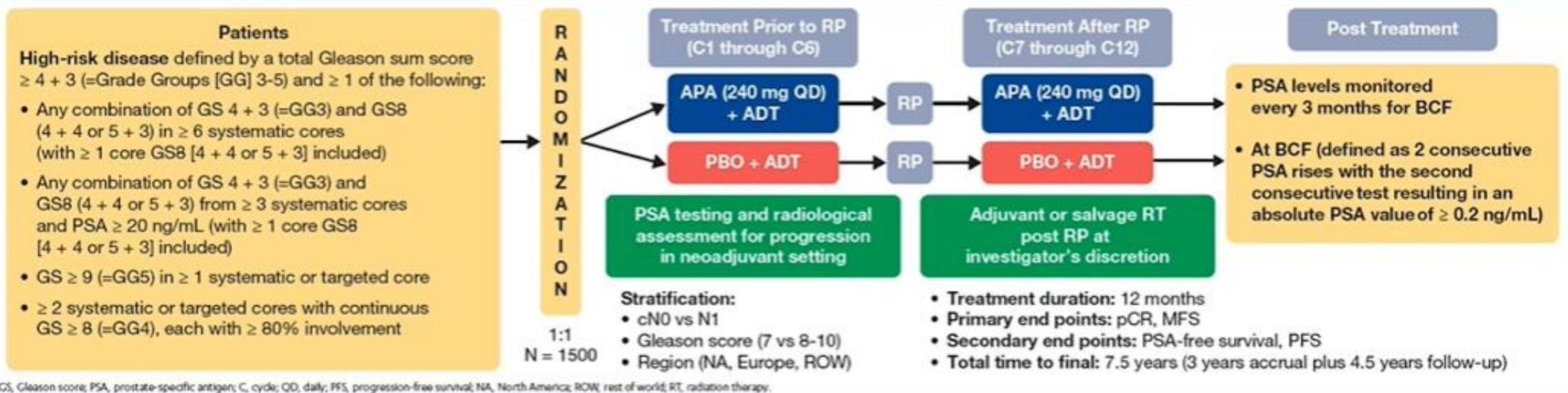
Univariate Analyses for association of pretreatment tumor characteristics with therapy effect



Devam Eden Çalışmalar

Proteus

Randomized, Double-blind, Placebo-Controlled, Phase 3 Study of Apalutamide in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Who are Candidates for Radical Prostatectomy



Neoadjuvant Chemotherapy+ADT

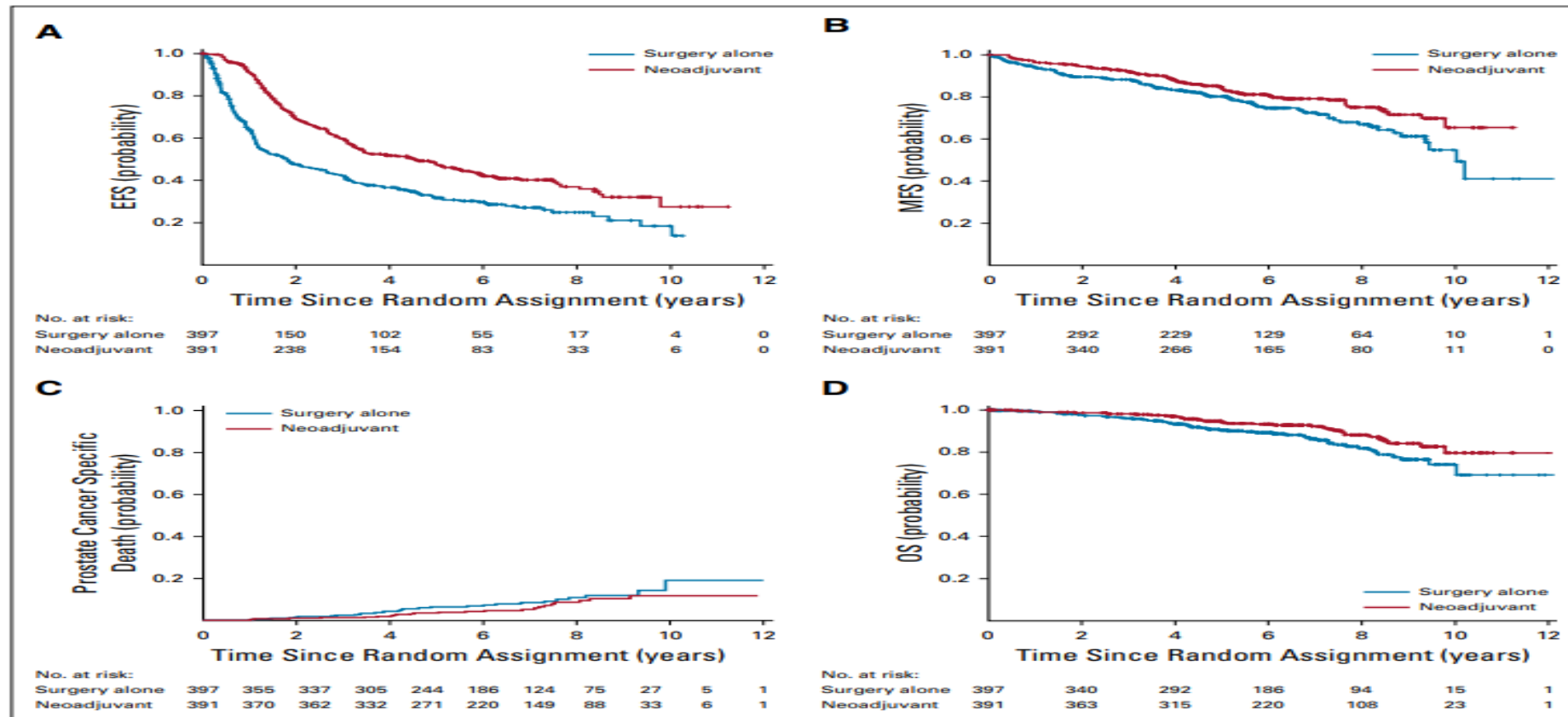


FIG 3. (A) Event-free survival (EFS) or the likelihood of not requiring additional treatment after radical prostatectomy in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy (designated neoadjuvant) versus radical prostatectomy alone (designated surgery alone). An event is 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($\text{PSA} \leq 3 \text{ ng/ml}$)

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, $\leq 3 \text{ ng/ml}$) 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)

ADJUVAN TEDAVİ



National
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NCCN Guidelines Version 4.2024 Prostate Cancer

[NCCN Guidelines Index](#)
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HIGH- OR VERY-HIGH-RISK GROUP

EXPECTED
PATIENT
SURVIVALⁿ

INITIAL THERAPY

ADJUVANT THERAPY

>5 y or
symptomatic^{ff}

RT^u + ADT^{c,y} (category 1)
or
RT^u + ADT^{c,y} + abiraterone^{gg} (for very-high-risk only^{hh})

RP^v + PLNDⁱⁱ

Adverse feature(s) and no lymph node metastases:^w
Monitoring (category 1, preferred)^x with
consideration of early RT for a detectable and rising
PSA or PSA >0.1 ng/mL ([PROS-9](#))
or
EBRT^u ± ADT^{c,y}

No adverse features or lymph node metastases

Lymph node metastasis:^{aa}
Monitoring with consideration of early treatment
for a detectable and rising PSA or PSA >0.1 ng/mL
([PROS-9](#))
or
ADT^{c,y,bb} ± EBRT^u

Undetectable
PSA after
RP or PSA
nadir^{cc} after
RT

See Monitoring
for Initial
Definitive
Therapy
([PROS-9](#))

PSA persistence/
recurrence^{dd,ee}

See Radical
Prostatectomy
PSA
Persistence/
Recurrence
([PROS-10](#))

See Radiation
Therapy
Recurrence
([PROS-11](#))

≤5 y and
asymptomatic

Observation^r
or
ADT^{c,y,jj}
or
EBRT^{u,jj}

Best supportive care

See Monitoring
([PROS-9](#))

Abirateron+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 $\pm$ enzalutamide + ADT vs ADT comparisons

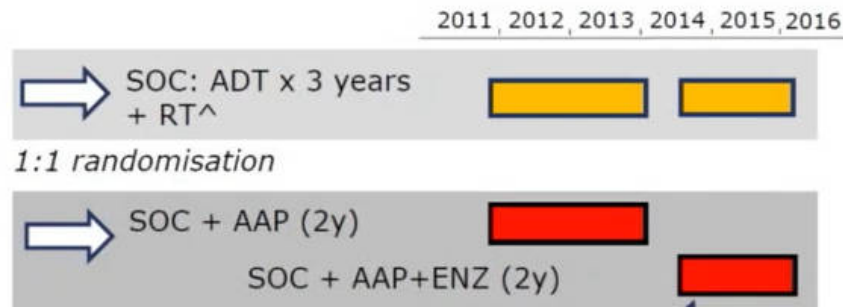
Newly diagnosed

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*

Solid bars: period of accrual

SOC, standard of care

- 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

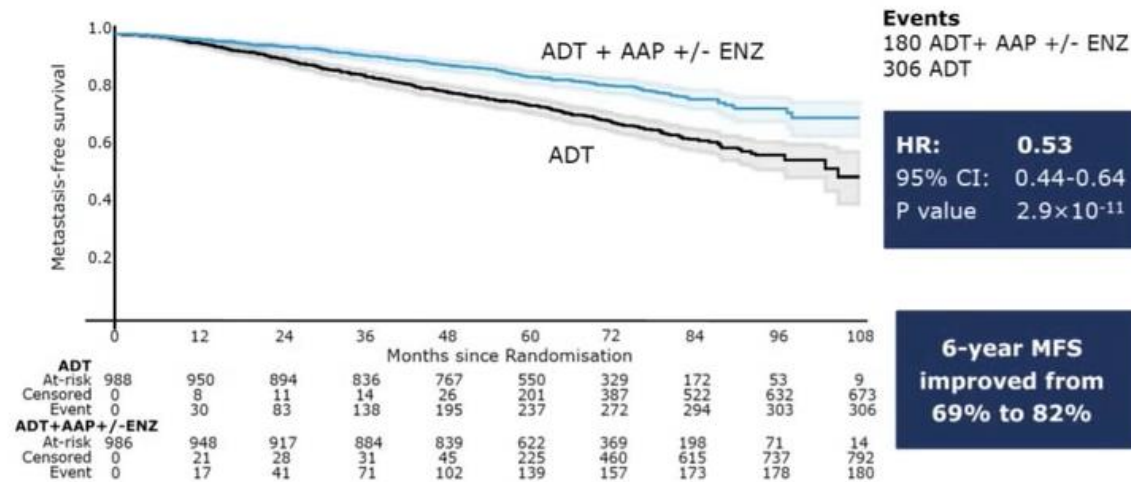
Abiraterone+ADT+RT

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)

Abiraterone+ADT+RT

Metastasis-free survival



Kaplan-Meier estimates with 95% CI in lighter shade

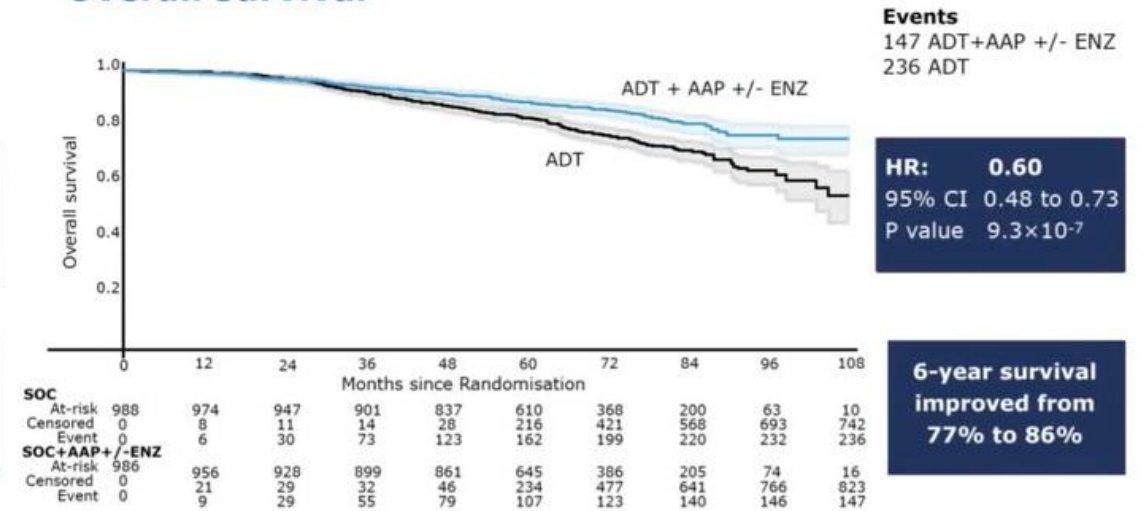


Gerhardt Attard MD FRCP PhD

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Non-proportional hazards $P=0.46$

Overall survival



Kaplan-Meier estimates with 95% CI in lighter shade



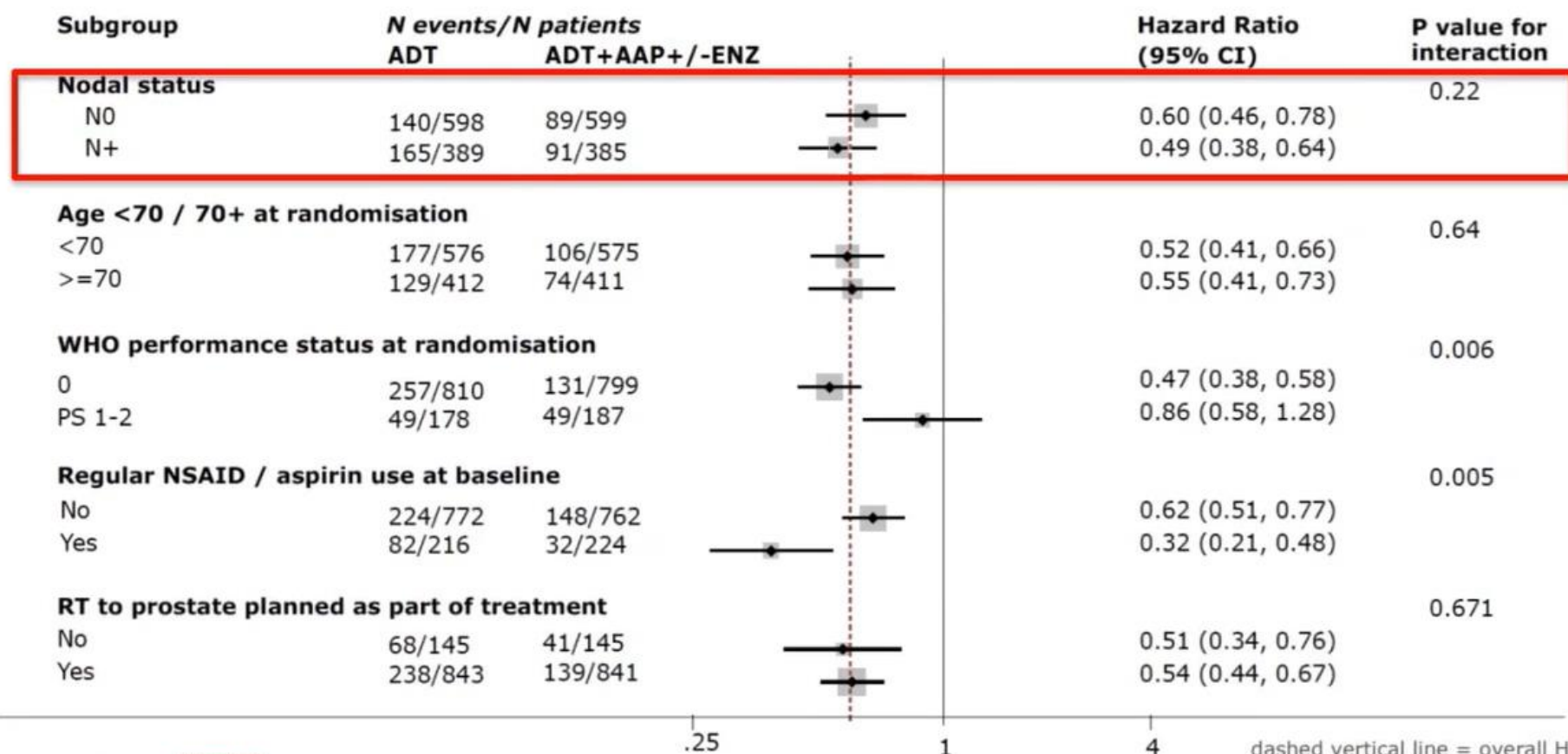
Gerhardt Attard MD FRCP PhD

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Non-proportional hazards $P=0.1$

Abiraterone+ADT+RT

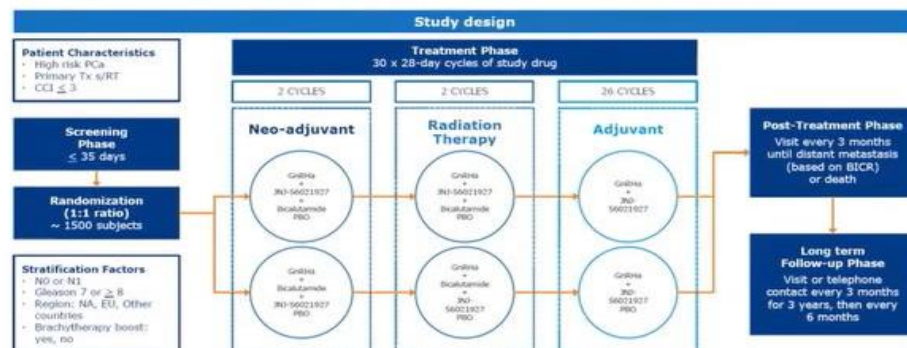
Metastasis-free survival: Subgroup analysis



Definitif RT+ADT+ Yeni Nesil AR-yolağı İnhibitörleri

Apalutamide

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



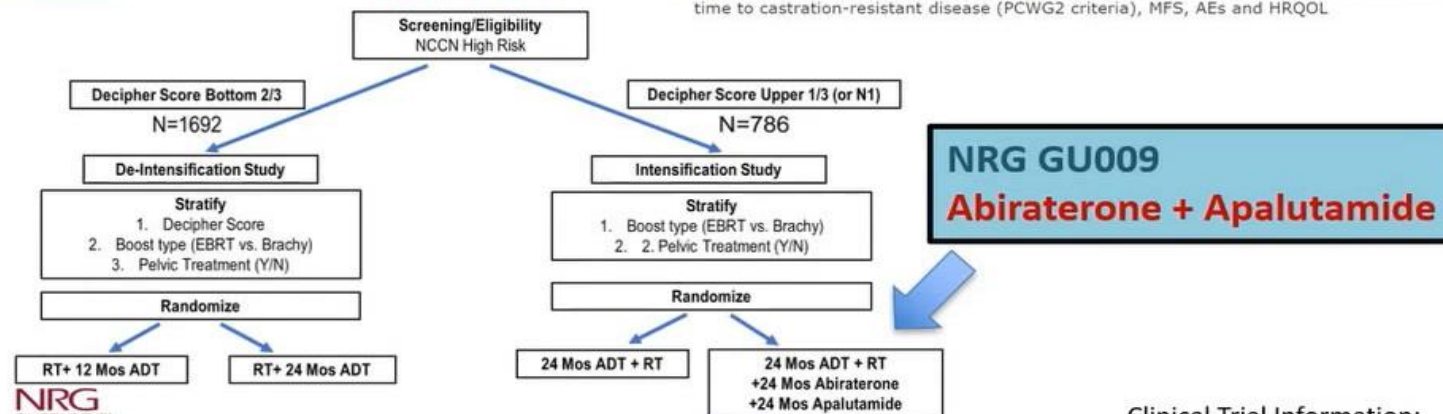
Enzalutamide

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



Clinical Trial Information:
NCT02531516; NCT02446444; NCT04513717

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Biyokimyasal Rekürens

Tanım

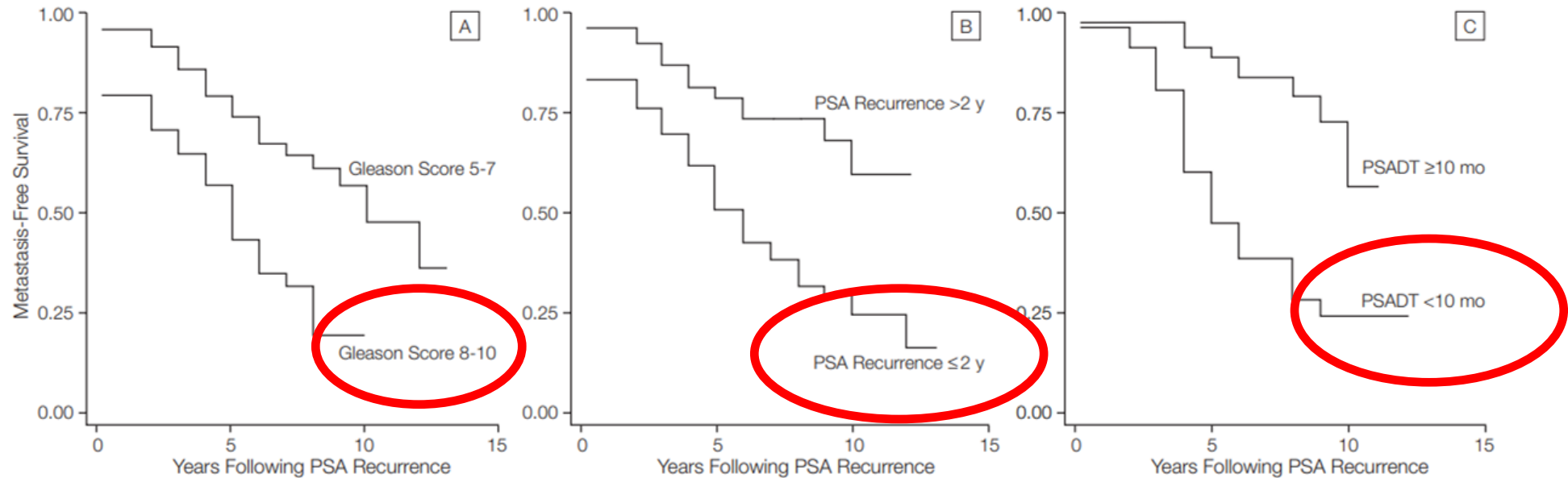
- ☐ ❶ Biyokimyasal Rekürens ; Daha önceleri EUA tanımlaması, Prostatektomi sonrası PSA değeri nadir düzeye düşen hastalarda PSA değerinin artarak ≥ 0.2 ng/ml olarak ölçülmesi ve bunun birkaç ölçümle doğrulanması
- ☐ ❷ NCCN tanımlaması; Prostatektomi sonrası PSA değeri nadir düzeye düşen hastalarda PSA 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 of Urology 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

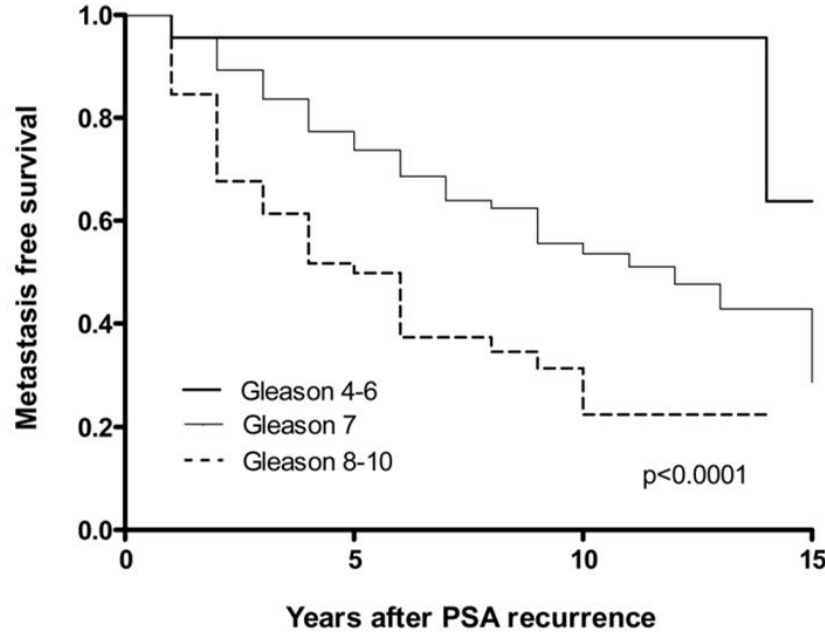
Biyokimyasal Rekürens ve PSA Persistansı Metastaz riski

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

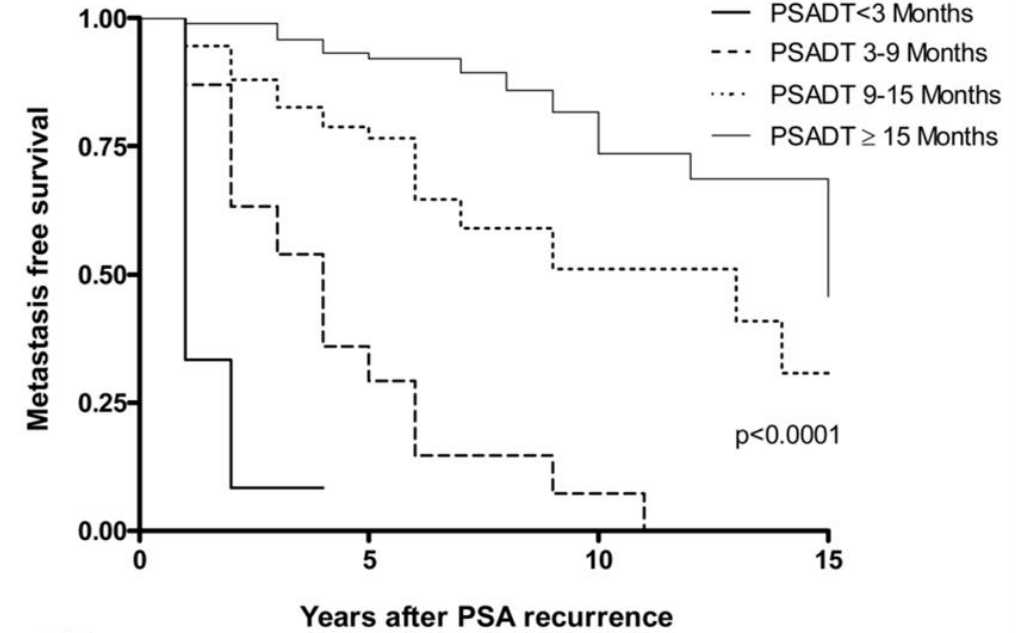


A, Based on Gleason scores in the radical prostatectomy specimen ($P < .001$). B, Based on years until initial biochemical recurrence ($P < .001$). C, Based on prostate-specific antigen doubling time (PSADT) ($P < .001$).

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



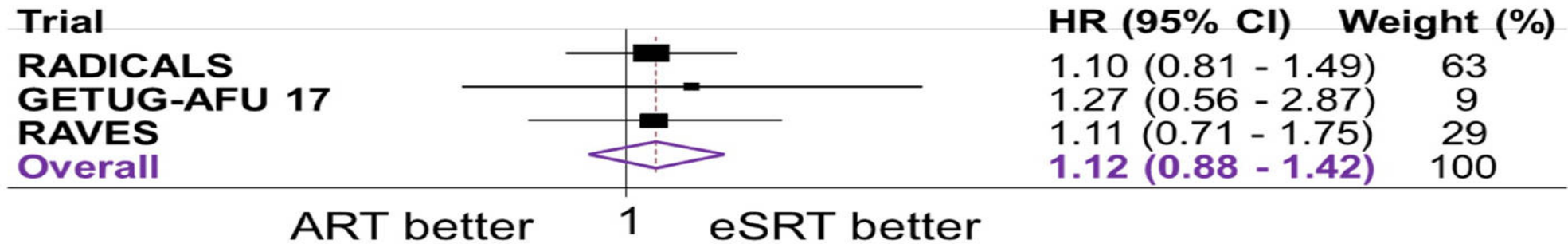
Number at risk				
PSADT < 3 Month	46	0	0	0
PSADT 3-9 Month	106	16	2	0
PSADT 9-15 Month	86	37	11	1
PSADT ≥ 15 Month	212	86	30	3

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

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)**

Radikal Prostatektomi sonrası Adjuvan RT > Salvage RT

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

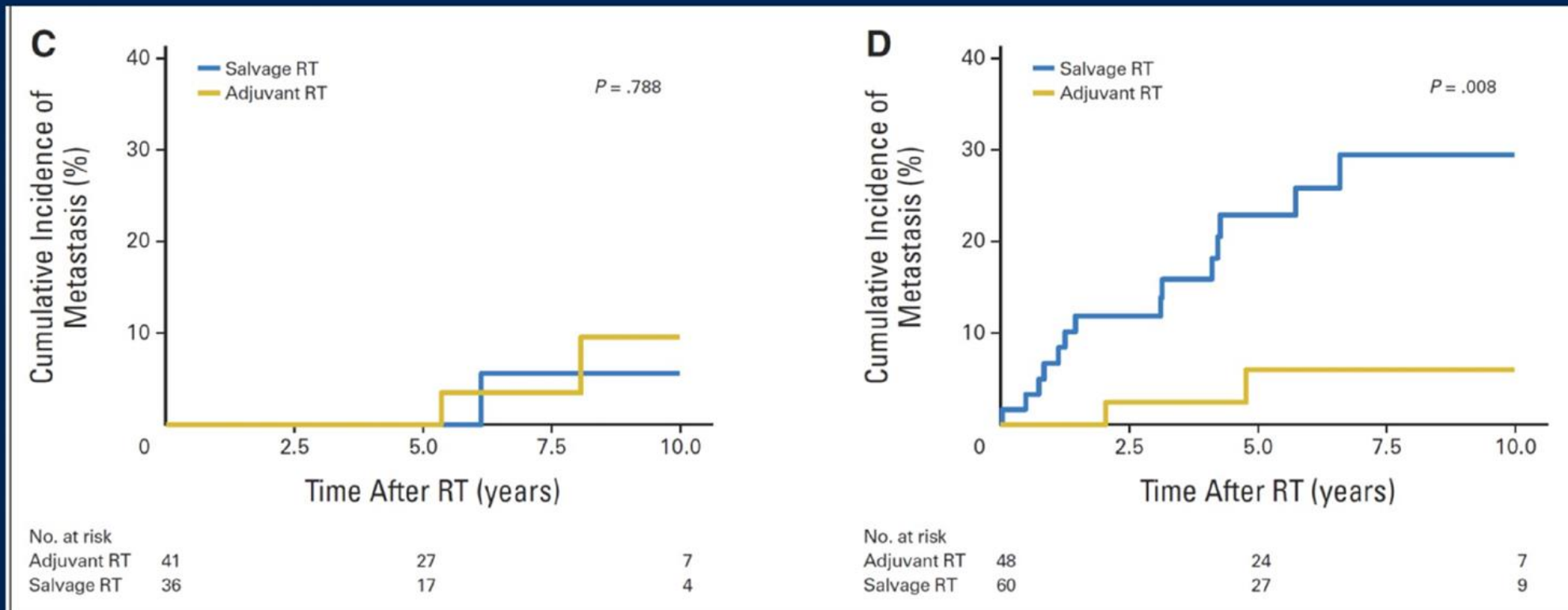
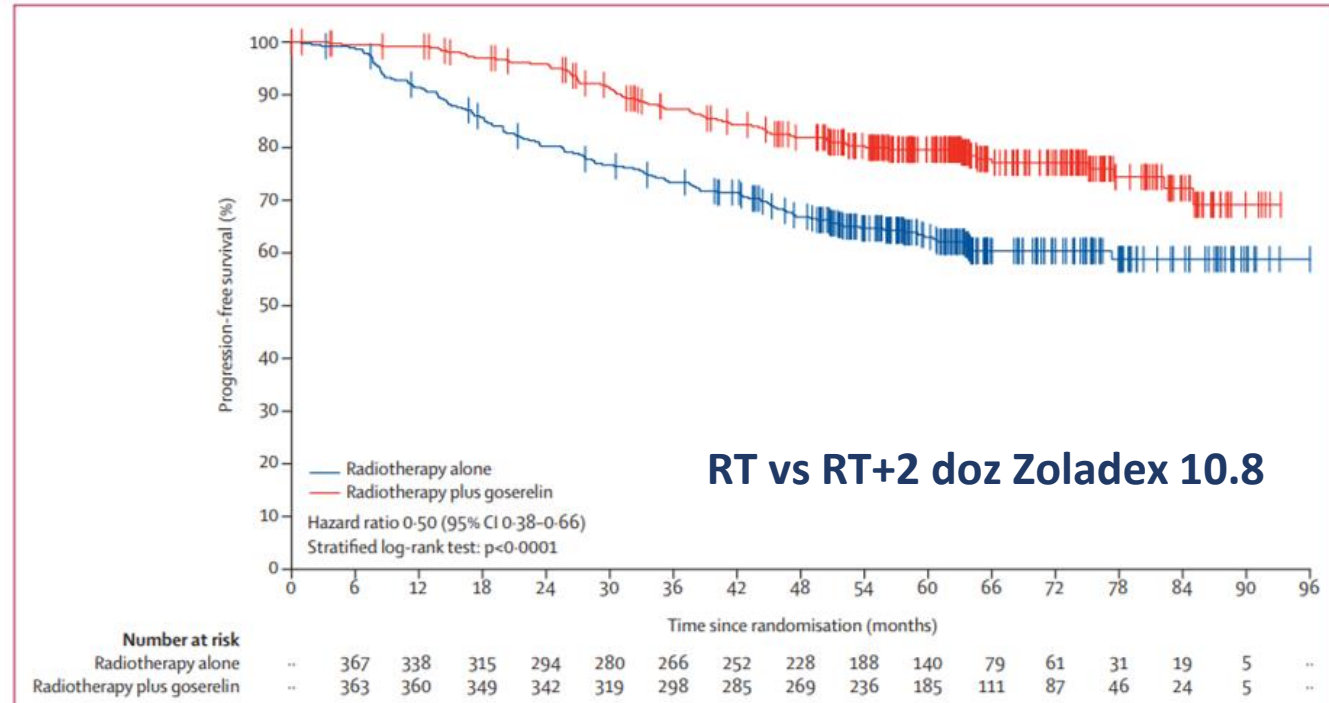


Fig 3. Cumulative incidence curves to evaluate benefit from adjuvant radiotherapy (RT) versus salvage RT stratified by (A and B) Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score and (C and D) genomic classifier (GC).

Biyokimyasal Rekürens ve PSA Persistansı

Prostat +/-pelvis RT+ADT

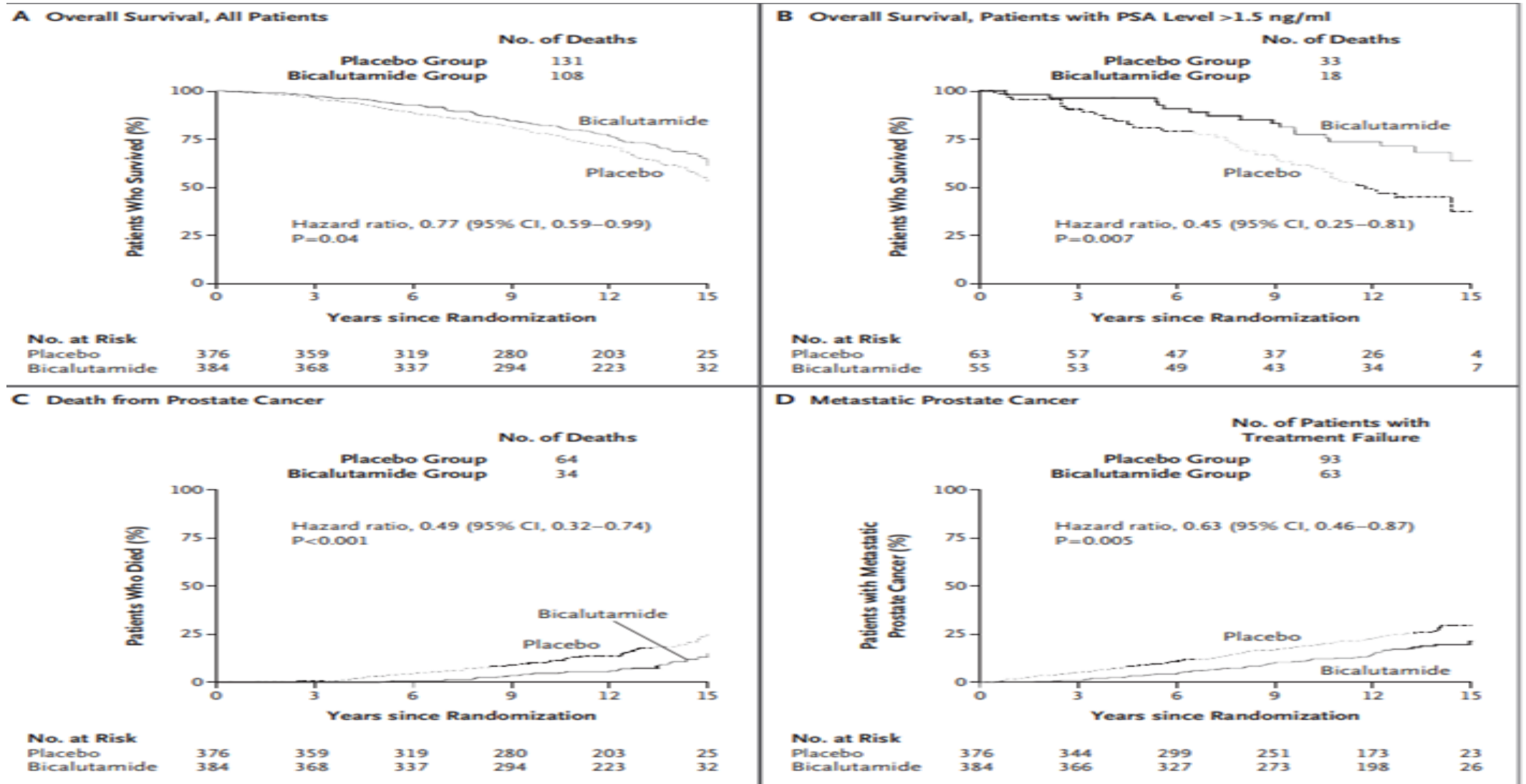
	Radiotherapy alone (n=373)	Radiotherapy and goserelin (n=369)
Age (years)	67 (52-85)	67 (49-80)
Gleason score		
<8	332 (89%)	329 (89%)
≥8	41 (11%)	40 (11%)
Pathological tumour stage (TNM 2005)		
pT2a	37 (10%)	29 (8%)
pT2b	76 (20%)	75 (20%)
pT2c	88 (24%)	92 (25%)
pT3a	121 (32%)	127 (34%)
pT3b	50 (13%)	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)



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

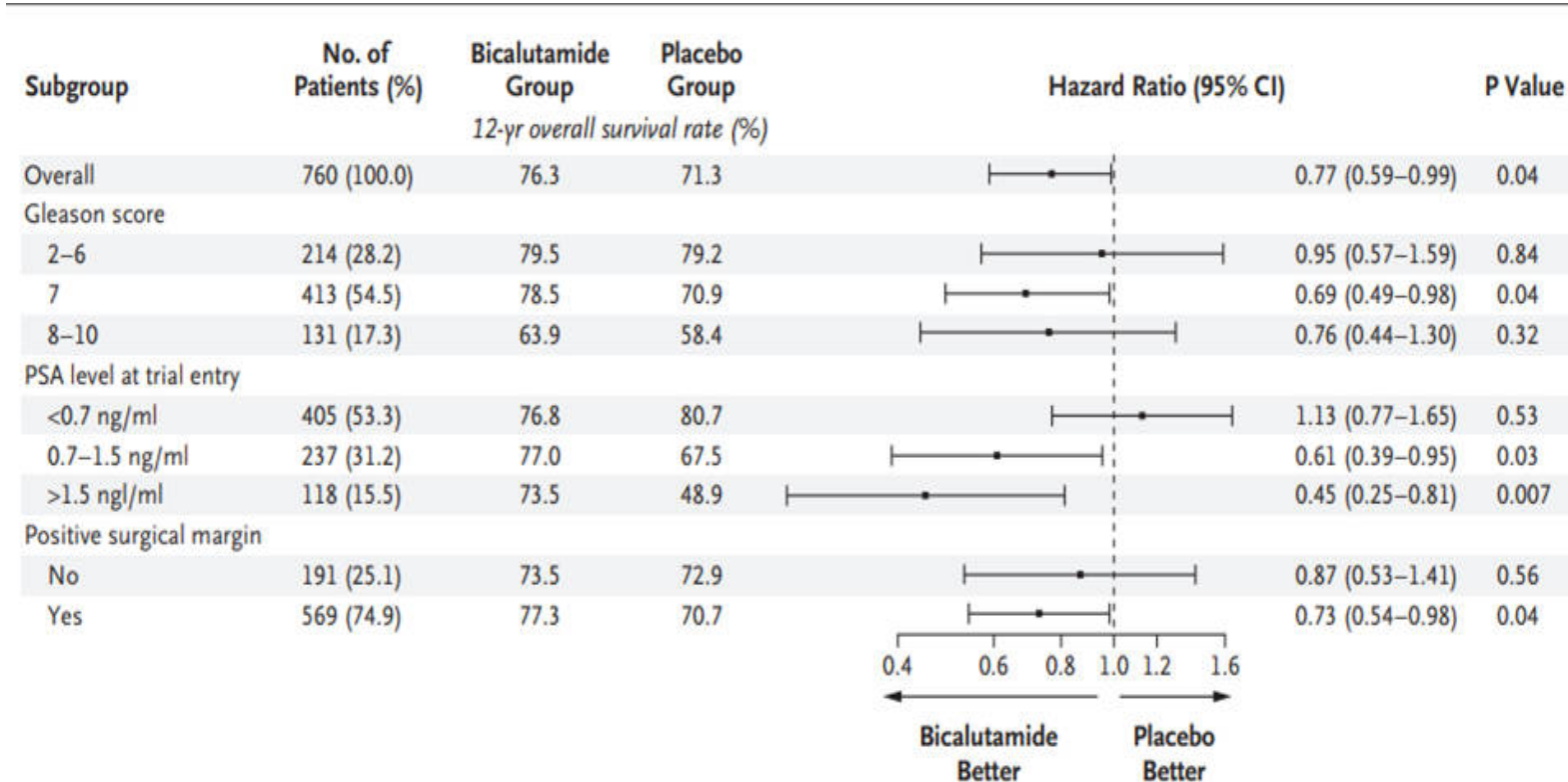
Biyokimyasal Rekürens ve PSA Persistansı

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



Biyokimyasal Rekürens ve PSA Persistansı

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

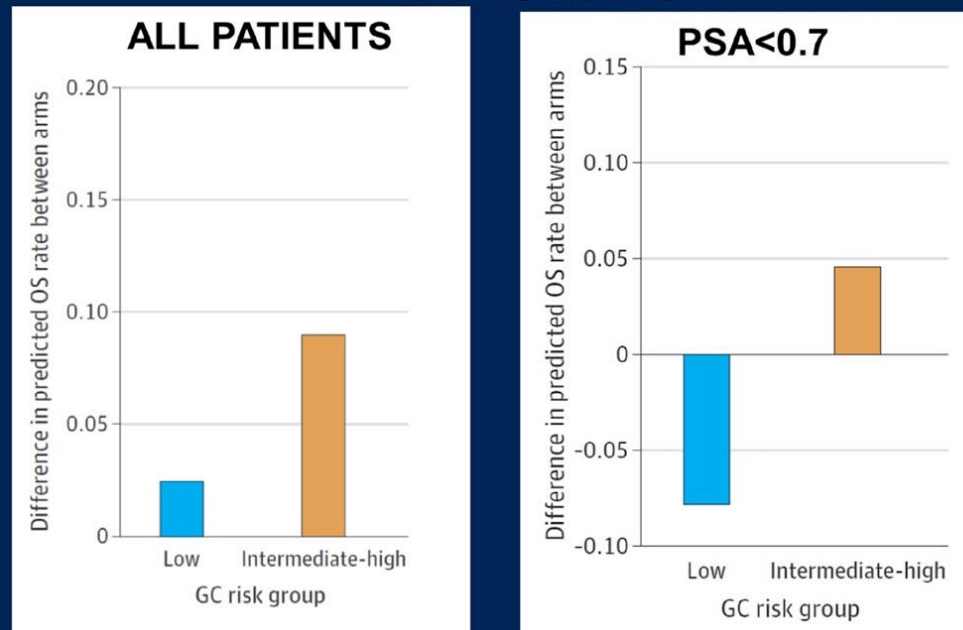


Resulting in 69.7% of the patients in the bicalutamide group having gynecomastia

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

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

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



Bars show %
Difference in OS
by Treatment Arm

Biyokimyasal Rekürens ve PSA Persistansı Prostat+pelvis RT+ADT Sonuçları

1-PBRT

2-PBRT+4-6 ay
LHRH

3-PBRT+PLNRT+2-
4 ay LHRH

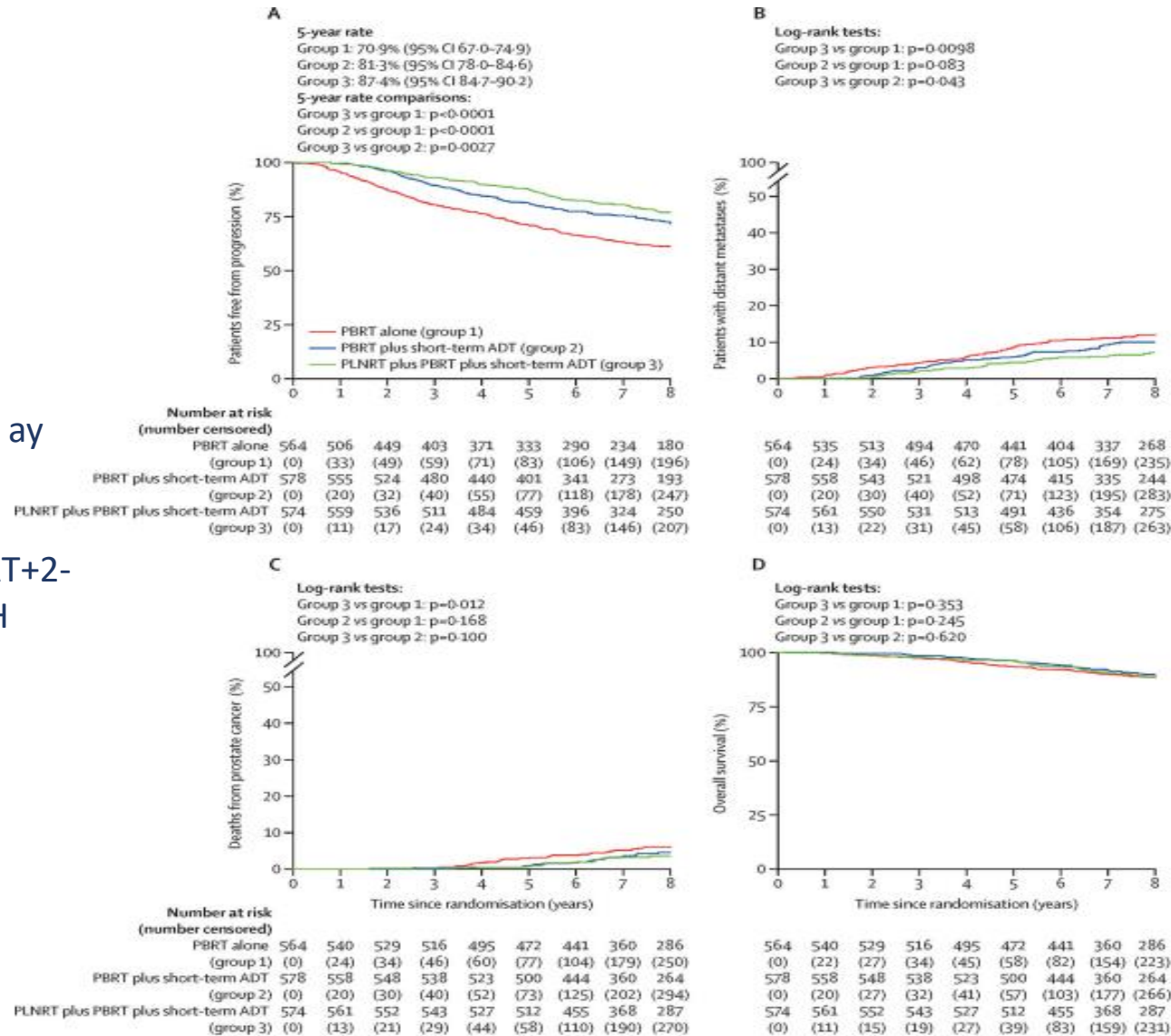


Figure 2:
Kaplan-Meier estimates and cumulative incidence curves: (A) Freedom from progression,

pT2/pT3

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

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

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

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)

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?

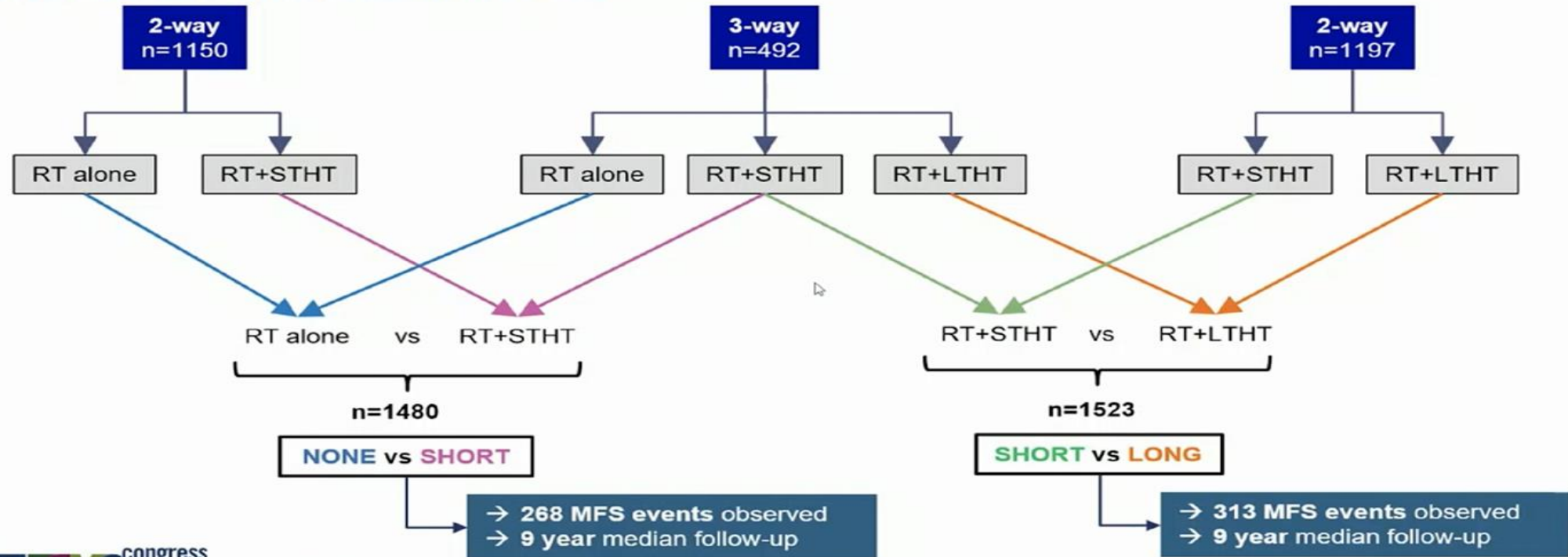
- ☐ Radiation therapy prostate bed alone: 6% (6 votes)
- ☐ Radiation therapy prostate bed plus pelvis: 4% (4 votes)
- ☐ Radiation therapy prostate bed plus short-term systemic therapy: 15% (15 votes)
- ☐ Radiation therapy prostate bed plus pelvis plus shortterm systemic therapy: 38% (37 votes)
- ☐ Radiation 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)

Biyokimyasal Rekürens ve PSA Persistansı

RT+uzun dönem ADT

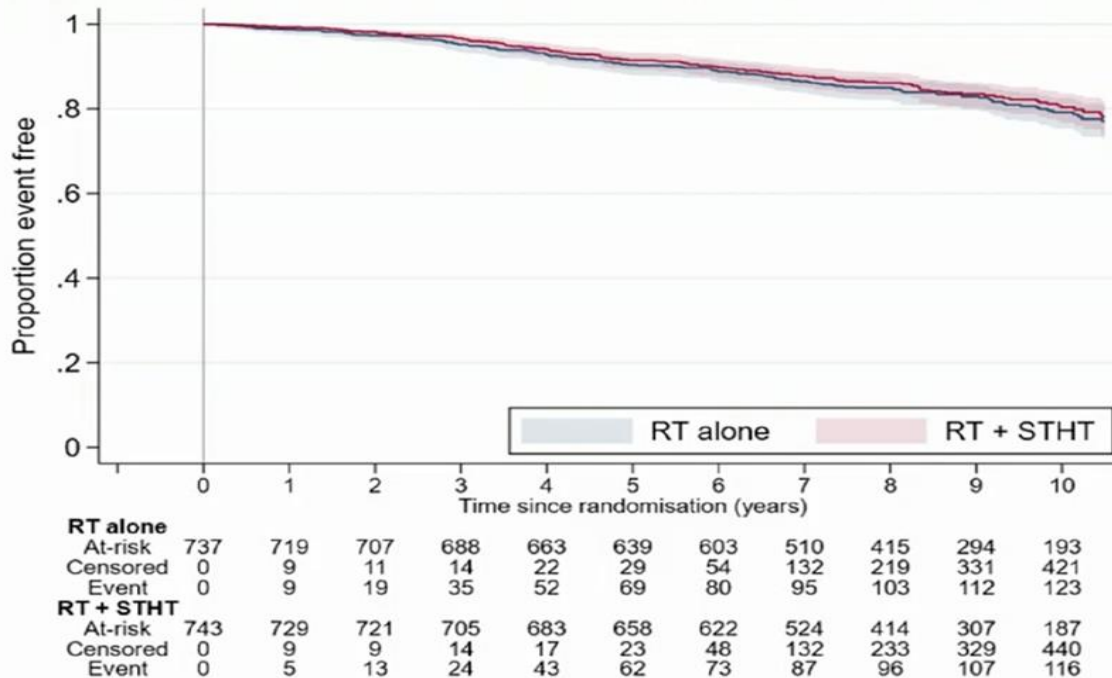
RADICALS-HD: Duration of ADT with post-op RT for prostate cancer

Recruitment and Randomisation



Biyokimyasal Rekürens ve PSA Persistansı RT+uzun dönem ADT

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



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

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

29% Received *Adjuvant RT*

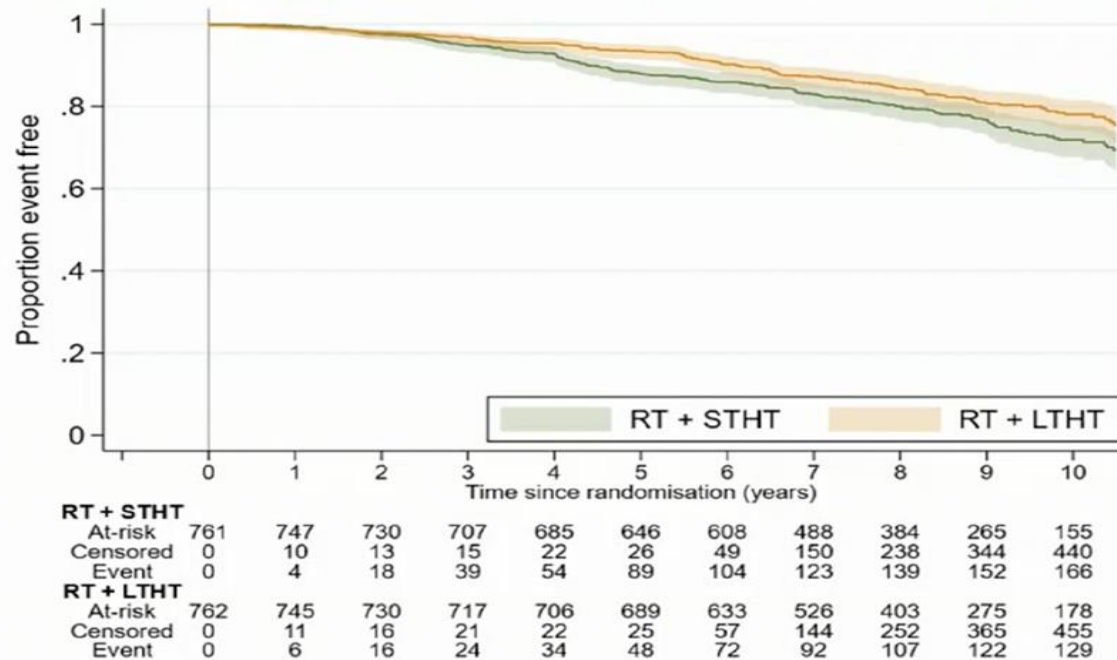
11% Gleason 8-10

Biyokimyasal Rekürens ve PSA Persistansı

RT+uzun dönem ADT

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

Short vs Long: Metastases-Free Survival (MFS)



SHORT vs LONG

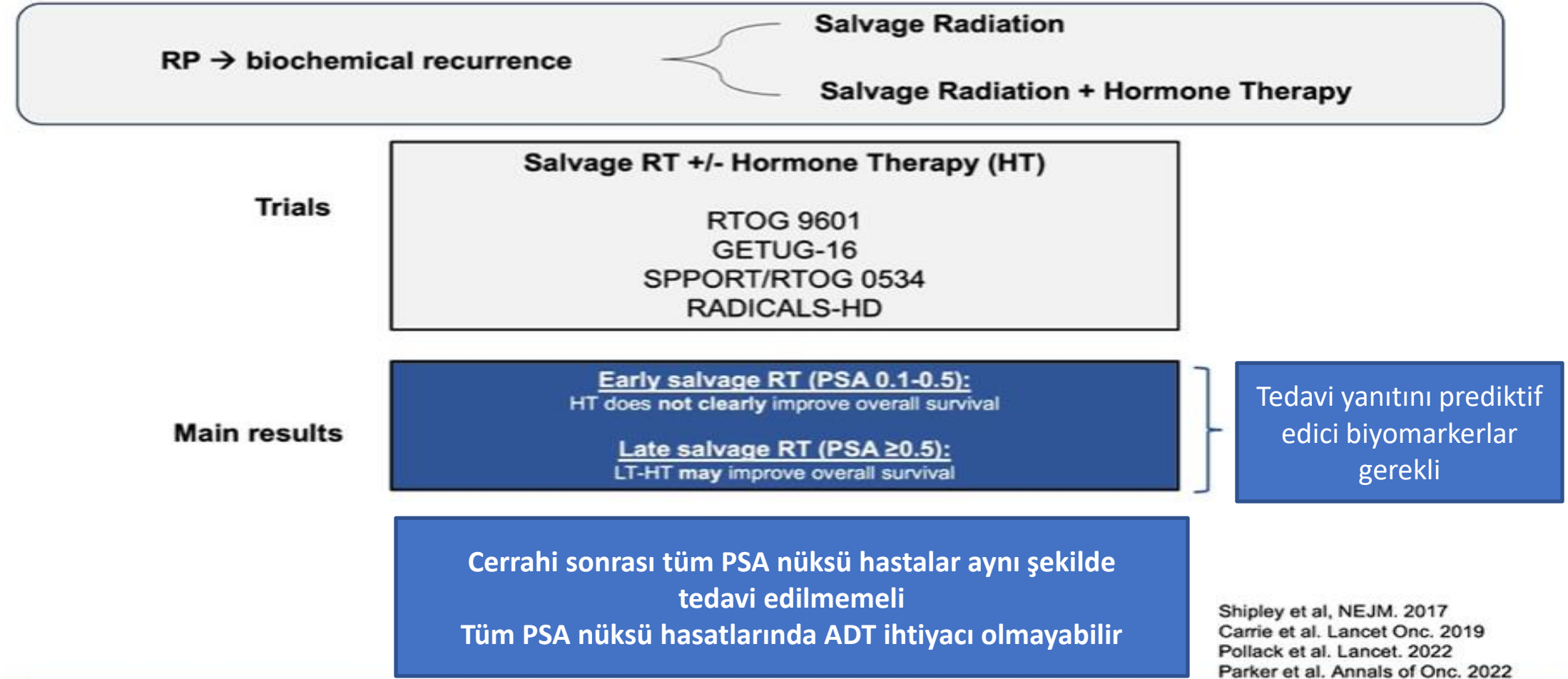
	RT+STHT (n=761)	RT+LTHT (n=762)
Events	174	139
HR (95%CI)	0.77 (0.61 to 0.97)	
P-value	0.03	
10yr event free	72%	78%

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

43% Received *Adjuvant RT*

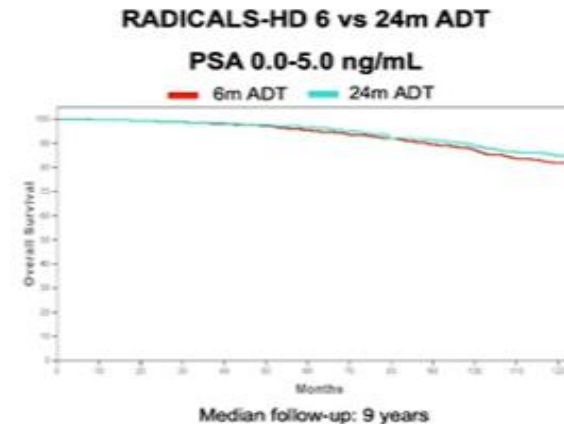
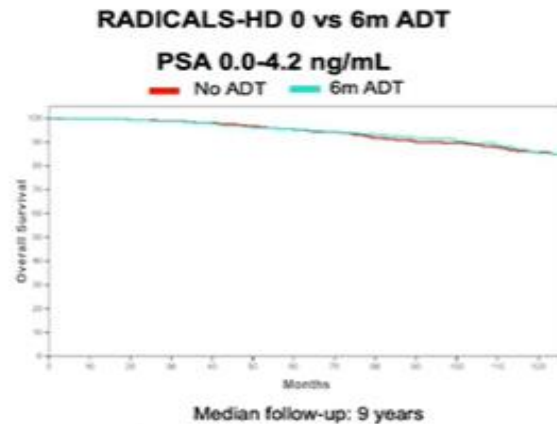
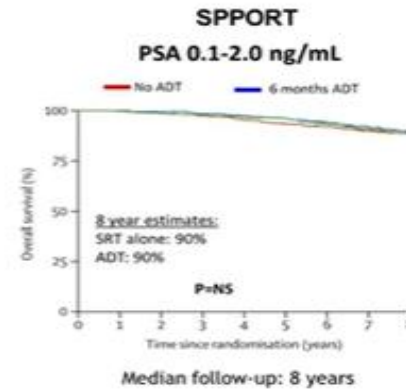
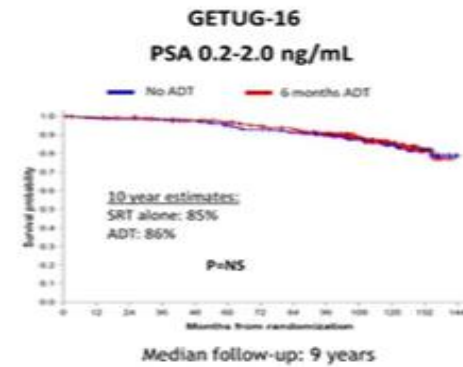
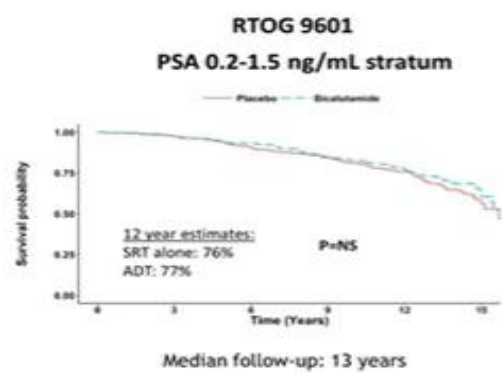
28% Gleason 8-10

Biyokimyasal Rekürens ve PSA Persistansı



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

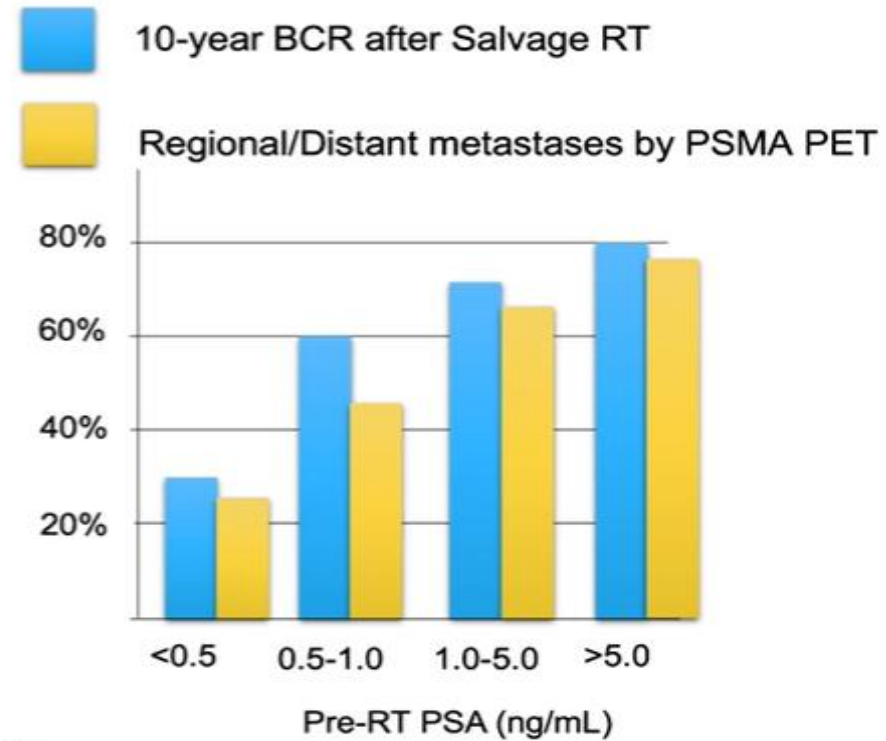
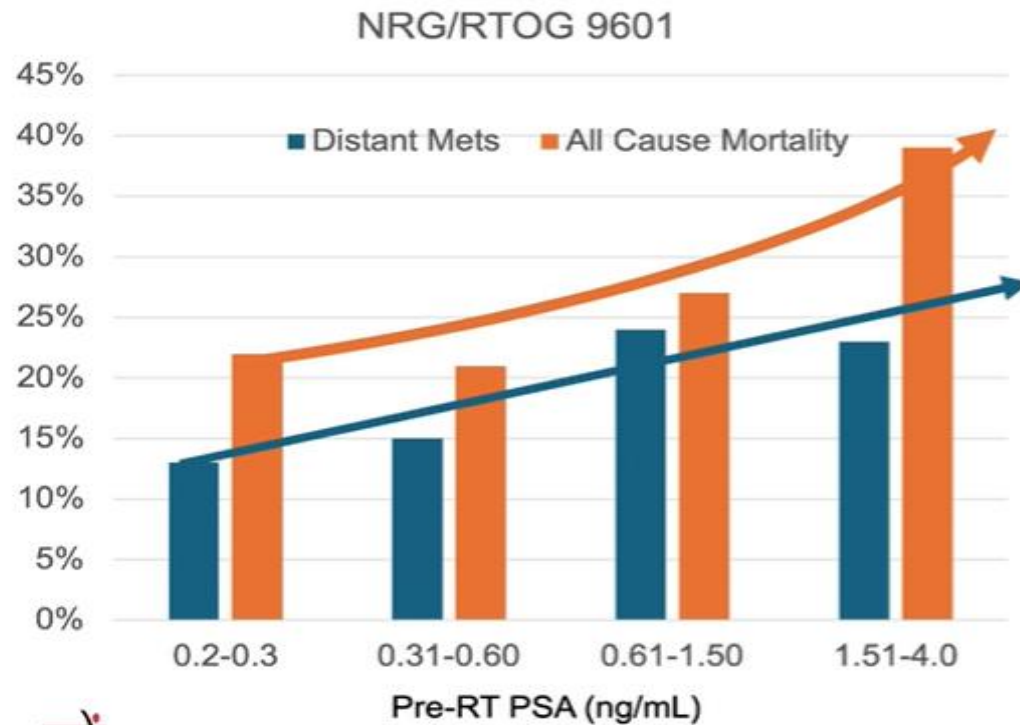
Consistent Results in >5,000 patients: Lack of Overall Survival Benefit



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



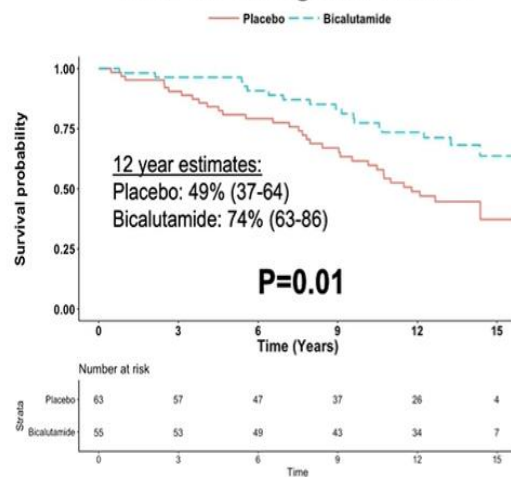
Tedavi öncesi PSA tedavi için güçlü prediktif marker

Personalizing ADT with Salvage RT

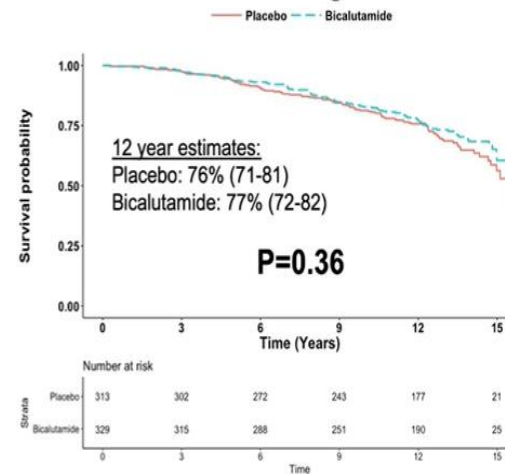
NRG/RTOG 9601

85% of the trial!

PSA 1.6-4.0 ng/mL stratum



PSA 0.2-1.5 ng/mL stratum



Dess et al. JAMA Onc 2020

Differential Benefit by pre-SRT PSA

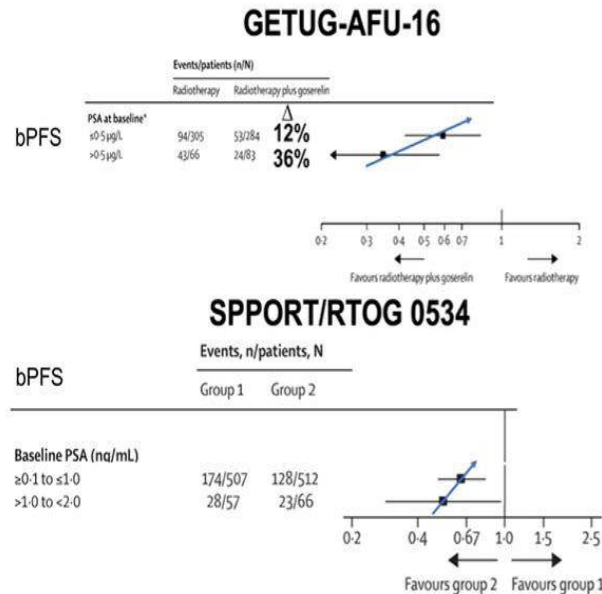
NRG/RTOG 9601

	PSA	Bicalutamide	Placebo	12-yr Absolute Difference	HR (95%)		Interaction p value
	Incidence/N	Incidence/N	Incidence/N	Bicalutamide - Placebo (CI 95%)			
OS	0.20-0.30	20/74	13/74	-0.13 (-0.27, 0.01)	1.78 (0.88, 3.57)		0.02
	0.31-0.60	36/127	35/114	0.02 (-0.09, 0.13)	0.94 (0.59, 1.5)		
	0.61-1.50	34/128	50/125	0.09 (-0.03, 0.20)	0.61 (0.39, 0.94)		
	1.51+	18/55	33/63	0.25 (0.07, 0.42)	0.45 (0.25, 0.81)		
Distant Metastasis	0.20-0.30	9/74	10/74	0.01 (-0.10, 0.13)	0.95 (0.39, 2.34)		0.03
	0.31-0.60	19/127	26/114	-0.08 (-0.17, 0.02)	0.65 (0.36, 1.17)		
	0.61-1.50	28/128	37/125	-0.10 (-0.21, 0.01)	0.69 (0.43, 1.12)		
	1.51+	7/55	20/63	-0.18 (-0.33, -0.03)	0.36 (0.15, 0.84)		

Dess et al. JAMA Onc 2020

Tedavi öncesi PSA metastaz için güçlü prognostik marker

Differential Benefit by pre-SRT PSA



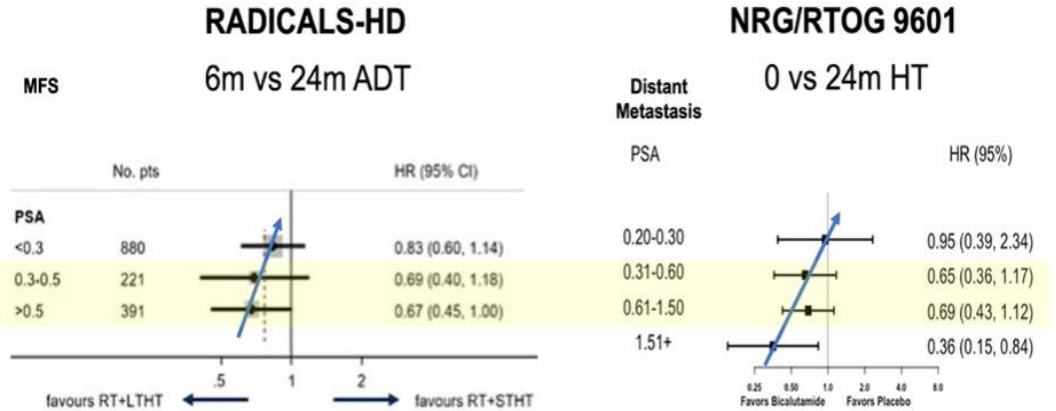
RADICALS-HD 0 vs 6m ADT

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

Differential Benefit by pre-SRT PSA



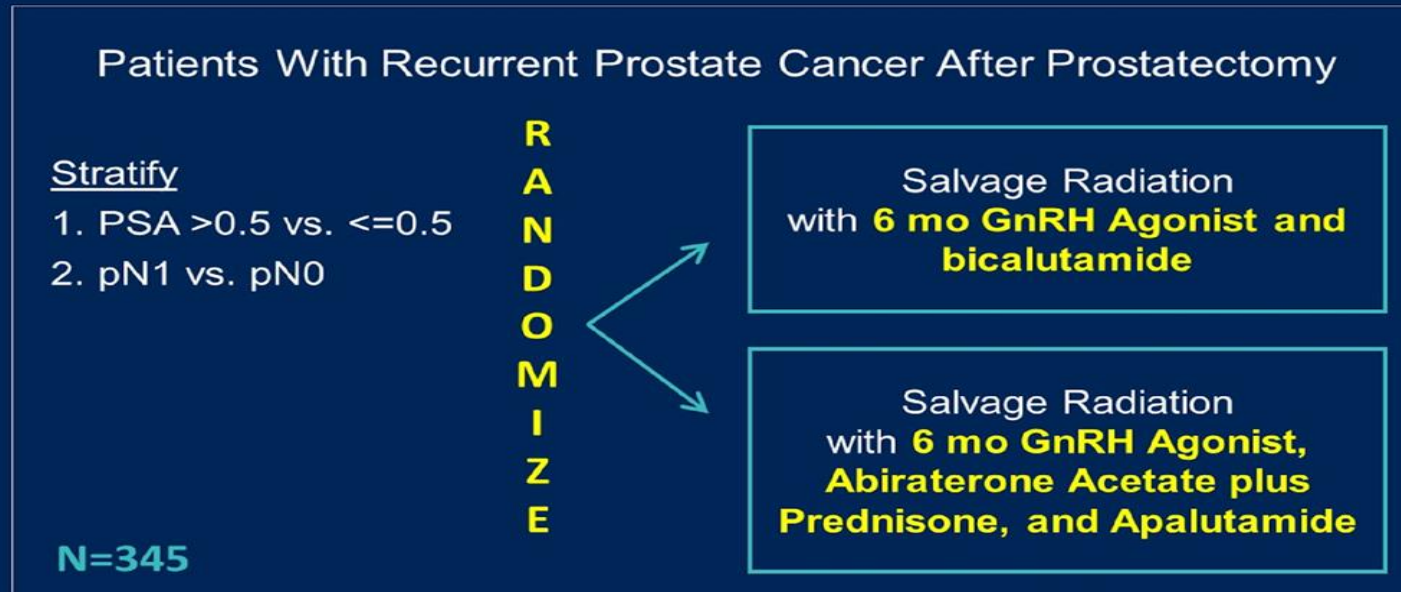
İzole PSA nüksünde hangi hastalara sistemik tedavi

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

FORMULA 509 Schema



Primary outcome: Progression-free survival

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



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Patient Characteristics

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

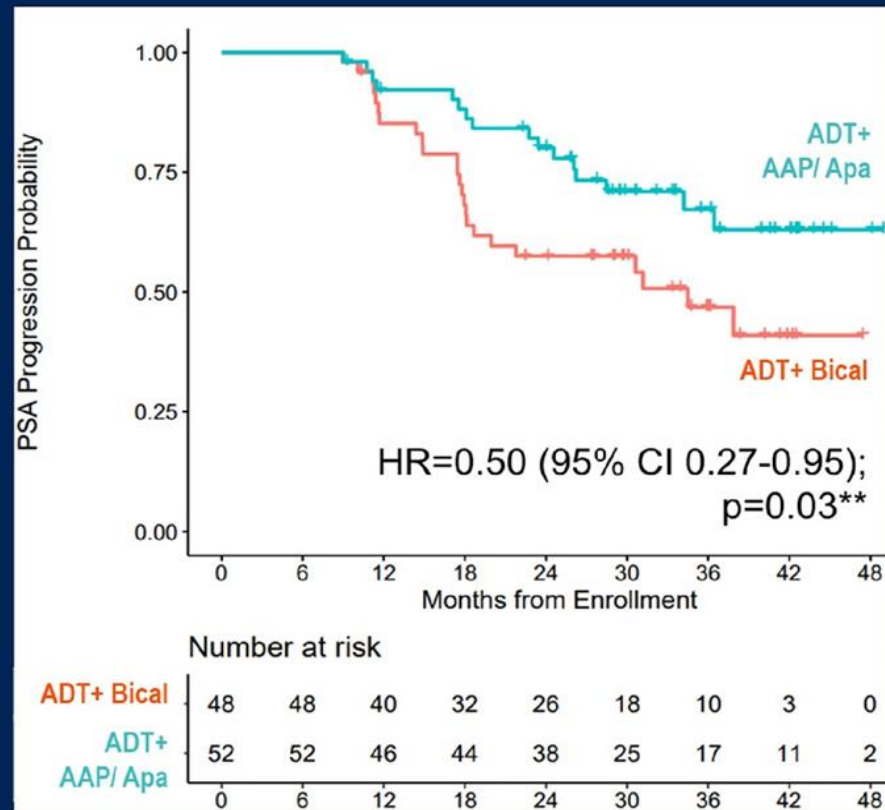
- Median age 65
- 35% Gleason 9
- Median PSA 0.3
- 31% PSA >0.5
- 29% pN1



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PFS Benefit Among PSA >0.5 (n=100)

11



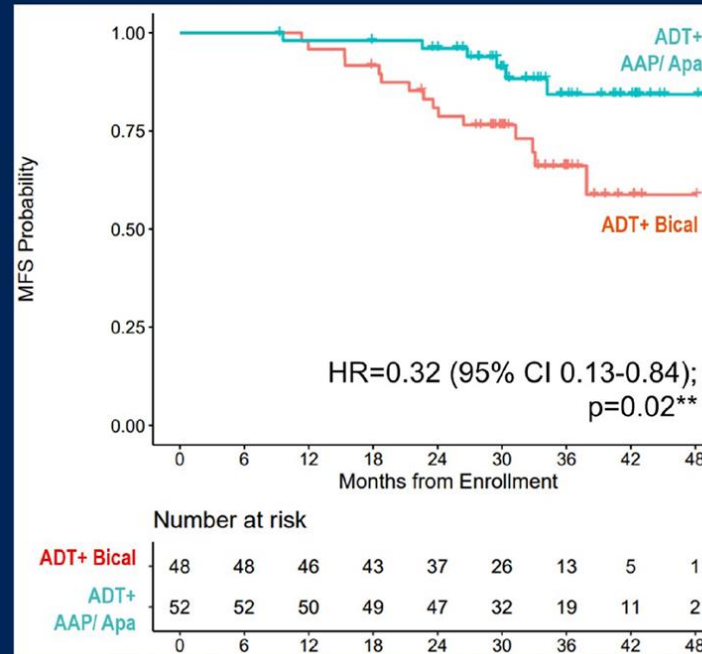
3 year PFS
67.2% vs. 46.8%

**two-sided



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

MFS Benefit Among PSA >0.5 (n=100)



3 year MFS
84.3% vs. 66.1%

Absolute improvement
18.2% at 3 years

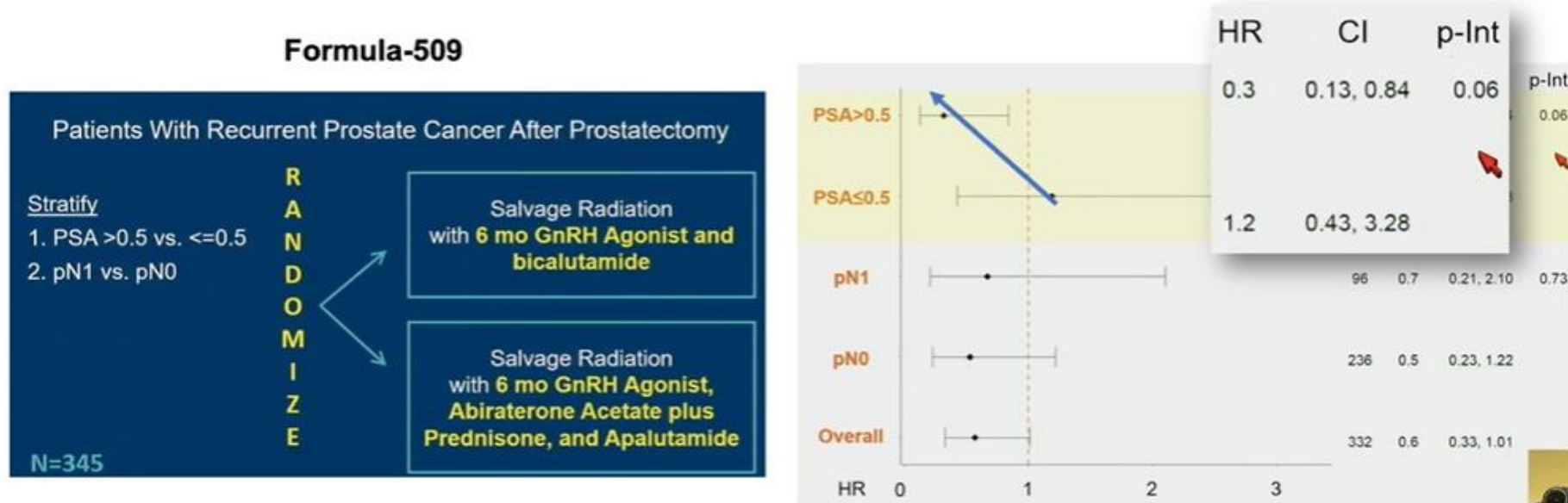
NNT = 5

**two-sided



Tedavi öncesi PSA düzeyi kombine tedaviler için prediktif

Differential Benefit by pre-SRT PSA



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

62

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

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

*one-sided
**two-sided

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

63

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

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

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

RISK CUTPOINTS WILL BE DIFFERENT FOR INTACT VS POST-OP

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

PARIS
2022

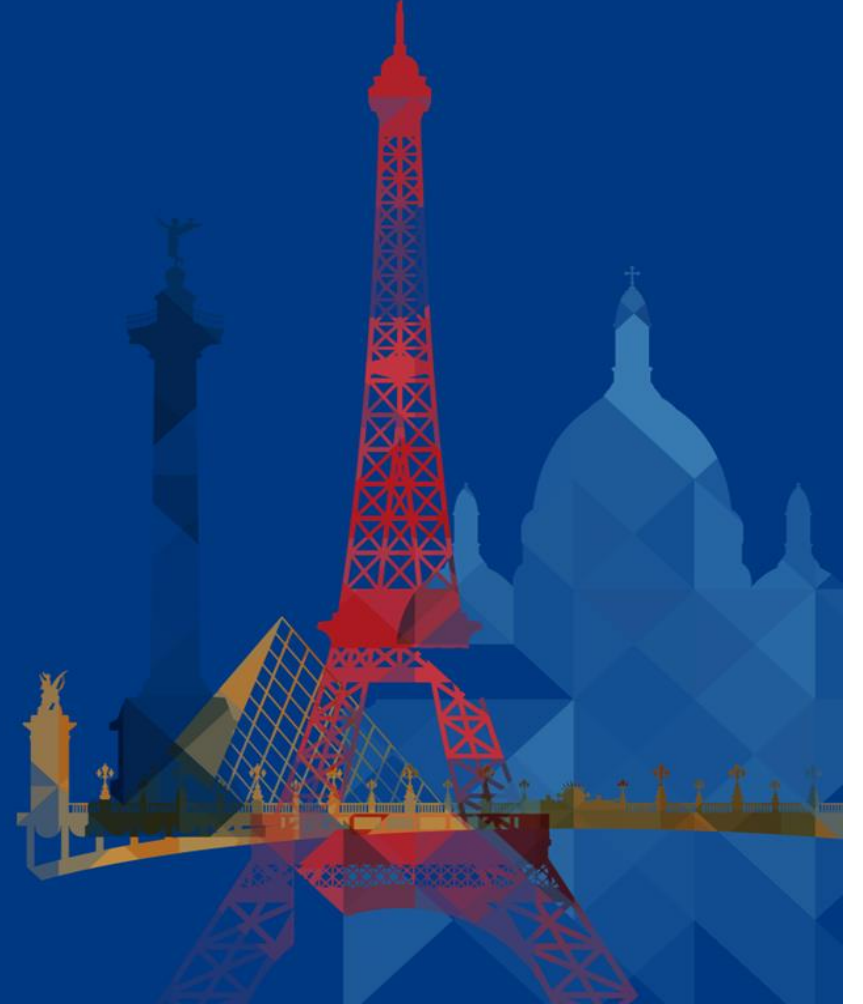
ESMO

Congress

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

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

Paris, France
11 SEP 2022



Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

Study Schema

Prior radical
prostatectomy

Biochemical recurrence
with PSA > 0.5 ng/mL

PSA-DT ≤ 9 months

No metastases on
conventional imaging

Last dose of ADT > 9
months prior to study
entry

Serum T > 150 ng/dL

Randomize 1:1:1

Arm A:
LHRH Analog

Arm B:
LHRH Analog +
Apalutamide

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

Follow up for PSA
Progression

Treatment per Investigator
Discretion

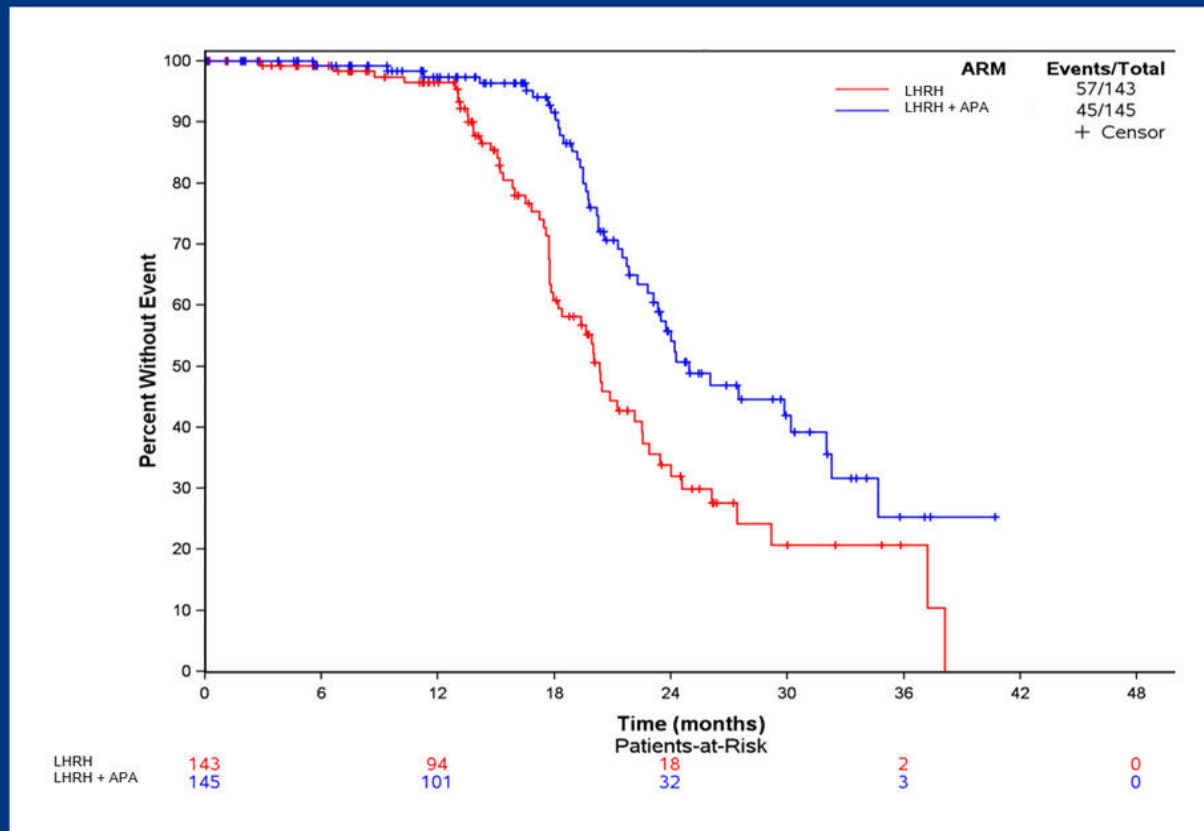
Long Term Follow Up

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

52 Weeks

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

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)

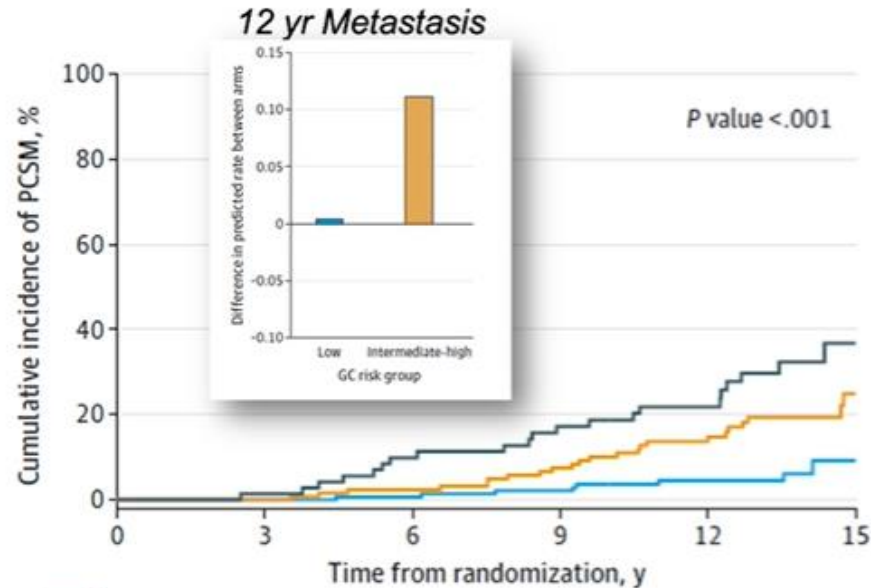
**Hazard ratio 0.52 (95%
CI: 0.35 – 0.77)**

One-sided p-value =
0.00047)

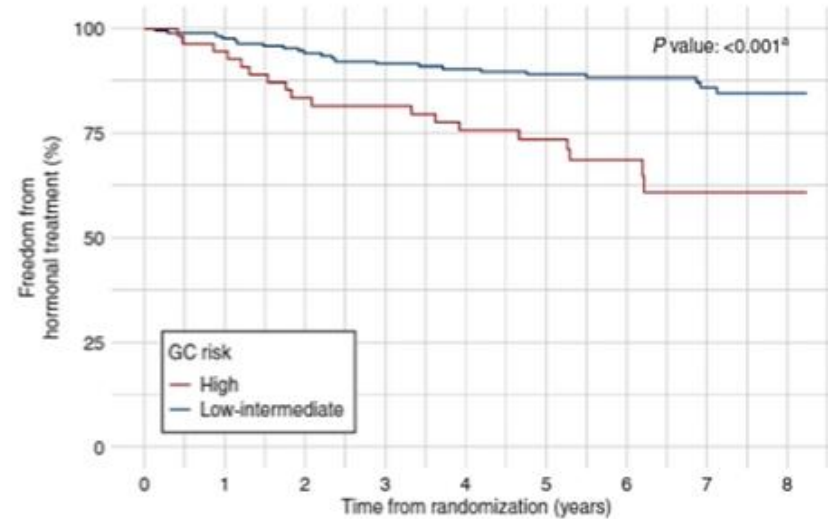
Sistemik tedaviler için yeni prediktif eden markerlar

22-Gene Genomic Classifier Post-RP

NRG/RTOG 9601



SAKK 09/10



Sistemik tedaviler için yeni prediktif markerlar



ROGEL CANCER CENTER
MICHIGAN MEDICINE

NRG
ONCOLOGY
Advancing Research. Improving Lives.™

University Hospitals
Seidman Cancer Center
Cleveland | Ohio

AI prognostic biomarker for recurrent prostate cancer after prostatectomy: development and validation using deep learning on digital histopathology from NRG/RTOG-0534 and NRG/RTOG-9601

Todd M. Morgan, Yi Ren, Siyi Tang, Wouter Zwerink, Emmalyn Chen, Akinori Mitani, Huei-Chung Huang, Jeffry P. Simko, Sandy DeVries, William U. Shipley, Alan Pollack, David Bowes, André-Guy Martin, Alexander G. Balogh, Jeff M. Michalski, Michael J. Greenberg, Jason A. Efstathiou, Jean-Paul Bahary, Ashley E. Ross, Andre Esteva, Timothy N. Showalter, Paul L. Nguyen, Karen E. Hoffman, Joseph P. Rodgers, Felix Y. Feng, Daniel E. Spratt

AUA 2024
MAY 3-6
San Antonio

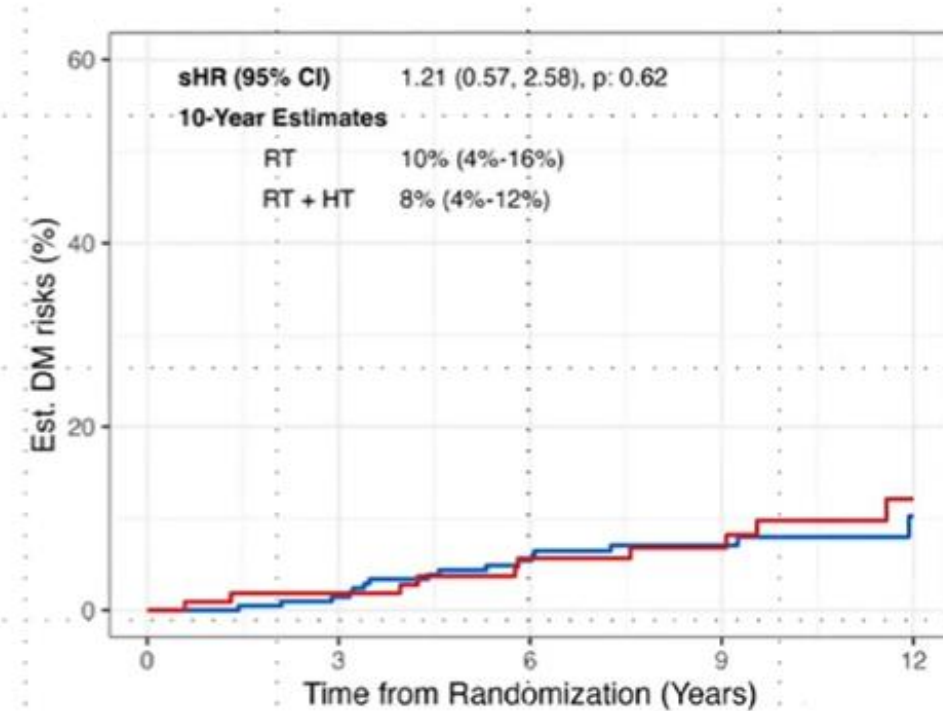
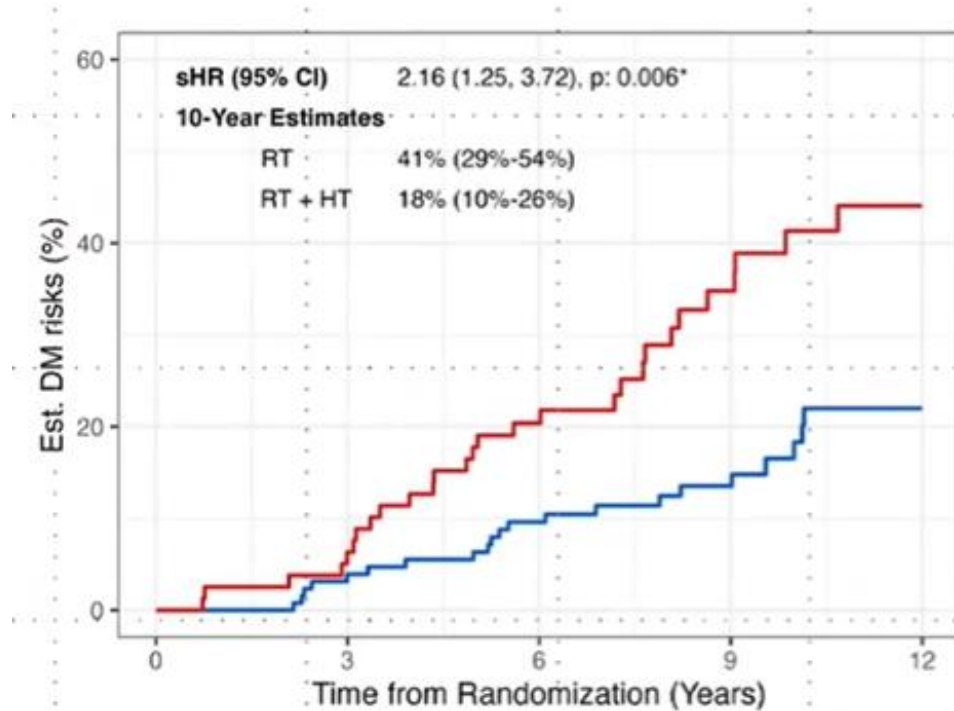
 @wandering_gu
@DrSpratticus
@NRGonc

NCI National Clinical Trials Network
A National Cancer Institute program

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

Sistemik tedaviler için yeni prediktif markerlar

New Artera Multi-modal AI model:



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

^aStudy treatment was suspended once at week 37 if PSA was < 0.2 ng/mL and restarted when PSA was ≥ 5.0 ng/mL (without prior RP) and ≥ 2 ng/mL (prior RP). ^bIntent-to-treat population. ^cPrimary endpoint and key secondary endpoints for enzalutamide combination and enzalutamide monotherapy are alpha-protected. ^dP-value to determine significance for OS of combination and monotherapy treatment comparisons was dependent on outcomes of primary endpoint and key secondary endpoints. ^eSafety population. BICR, blinded independent central review; CT, computed tomography; d, day; EBRT, external beam radiotherapy; IM, intramuscular; MFS, metastasis-free survival; mo, month; MRI, magnetic resonance imaging; OS, overall survival; PSA, prostate-specific antigen; PSADT, PSA doubling time; q, every; R, randomization; RP, radical prostatectomy; w, weeks.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023

CHICAGO ★ APR 28-MAY 1

Demographics



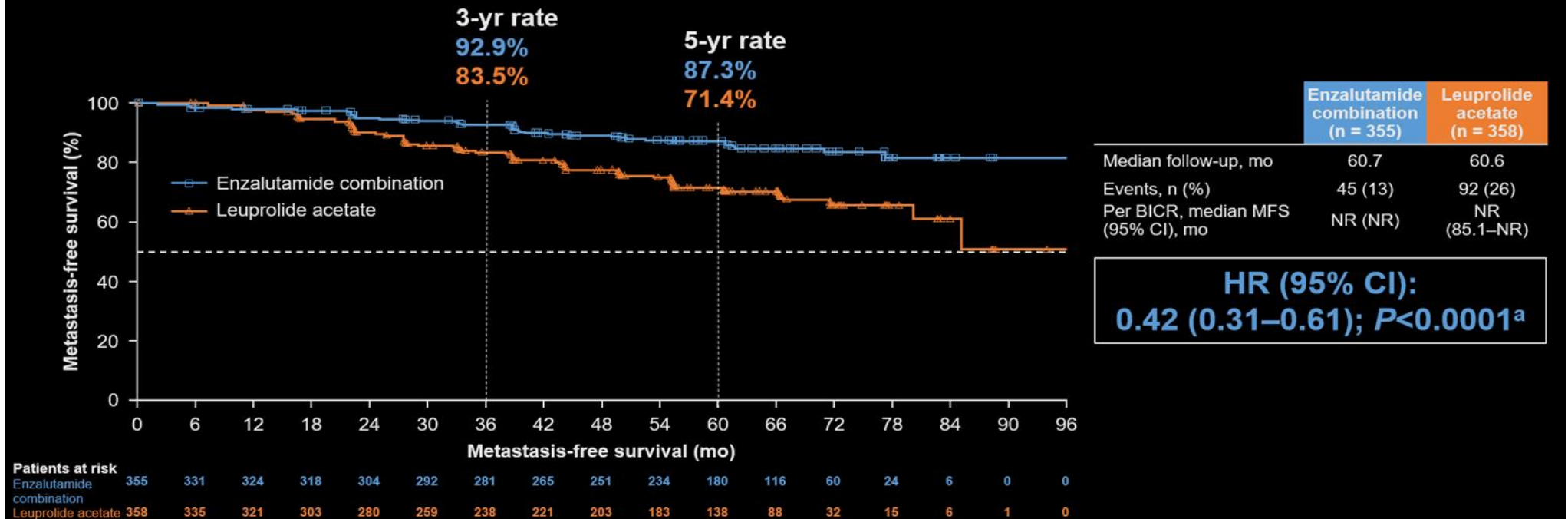
Characteristic	Enzalutamide combination (n = 355)	Leuprolide acetate (n = 358)	Enzalutamide monotherapy (n = 355)
Age, median (range), yr	69 (51–87)	70 (50–92)	69 (49–93)
Race, n (%) ^a			
White	293 (82.5)	301 (84.1)	295 (83.1)
Asian	26 (7.3)	26 (7.3)	26 (7.3)
Black	16 (4.5)	16 (4.5)	15 (4.2)
Other ^b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

^aNot reported included: enzalutamide combination, n = 10 (2.8%); leuprolide acetate, n = 5 (1.4%); enzalutamide monotherapy, n = 14 (3.9%). ^bIncludes patients who identified as multiple races (enzalutamide combination, n = 5; leuprolide acetate, n = 9; enzalutamide monotherapy, n = 5). American Indian or Alaskan Native (enzalutamide combination, n = 4; leuprolide acetate, n = 1; enzalutamide monotherapy, n = 0), Native Hawaiian or other Pacific Islander (enzalutamide combination, n = 1; leuprolide acetate and enzalutamide monotherapy, n = 0). ^cMissing included n = 1 (0.3%) for each treatment group. ^dMissing included: leuprolide acetate, n = 2; enzalutamide monotherapy, n = 1. RT, radiation therapy, yr, year.

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023
CHICAGO ★ APR 28-MAY 1

Primary endpoint — MFS for enzalutamide combination vs. leuprolide acetate



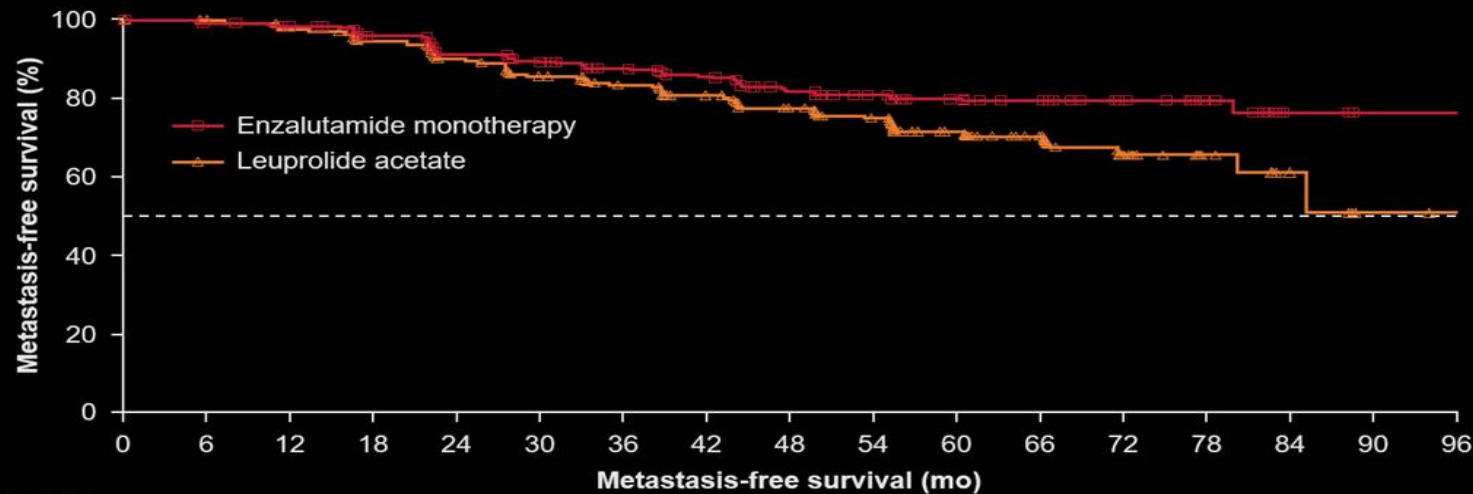
A consistent treatment effect was seen for investigator-assessed MFS: HR (95% CI): 0.47 (0.37–0.67); $P < 0.0001$

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

Biyokimyasal Rekürens ve PSA Persistansı Doz Yoğun Tedavi

AUA 2023
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**Key secondary endpoint — MFS for
enzalutamide monotherapy vs.
leuprolide acetate**



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

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

Patients at risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Enzalutamide monotherapy	355	342	328	309	287	273	260	247	228	209	171	108	52	26	5	0	0	0
Leuprolide acetate	358	335	321	303	280	259	238	221	203	183	138	88	32	15	6	1	0	0

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

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

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

Özet

- ❑ Neoadjuvan tedavi özel durumlar dışında rutin olarak önerilmez
- ❑ Yeni nesil AR-yolak inhibitörleriyle bir grup hastada iyi sonuçlar elde edilmiştir
- ❑ Özellikle 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 $12\text{ay} \leq$ olanlarda tedavi düşünülmelidir
- ☐ Salvage RT ve ADT (6ay)düşünülmelidir
- ☐ Uzun dönem 24 ay adjuvan ADT($pT3 \geq$ ve gleason skoru ≥ 8) ve pelvik lenf nodu pozitif
- ☐ Pelvik RT nüks riski yüksek hastalarda düşünülebilir(Gleason ≥ 8 , $\geq pT3$, 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