Lokal İleri Prostat Kanserinde Neoadjuvan Tedavi

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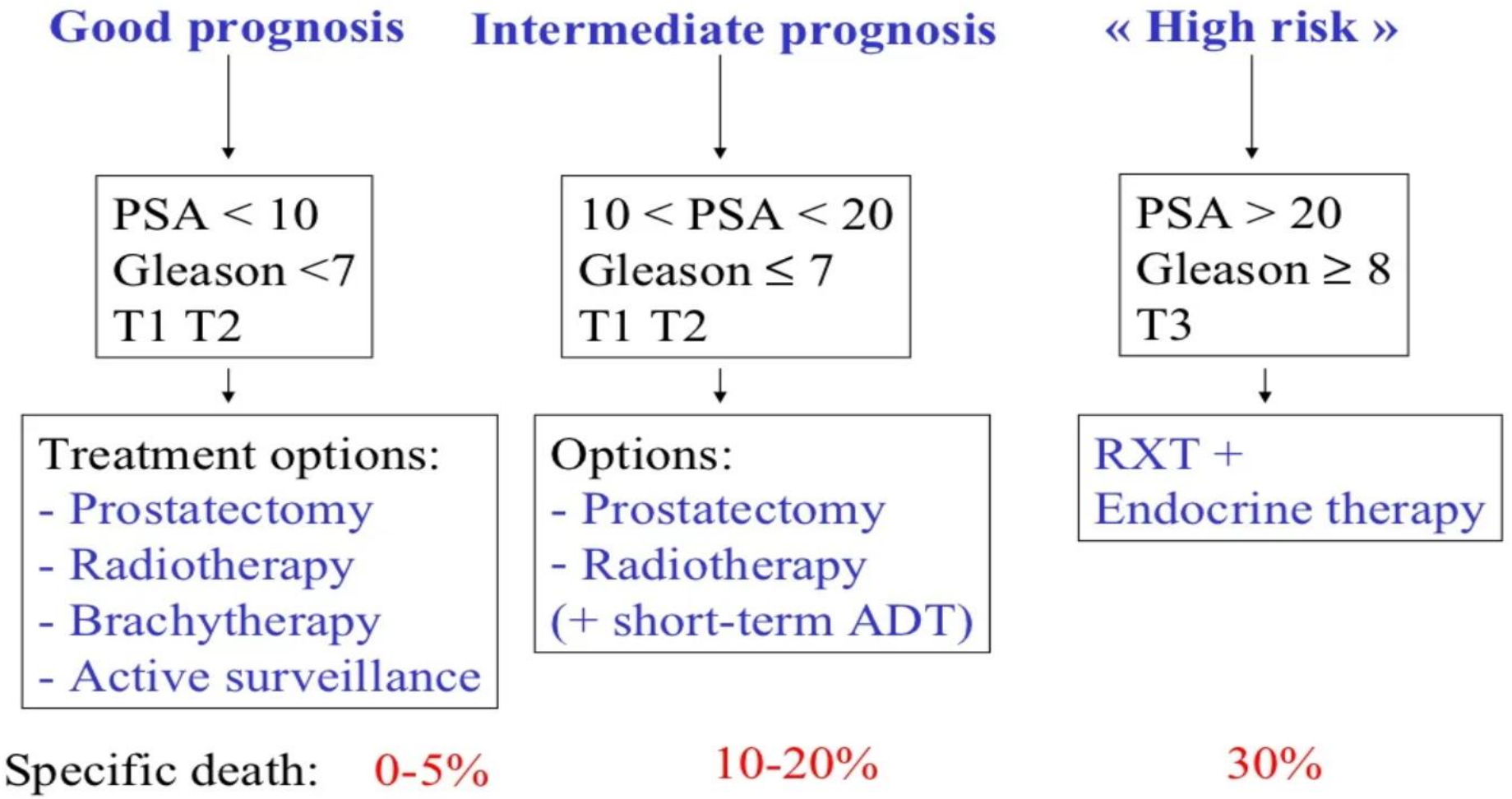
Tıbbi Onkoloji

Ders Planı

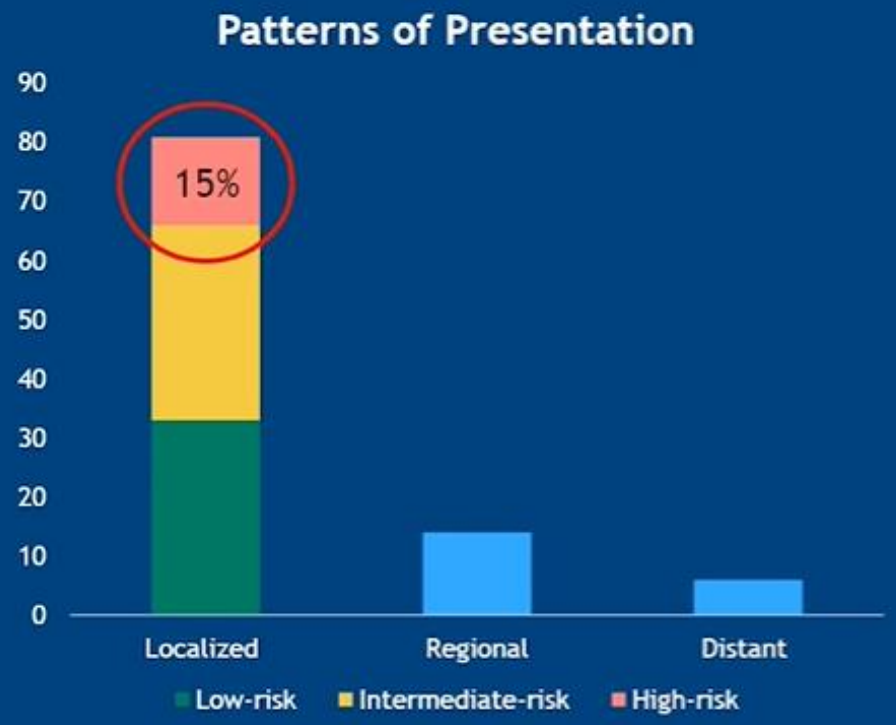
- ❑ Lokal ileri prostat kanserinde nüks riski
- ❑ Lokal ileri prostat kanserinde standart tedavi
- ❑ Neden neoadjuvan tedavi
- ❑ Neoadjuvan çalışma sonuçları
- ❑ Gelecek perspektif
- ❑ Sonuç

Lokalize Prostat Kanserin Sınıflandırılması



Lokalize Yüksek Riskli Prostat Kanseri

Localized High-Risk Prostate Cancer



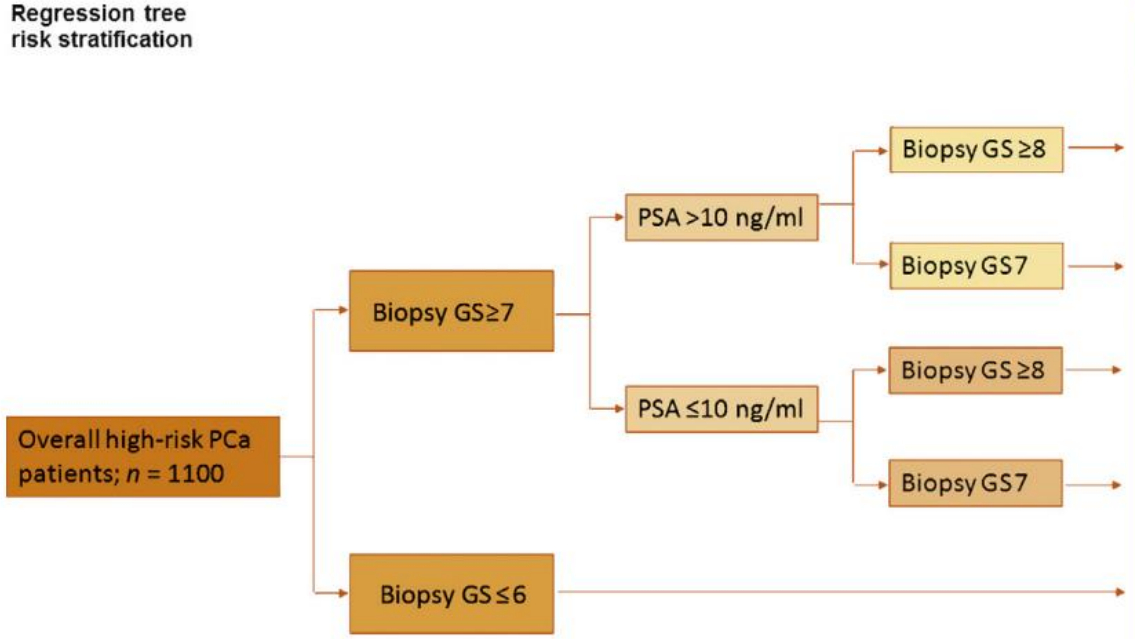
Increased Mortality in High-Risk Prostate Cancer

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

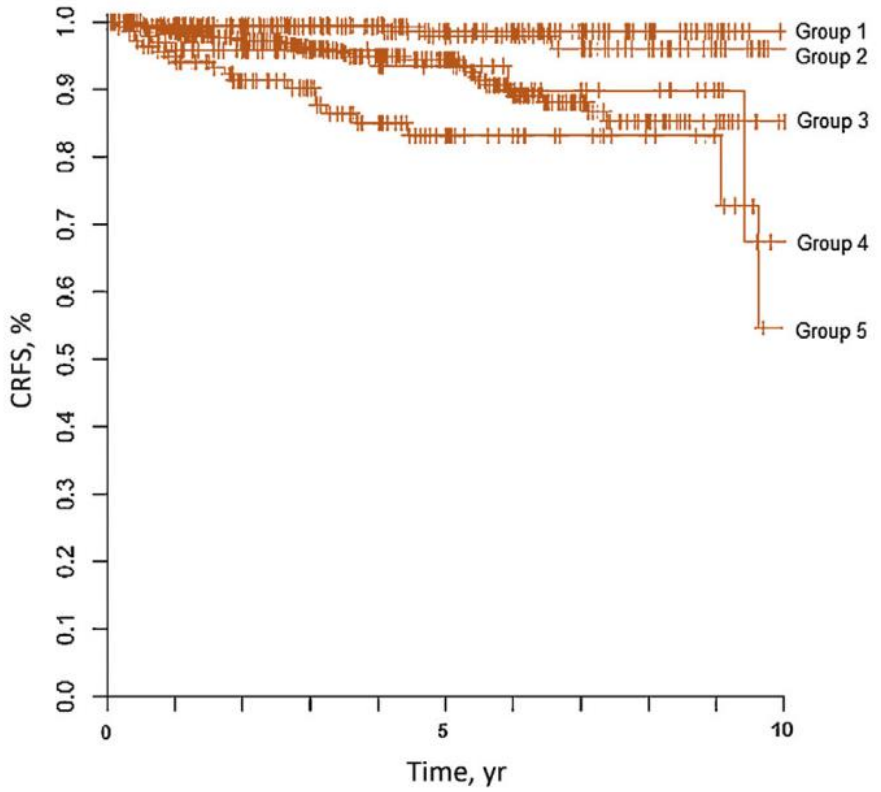


	10-yr BCR-free survival (95% CI)
Risk Group 5 (PSA >10 ng/ml, and GS ≥8)	26.2 (17.8–38.4)
Risk Group 4 (PSA >10 ng/ml, and GS 7)	30.6 (19.1–44.7)
Risk Group 3 (PSA ≤10 ng/ml, and GS ≥8)	36.2 (25.3–51.6)
Risk Group 2 (PSA ≤10 ng/ml, and GS 7)	69.8 (58.5–83.1)
Risk Group 1 (GS ≤6)	85.5 (79.0–92.6)

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.

Lokalize Yüksek Riskli Prostat Kanseri

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



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

$p < 0.001$
Harrell's C = 0.69

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

Lokalize Yüksek Riskli Prostat Kanseri

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Prostate Cancer

NCCN Guidelines Index
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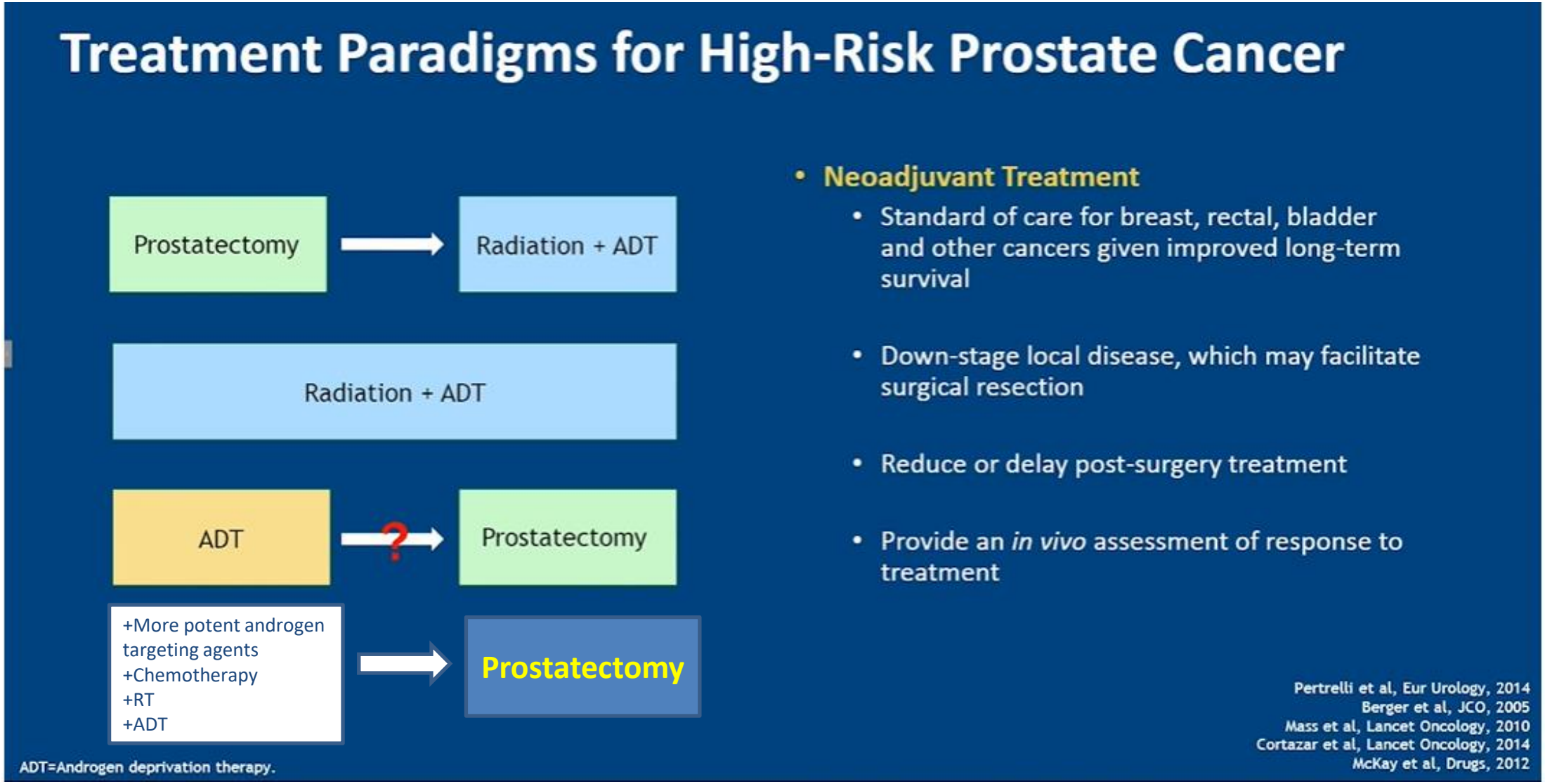
Discussion

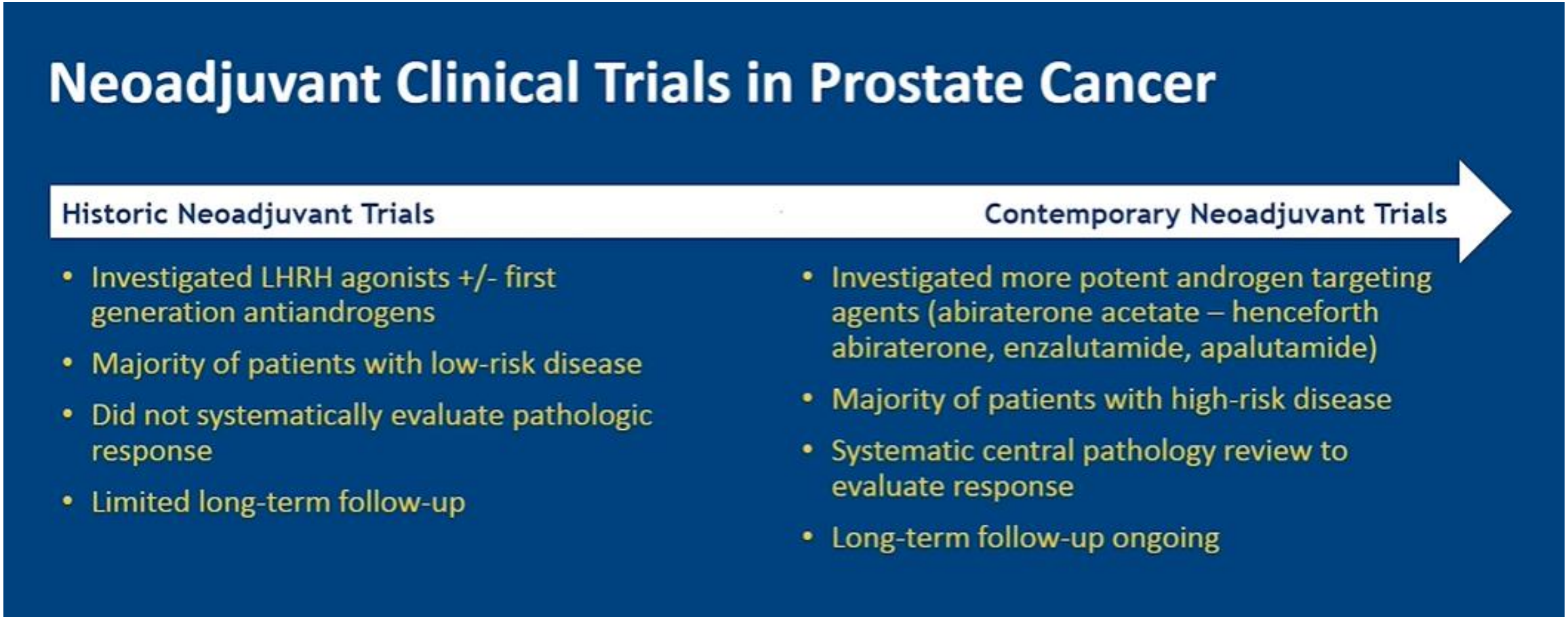
INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[d]

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation[g,h]	Initial Therapy
Very low[e]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g			• Consider confirmatory mpMRI ± prostate biopsy if MRI not performed initially. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.	See PROS-3
Low[e]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Consider confirmatory mpMRI ± prostate biopsy and/or molecular tumor analysis if MRI not performed inititally to establish candidacy for active surveillance. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.	See PROS-4
Intermediate[e]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[f]	• Consider confirmatory mpMRI ± prostate biopsy and/or molecular tumor analysis if MRI not performed initially for those considering active surveillance. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]	Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

Neoadjuan Tedavi Gerekçesi



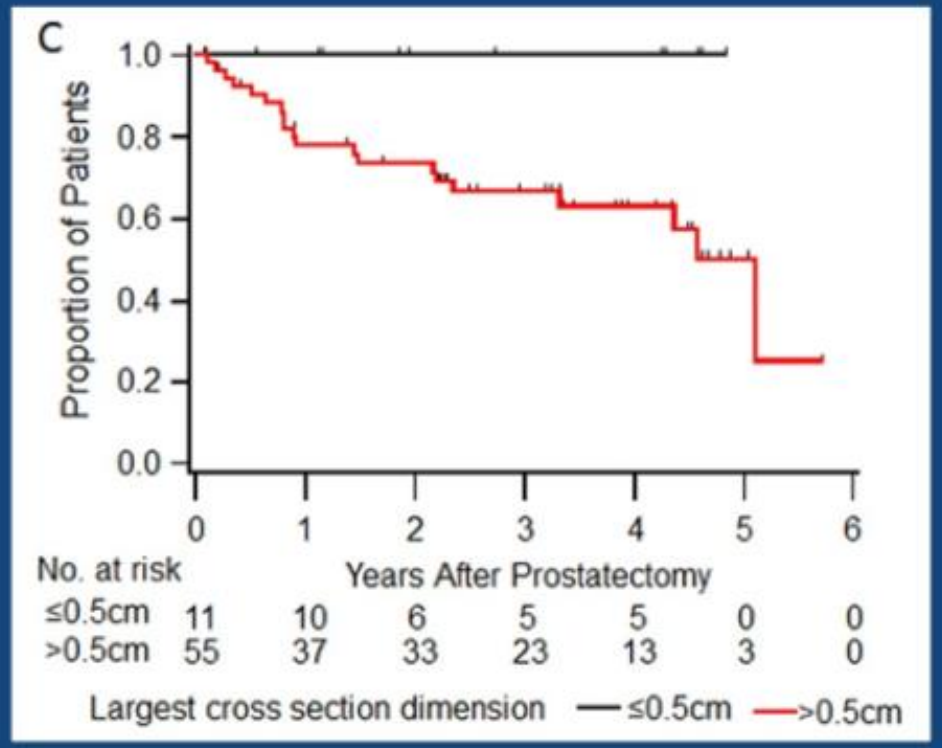
Neoadjuan Tedavi Gerekçesi



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

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 Kemoterapi+ADT

Characteristic	Neoadjuvant Patients (n = 391)	Surgery Alone Patients (n = 397)
Age, years		
Median	62	63
Range	40–78	33–84
Race[a]		
White	330 (84)	337 (85)
Black	40 (10)	38 (10)
Other	15 (4)	9 (2)
Unknown	6 (2)	13 (3)
Clinical stage by digital rectal examination		
T1	102 (26)	129 (33)
T2	219 (56)	204 (51)
T3a	70 (18)	64 (16)
Biopsy Gleason score		
6 (3 + 3)	2 (1)	2 (1)
7 (3 + 4)	15 (4)	28 (7)
7 (4 + 3)	25 (6)	31 (8)
8	153 (39)	147 (37)
9-10	196 (50)	189 (48)
Prostate-specific antigen level before biopsy, ng/mL		
Median	9.5	10.2
Range	0.3–125.5	0.1–93.0
Risk group[b]		
1	52 (13)	50 (13)
2	67 (17)	68 (17)
3	94 (24)	96 (24)
4	178 (46)	183 (46)
Prior androgen-deprivation therapy		
No	339 (87)	344 (87)
Yes	52 (13)	53 (13)

NOTE. Data presented as No. (%) unless otherwise indicated.

[a]Race was self-reported.

[b]Men were stratified into risk groups based on their nomogram-predicted biochemical progression–free survival at 5 years (group 1, 0%-20.9%; group 2, 21%-39.9%; group 3, 40%-59.9%; and group 4, Gleason score 8-10 with nomogram-predicted biochemical

Neoadjuvan Kemoterapi+ADT

TABLE 2. Pathologic Outcomes in Men Treated With Neoadjuvant Chemohormonal Therapy Plus Radical Prostatectomy (designated neoadjuvant) or Radical Prostatectomy Alone (designated surgery alone)

	No. of Patients (%)		
Outcome	**Neoadjuvant**	**Surgery Alone**	**Adjusted *P***
Gleason score in surgical specimen	243	350	.10
6 (3 + 3)	5 (2)	4 (1)	
7 (3 + 4)	36 (15)	55 (16)	
7 (4 + 3)	47 (19)	98 (28)	
8	41 (17)	45 (13)	
9-10	114 (47)	148 (42)	
Pathologic T stage	358	366	< .001
T1/2	145 (41)	83 (23)	
T3	211 (59)	274 (75)	
T4	2 (1)	9 (2)	
Seminal vesicle invasion	365	366	.05
Yes	116 (32)	151 (41)	
No	249 (68)	215 (59)	
Pathologic nodal stage	352	356	.05
N0	280 (80)	250 (70)	
N1	68 (19)	97 (27)	
NX	4 (1)	9 (3)	
Surgical margins	303	281	< .001
Positive	56 (18)	126 (45)	
Negative	247 (82)	155 (55)	

NOTE. Summary statistics are calculated for the number of patients with available data for each characteristic.

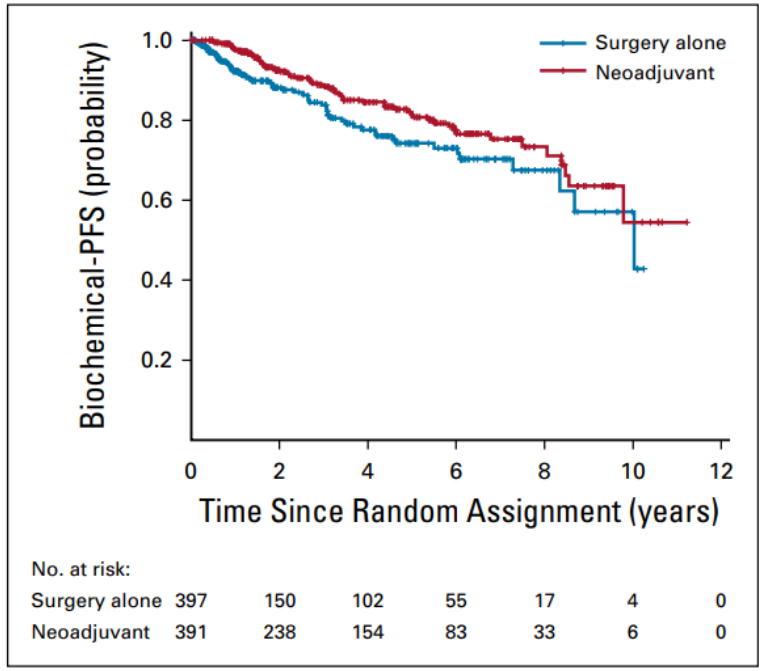


FIG 2. Biochemical progression–free survival (BFS) was compared between men treated with neoadjuvant chemohormonal therapy and radical prostatectomy (designated neoadjuvant) versus radical prostatectomy alone (designated surgery alone). Biochemical failure was defined as a serum prostate-specific antigen (PSA) level > 0.2 ng/mL that increased on 2 consecutive occasions that were at least 3 months apart. The time of biochemical failure is measured from the date of randomization to the date of the first PSA level > 0.2 ng/mL.

Neoadjuvan Kemoterapi+ADT

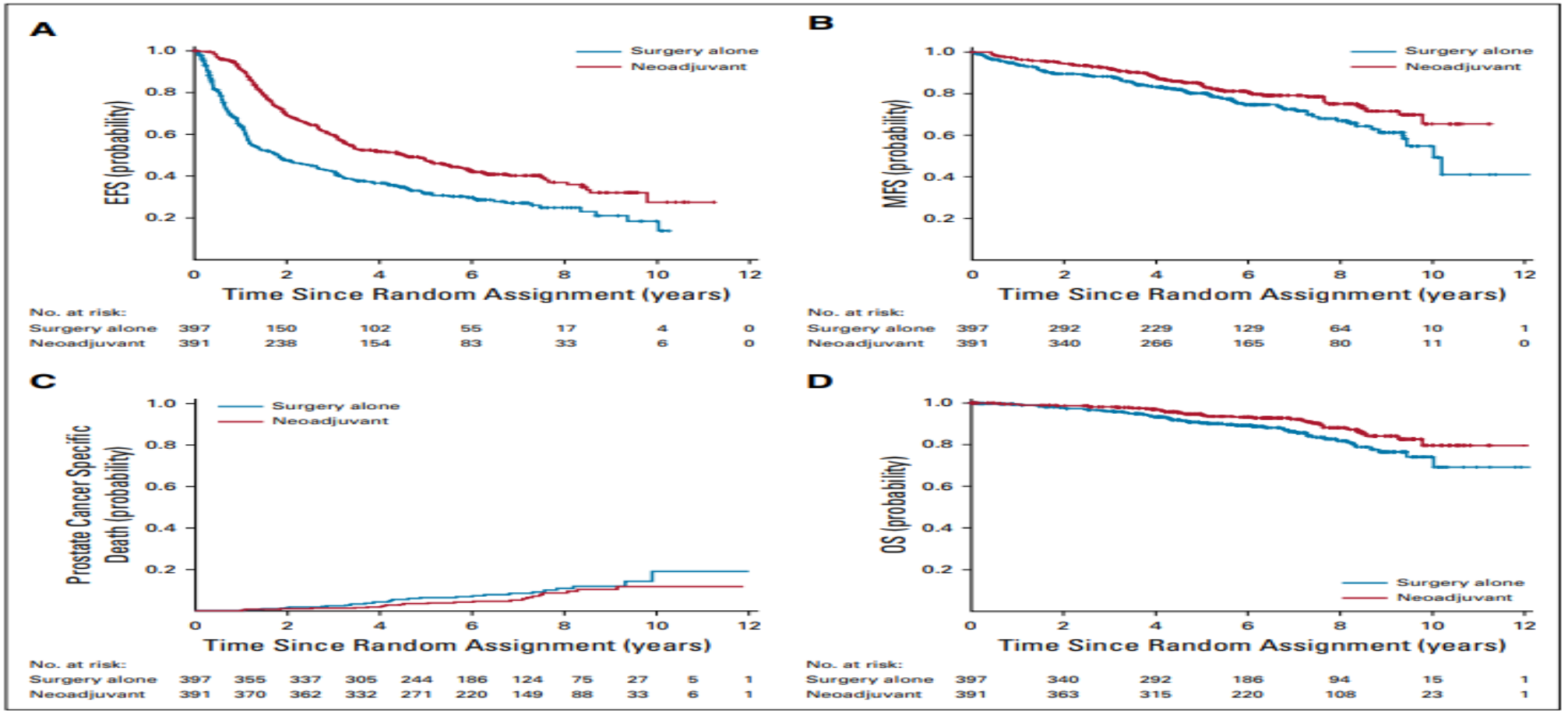


FIG 3. (A) Event-free survival (EFS) or the likelihood of not requiring additional treatment after radical prostatectomy in men treated with neoadjuvant chemohormonal therapy plus radical prostatectomy (designated neoadjuvant) versus radical prostatectomy alone (designated surgery alone). An event is 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.

Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Pathologic Responses from Potent Neoadjuvant Therapy

Conducted a series of neoadjuvant trials over the last 10 years

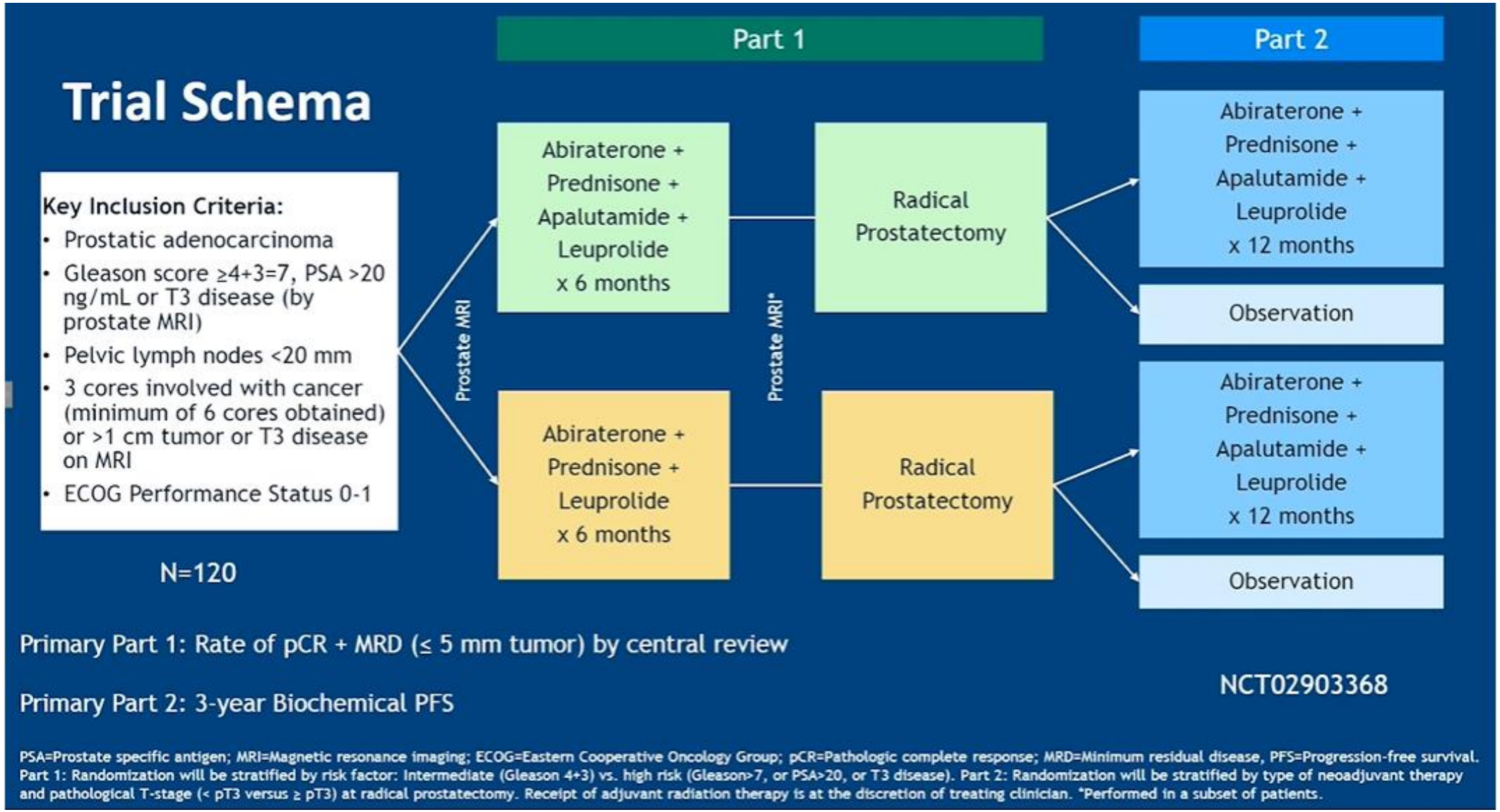
Phase 2 biomarker integrated trials evaluating potent neoadjuvant hormone therapy

	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



Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Pathologic Outcomes

		APL (n=59)	APAL (n=55)
Pathologic Response	pCR	6 (10%)	7 (13%)
	MRD (≤5 mm)*	6 (10%)	5 (9%)
	pCR or MRD	12 (20%)	12 (22%)
ypT stage, n (%)	T0	6 (10%)	7 (13%)
	T2	19 (32%)	21 (38%)
	T3	34 (58%)	27 (49%)
pN1, n (%)		10 (17%)	4 (7%)
Positive surgical margins, n (%)		7 (12%)	4 (7%)
Seminal vesicle invasion, n (%)		16 (27%)	15 (27%)
Percent cellularity, % (range)**		5% (0-50%)	5% (0-80%)
RCB (cm^3)		0.07 (0-6.8)	0.02 (0-7.8)

APAL=Abiraterone, prednisone, apalutamide, leuprolide; APL=Abiraterone, prednisone, leuprolide; pCR=Pathologic complete response; MRD=Minimum residual disease; RCB=Residual cancer burden. *Minimum residual disease was defined as residual tumor in the radical prostatectomy specimen measuring ≤5 mm. **Residual cancer burden calculated as tumor volume (cm3) x percent cellularity.

Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

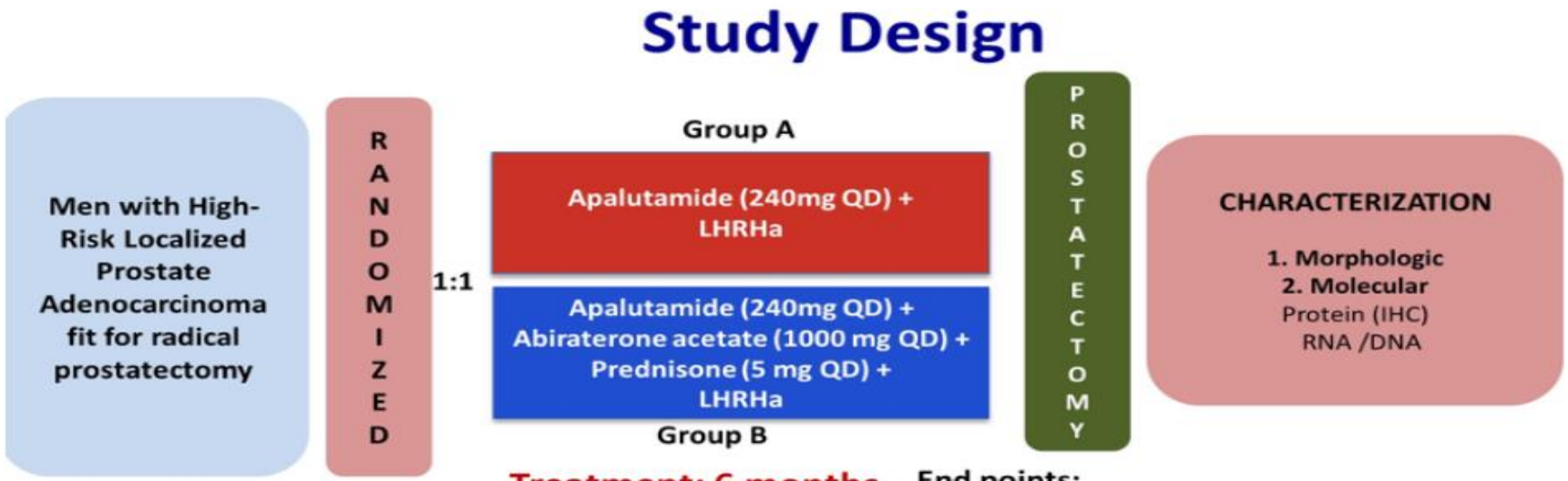
Treatment-Related Adverse Events (≥10% patients)

	APL				APAL				Total
Toxicity	Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total	Total
Hot Flashes	48	1		49 (83%)	47	4		51 (86%)	100 (85%)
Fatigue	28	1		29 (49%)	27	3		30 (51%)	59 (50%)
ALT Increase	15	5	2	22 (37%)	13		1	14 (24%)	36 (31%)
AST Increase	17	1	2	20 (34%)	12		1	13 (22%)	33 (28%)
Hypertension	1	7	1	9 (15%)	4	6	5	15 (25%)	24 (20%)
ED	5	3		8 (14%)	5	4		9 (15%)	17 (14%)
Insomina	4			4 (7%)	5	2	1	8 (14%)	12 (10%)

13 patients (11%) experienced grade 3 TRAE (APAL n=8; APL n=5). There were no grade 4-5 TRAEs.
24 patients (APAL n=14; APL n=10) had abiraterone and 17 patients had apalutamide dose modifications.

APAL=Abiraterone, prednisone, apalutamide, leuprolide; APL=Abiraterone, prednisone, leuprolide; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; ED=Erectile dysfunction; TRAE=Treatment-related adverse events.

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri



End points:

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

Eligibility:

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

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*

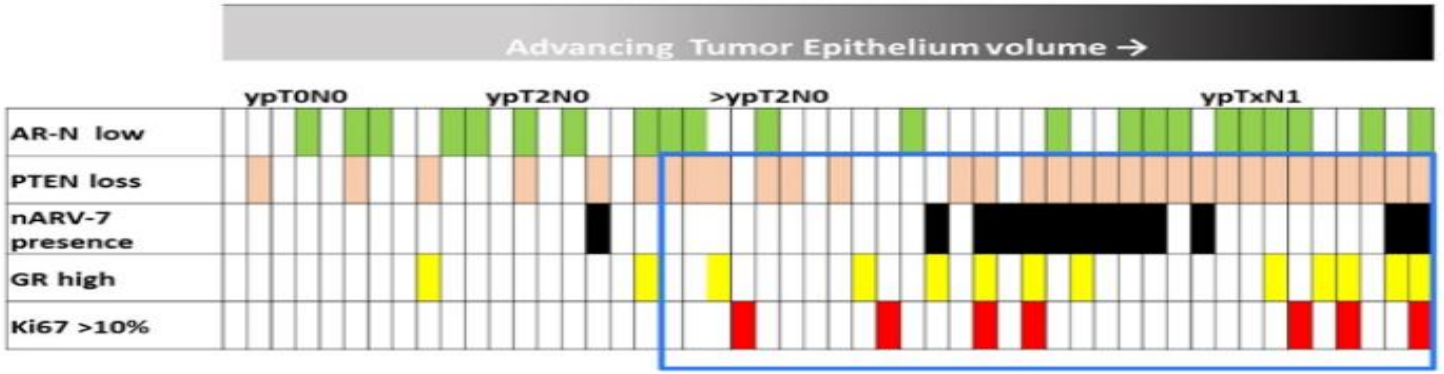
Tumor volume and tumor cellularity varied significantly. The finding of ≤ypT2N0 did not correlate with Gleason score, but did correlate with a pre-specified molecular signature, PTEN expression, and absence of cribriform/intraductal spread.

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri

Tumor volume and tumor cellularity varied significantly. The finding of ≤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

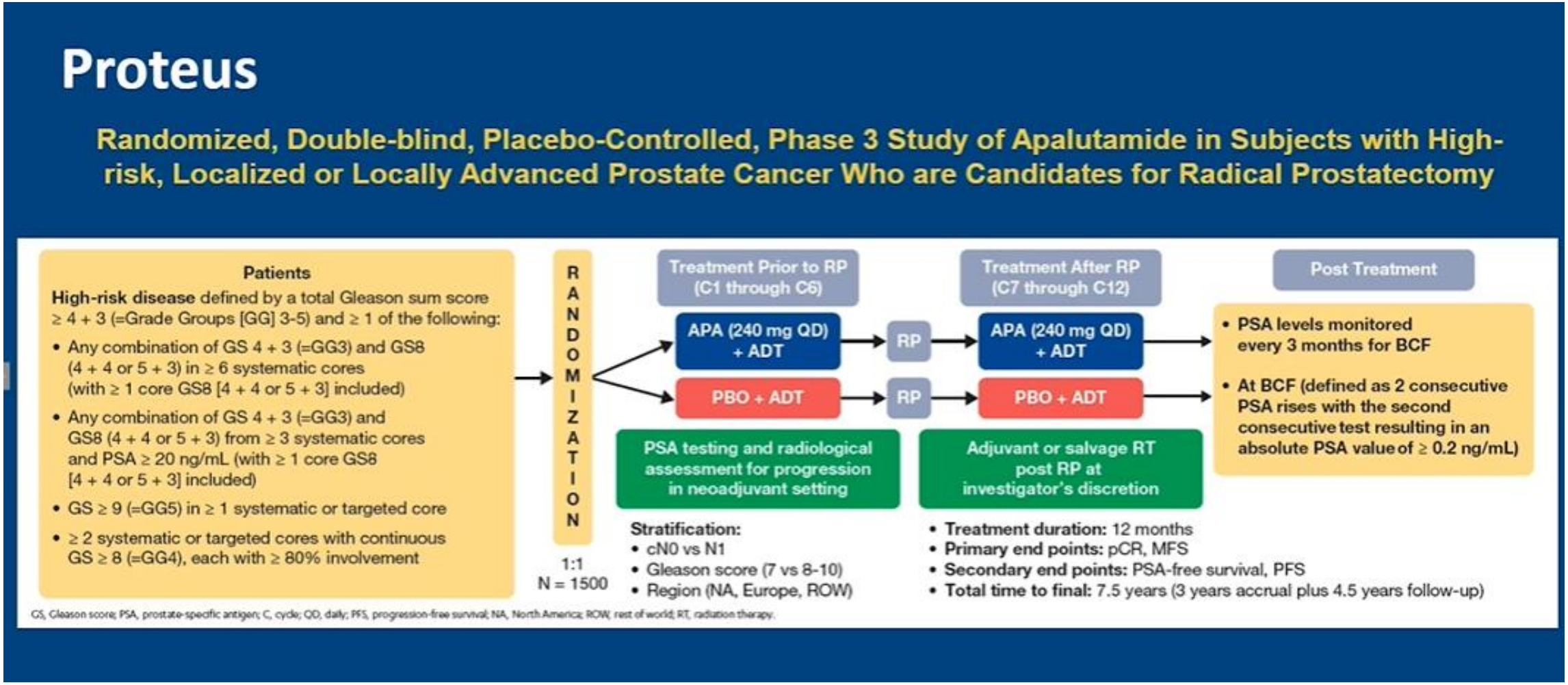


Marker		Pathology Stage >ypT2N0 N(%)	Pathology Stage ≤ypT2N0 N(%)	Fisher exact test p-value
AR-N	Low	13(42)	9(47)	0.77
	High	18(58)	10(53)	
PTEN	Loss	**24(77)**	**7(37)**	**0.007**
	Intact	**7(23)**	**12(63)**	
ARV7 nuclear	absence	**19(61)**	**18(95)**	**0.009**
	presence	**12(39)**	**1(5)**	
GR	Low	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



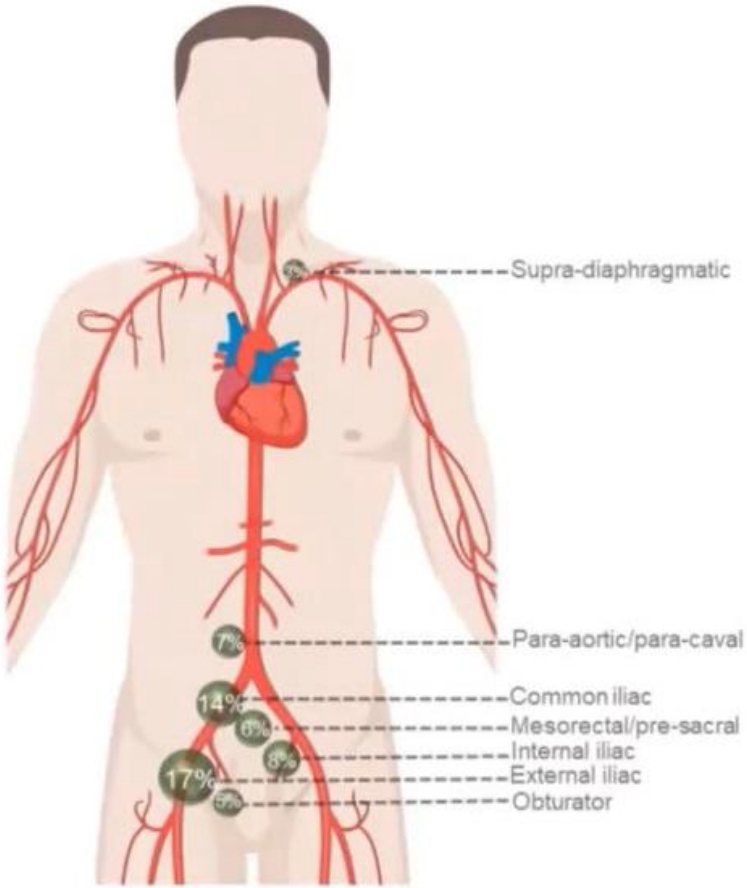
Lokalize Yüksek Riskli Prostat Kanseri
İdeal Görüntüleme

Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study

*Michael S Hofman, Nathan Lawrentschuk, Roslyn J Francis, Colin Tang, Ian Vela, Paul Thomas, Natalie Rutherford, Jarad M Martin, Mark Frydenberg, Ramdave Shakher, Lih-Ming Wong, Kim Taubman, Sze Ting Lee, Edward Hsiao, Paul Roach, Michelle Nottage, Ian Kirkwood, Dickon Hayne, Emma Link, Petra Marusic, Anetta Matera, Alan Herschtal, Amir Iravani, Rodney J Hicks, Scott Williams, Declan G Murphy, for the proPSMA Study Group Collaborators**

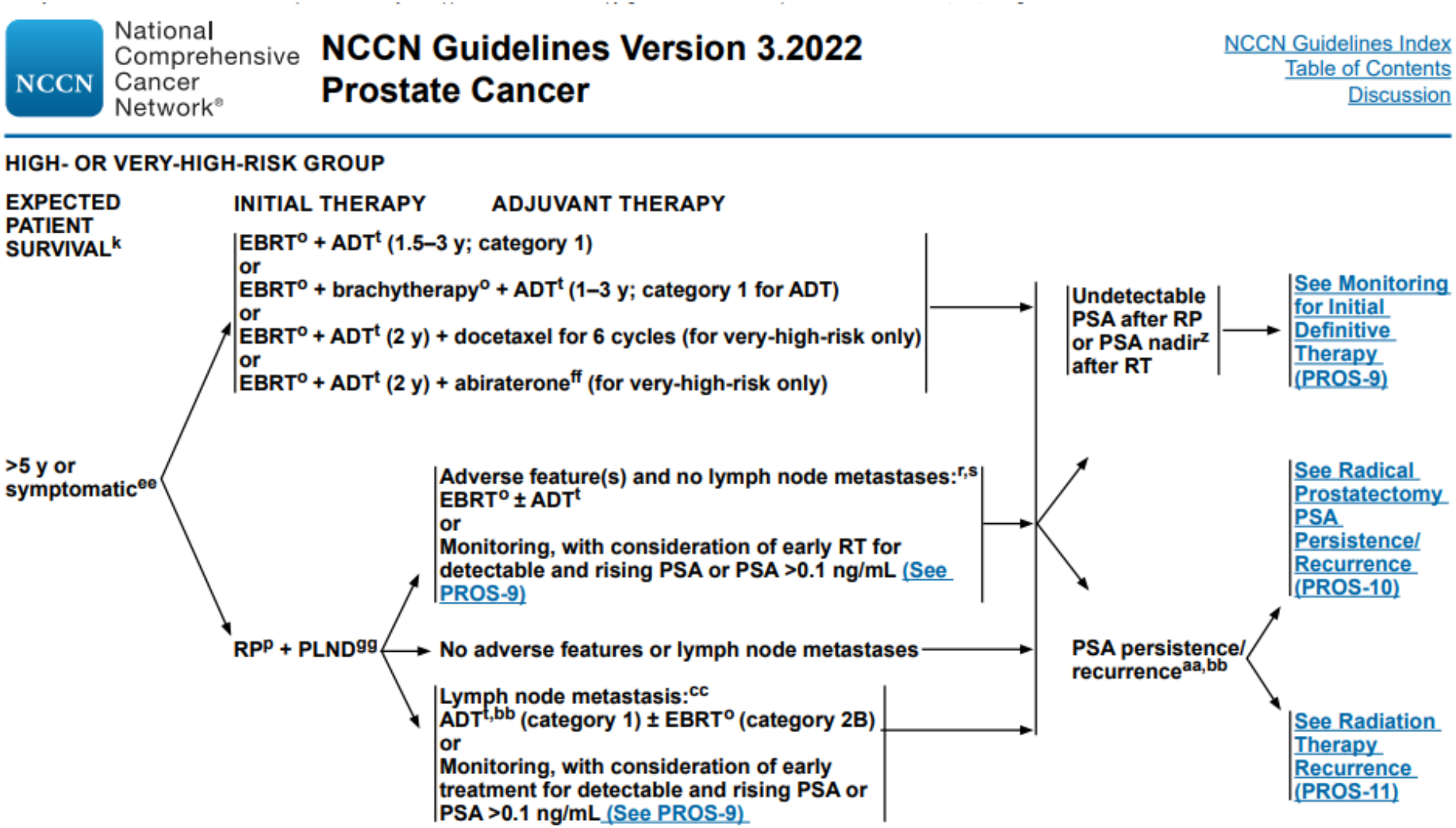
Pelvic nodal disease, n (%)	1st line Conv. Imaging	1st line PSMA	2nd line Conv. Imaging	2nd line PSMA
Negative	130 (85.5%)	116 (78.4%)	122 (89.7%)	107 (73.3%)
Equivocal	9 (5.9%)	2 (1.4%)	2 (1.5%)	5 (3.4%)
Positive	13 (**8.6%**)	30 (**20.3%**)	12 (**8.8%**)	34 (**23.3%**)

Question: PSMA-PET imaging improves clinical outcome?



Hofman et al. Lancet. 2020 Apr

Lokalize Çok Yüksek Riskli Grup



Lokalize Çok Yüksek Riskli Grup

AS + RT ± Docetaxel in High-Risk Prostate Cancer

TABLE 1. RTOG 0521: Pretreatment Characteristics (continued)

Characteristic	No. (%)		
	AS + RT (n = 281)	AS + RT + CT (n = 282)	Total (N = 563)
T3	67 (23.8)	76 (27.0)	143 (25.4)
T4	5 (1.8)	5 (1.8)	10 (1.8)
N stage pathologic			
pN0	100 (35.6)	85 (30.2)	185 (32.9)
pNX (no regional node sampling)	181 (64.4)	196 (69.8)	377 (67.1)
N stage clinical			
N0	279 (99.3)	279 (98.9)	558 (99.1)
NX	2 (0.7)	3 (1.1)	5 (0.9)
M stage			
M0	281 (100.0)	282 (100.0)	563 (100.0)

Abbreviations: AS, androgen suppression; CT, chemotherapy; PSA, prostate-specific antigen; Q, quartile; RT, radiotherapy; RTOG, Radiation Therapy

Lokalize Çok Yüksek Riskli Grup

For patients with high-risk nonmetastatic prostate cancer, CT with docetaxel improved OS from 89% to 93% at 4 years, with improved disease-free survival and reduction in the rate of distant metastasis. The trial suggests that docetaxel CT may be an option to be discussed with selected men with high-risk prostate cancer.

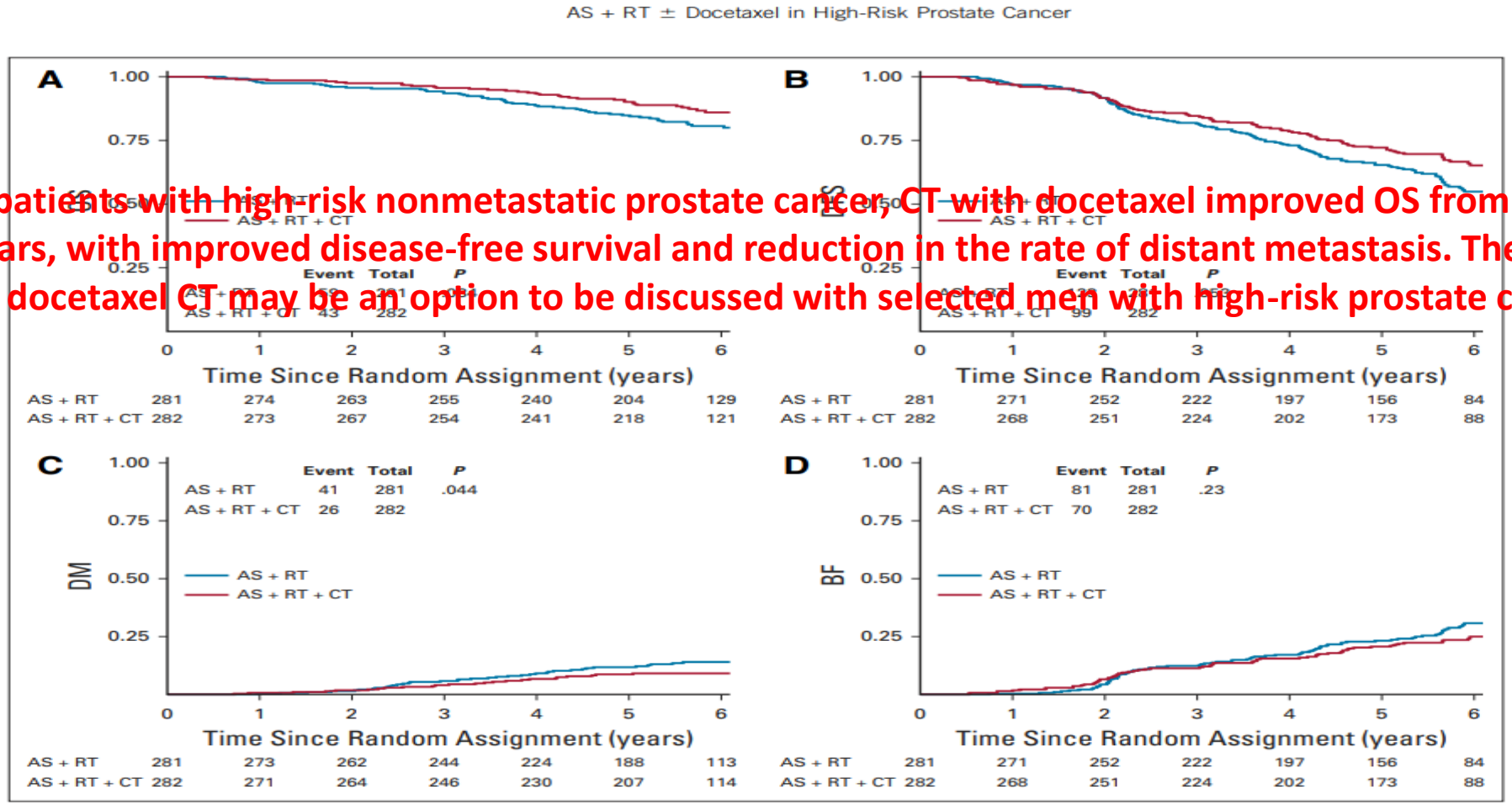


FIG 2. RTOG 0521 Kaplan-Meier curves for (A) OS, (B) DFS, (C) DM, and (D) BF. *P* values are from stratified log-rank tests. AS, androgen suppression; BF, biochemical failure; CT, chemotherapy; DFS, disease-free survival; DM, distant metastasis; OS, overall survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

Adjuvan Kemoterapi+ADT

Urol Int 2021;105:394–401
DOI: 10.1159/000513941

Table 1. Demographics and baseline characteristics

Author	Study	Publishing time	Country	Study type	Follow-up time	Control	Treatment	Primary endpoints (HR, 95% CI)	OS, number of events		PFS/DFS, number of events	
									Inter-vention	Control	Inter-vention	Control
Hussain et al. [11]	SWOG S9921	2018	America	RCT	1999–2007	RP + ATD	SOC + mitoxantrone	OS (1.06, 0.79–1.43)	91/480	85/481	*150/480	148/481
James et al. [10]	STAMPEDE	2016	America	RCT	2005–2013	RT + ATD	SOC + docetaxel	OS (1.11, 0.67–1.85)	24/168	44/130	–	–
Lin et al. [18]	#553	2019	America	RCT	2006–2011	RP + observation	SOC + docetaxel	PFS (0.80, 0.58–1.11)	11/140	17/157	#66/140	84/157
Ahlgren et al. [19]	SPCG-12	2018	Northern Europe	RCT	2005–2010	RP + observation	SOC + docetaxel	PSA PFSl	–	–	–	–
Oudard et al. [12]	–	2019	France	RCT	2003–2007	RP/RT + ATD	SOC + docetaxel	PSA PFS (0.85, 0.62–1.16)	40/125	46/125	#79/125	81/125
Rosenthal et al. [15]	RTOG 0521	2019	America	RCT	2005–2009	RT + ATD	SOC + docetaxel	OS (0.69, 0.49–0.97)	43/282	59/281	*99/282	123/281
Carles et al. [16]	–	2018	Spanish	RCT	2008–2012	RT + ATD	SOC + docetaxel	OS (0.80, 0.21–2.96)	–	–	*12/65	7/64

RCT, randomized controlled trial; OS, overall survival; PFS, progression-free survival; SOC, standard of care; RP, radical prostatectomy; RT, radiotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval. * Endpoint was DFS. # Endpoint was PFS.

Adjuvan Kemoterapi+ADT

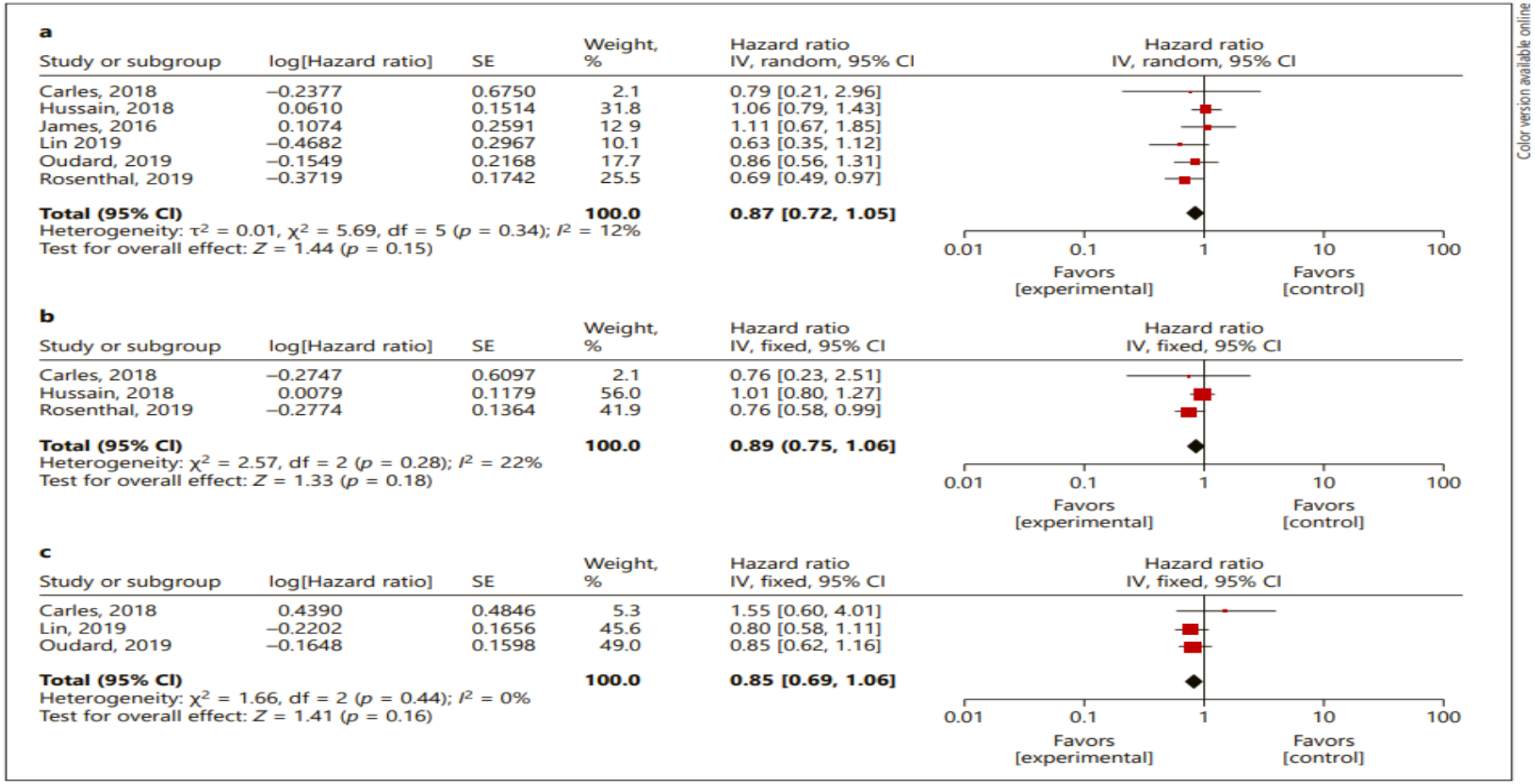


Fig. 2. Forest plots of the effect of adjuvant chemotherapy on the OS (**a**) and DFS (**b**) and BRFS (**c**) of high-risk prostate cancer. OS, overall survival; DFS, disease-free survival; BRFS, biochemical recurrence-free survival.

Abireteron+ADT+RT

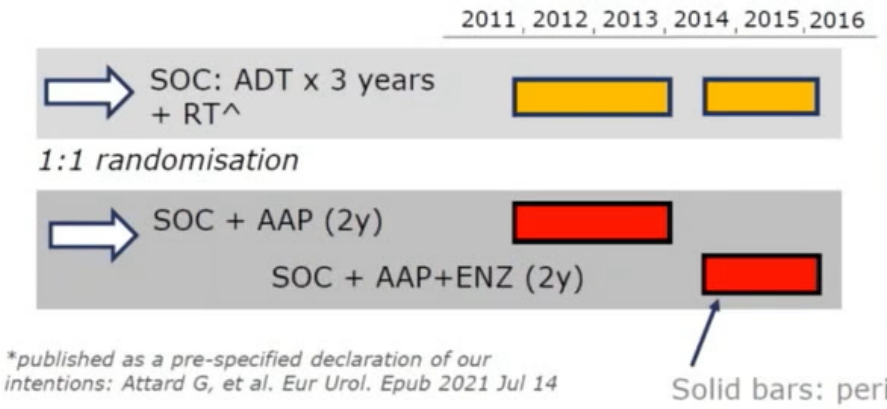
Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

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

Abireteron+ADT+RT

Patient characteristics

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

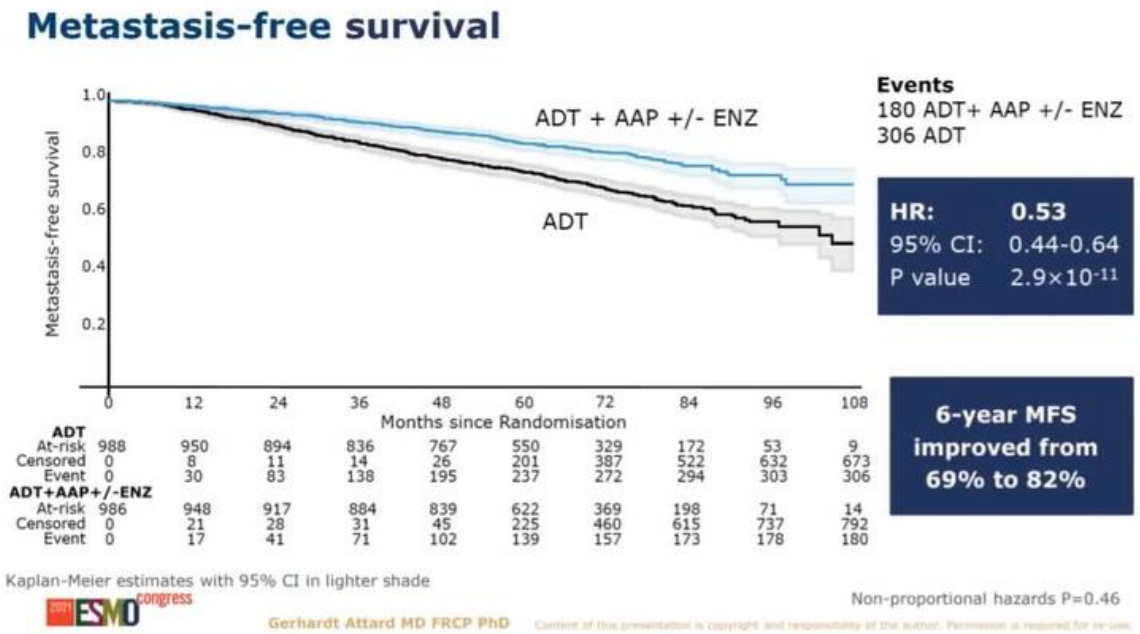
- Median age = 68 years
- Median PSA = 34 ng/ml
- N1 = 39%
- 3% relapsing after prior treatment

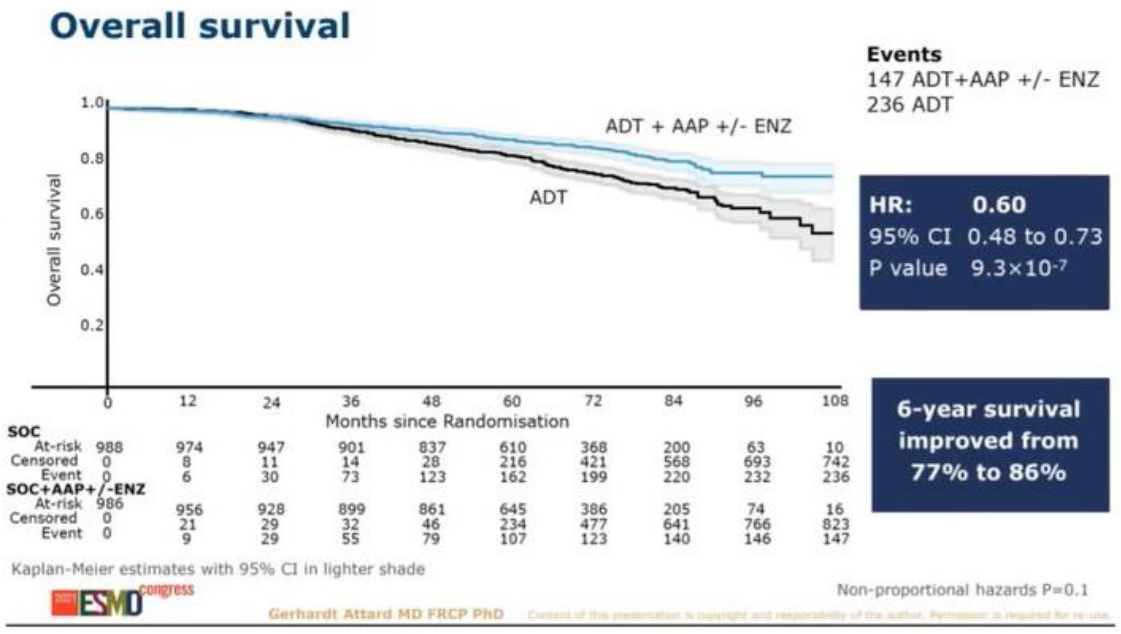
- Planned for local radiotherapy: - 99% newly-diagnosed, N0
  - 71% newly-diagnosed, N1
  - 7% previously-treated patients

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

Attard al. Lancet. 2022 Jan

Abireteron+ADT+RT

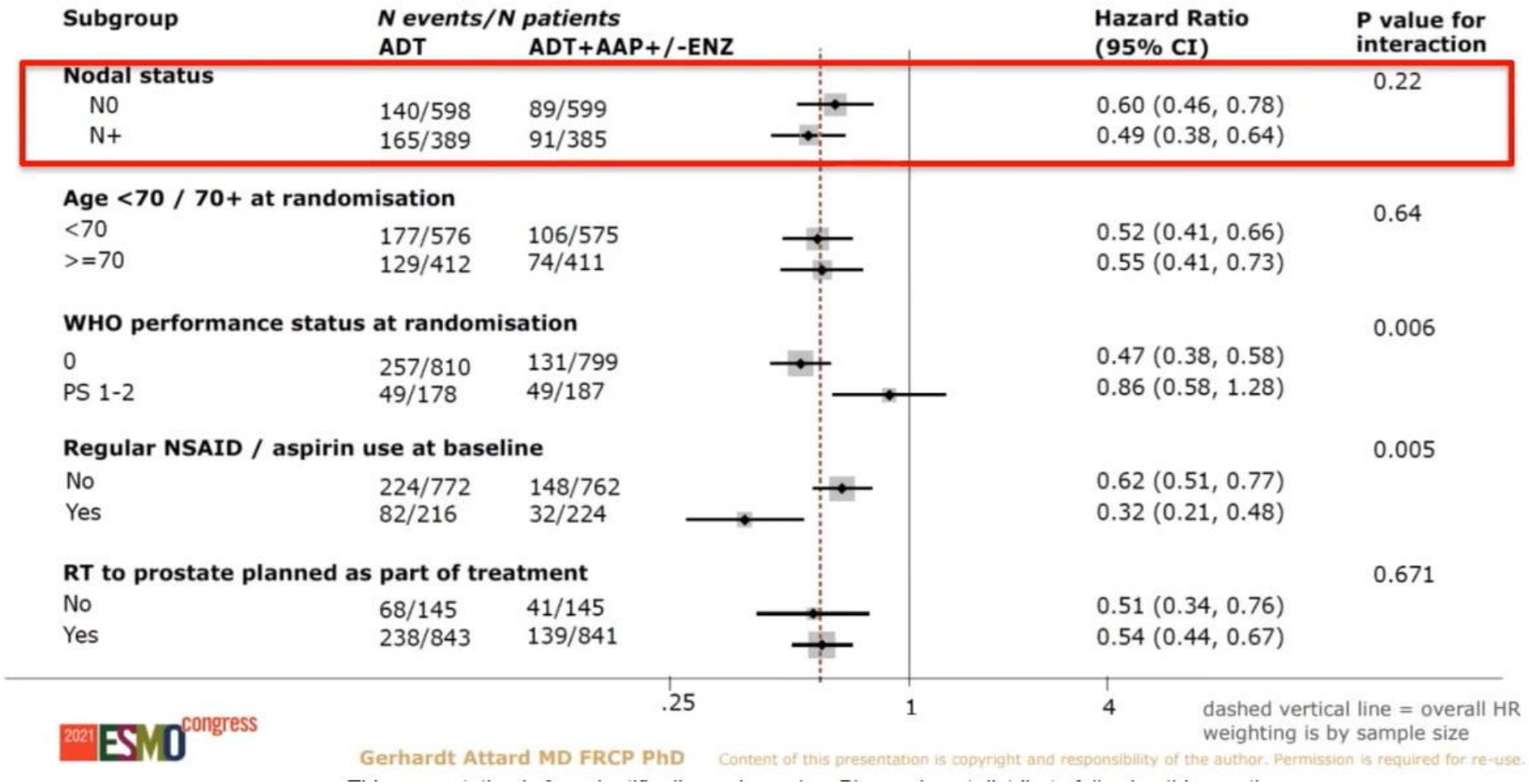




Attard al. Lancet. 2022 Jan

Abireteron+ADT+RT

Metastasis-free survival: Subgroup analysis



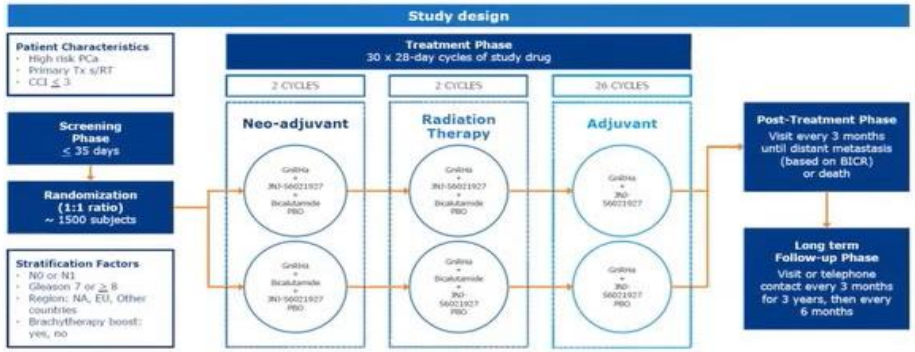
2021 ESMO congress

Gerhardt Attard MD FRCP PhD

Definitif RT+ADT+ Yeni Nesil AR-yolağı İnhibötörleri

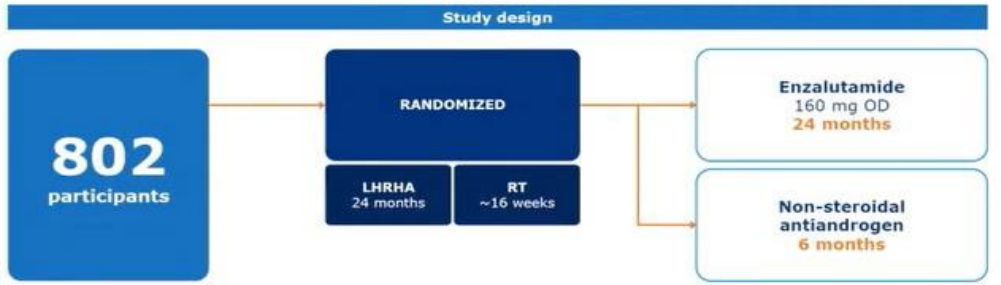
Apalutamide

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



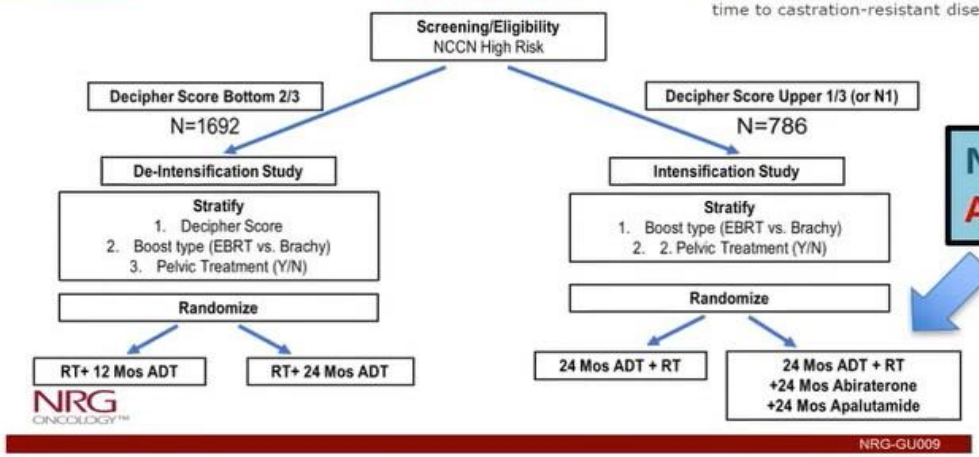
Enzalutamide

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

Devam Eden Çalışmalar

Name (trial number)	Location	Phase	Abbreviated Oncologic Eligibility	Treatment arms
Neoadjuvant Degarelix With or Without Apalutamide Followed by Radical Prostatectomy (ARNEO) (NCT03080116)	Leuven, Belgium	II	-Intermediate risk: at least 2 of the following factors: cT2b, biopsy GS 7, PSA 10-20ng/ml -High risk: cT≥2c and/or biopsy GS≥8 and/or PSA>20ng/ml -cN0-cN1, cM0	-Apalutamide + Degarelix -Placebo + Degarelix
Neoadjuvant Pembrolizumab Plus Androgen Axis Blockade Prior to Prostatectomy for High Risk Localized Prostate Cancer (NCT03753243)	Portland, OR, USA	II	- Any one of the following three high risk features: Gleason grade > 8-10, PSA > 20 ng/ml, cT3a -cM0	-Pembrolizumab + Enzalutamide + GNRH agonist (Single arm)
Neoadjuvant Atezolizumab-Based Combination Therapy in Men With Localized Prostate Cancer Prior to Radical Prostatectomy (NCT03821246)	San Francisco, CA, USA	II	-Only high risk patients in the safety-lead in for each cohort -Intermediate risk patients eligible once safety confirmed on interim analysis -cM0	-Atezolizumab +/- either Tocilizumab OR Etrumadenant (Non-randomized, sequential cohorts)
A Study of Neoadjuvant Hormone Therapy in Patient With Advanced Prostate Cancer Undergoing Radical Prostatectomy. (NCT03971110)	Guangzhou, China	IV	-cT3/4, cN0/1, cM0/1 (with five or fewer extra-pelvic lesions)	-Zoladex + Casodex (Single Arm)
Ibrutinib as Neoadjuvant Therapy in Localized Prostate Cancer (NCT02643667)	San Francisco, CA, USA	II	-Suitable for radical prostatectomy -cM0	-Ibrutinib (Single Arm)
Biomarkers for Neoadjuvant Pembrolizumab in Non-Metastatic Prostate Cancer Positive by 18FDG-PET Scanning (NCT04009967)	Laval, Québec, Canada	II	-Gleason Score ≥ 8, cM0 -Intraprostatic maximum standardized uptake value (SUVmax) ≥4 at 18-FDG-PET/CT exam	-Pembrolizumab (Single arm)
Neoadjuvant Hiltonol® (PolyICLC) for Prostate Cancer (NCT03262103)	New York, NY, USA	I	-Gleason 7 – 10, cT2a - cT3b adenocarcinoma of the prostate with plans for radical prostatectomy and PSA ≥ 4 ng/ml -Tumor visible on multiparametric MRI	Intratumoral injection of Poly-ICLC
177Lu-PSMA-I&T Prior to Radical Prostatectomy for Locally Advanced Disease (NCT04297410)	Petach Tikva, Israel	NA	-cT3/4 and/or Gleason score ≥8 and/or PSA ≥ 20 ng/dl) -Loco-regional prostate cancer (pelvic lymphadenopathy of ≥2 cm on axial imaging) -High PSMA expression: with tracer uptake greater than normal liver (maximal SUV ≥1.5 of liver)	- 177Lu-PSMA-I&T Radionuclide (Single arm)
Neoadjuvant Therapy With Proxalutamide Combined With Androgen Deprivation Therapy (ADT) for High Risk Prostate Cancer (NCT05076851)	Nanjing, Jiangsu, China	II	- High-risk prostate cancer (cT≥2c or Gleason score ≥8 or PSA≥20ng/ml) -cM0	-Proxalutamide +ADT -Placebo + ADT

Devam Eden Çalışmalar

Name (trial number)	Location	Phase	Abbreviated Oncologic Eligibility	Treatment arms
Androgen Receptor Antagonist ARN-509 With or Without Abiraterone Acetate, Gonadotropin-Releasing Hormone Analog, and Prednisone in Treating Patients With High-Risk Prostate Cancer Undergoing Surgery (NCT02949284)	New Jersey, NJ, USA	II	-Gleason > 8 OR PSA > 20 and more than 1 positive core -cT ≤ 3 on CT or MRI	-Apalutamide -Apalutamide + Abiraterone + GNRH agonist -Prostatectomy alone
Aspirin and Rintatolimod With or Without Interferon-alpha 2b in Treating Patients With Prostate Cancer Before Surgery (NCT03899987)	Buffalo, NY, USA	II	- Localized prostatic adenocarcinoma and planning on prostatectomy	- aspirin, interferon alpha, rintatolimod, surgery - aspirin, rintatolimod, surgery -surgery alone
Neoadjuvant Androgen Deprivation Therapy Combined With Enzalutamide and Abiraterone Using Multiparametric MRI and 18FDCFPyL PET/CT in Newly Diagnosed Prostate Cancer (NCT03860987)	Bethesda, MD, USA	II	-Intermediate or high risk prostatic adenocarcinoma -cN0/1 -cM0	-Enzalutamide + Abiraterone + GNRH agonist
Neoadjuvant Androgen Deprivation, Darolutamide, and Ipatasertib in Men With Localized, High Risk Prostate Cancer (NCT04737109)	Chicago, IL, USA	II	- Histologically-confirmed diagnosis of localized, untreated prostate cancer with high-risk features. Including: Grade group 4 or higher, OR Stage T3-4, M0 -PTEN loss	- ADT + Ipatasertib + Darolutamide
Genomic Biomarker-Selected Umbrella Neoadjuvant Study for High Risk Localized Prostate Cancer (GUNS) (NCT04812366)	Vancouver, British Columbia, Canada	II	-High-risk localized prostate cancer as defined by: PSA >20, ISUP 4 or greater or high volume Gleason pattern 4 or 5 Participants with oligometastatic (< 3) metastases by PSMA imaging only who are deemed candidates for radical prostatectomy are eligible	-LHRHa + Apalutamide +/- Abiraterone -LHRHa + Abiraterone +/- either Docetaxel or niraparib
Non-fucosylated Anti-CTLA-4 (BMS-986218) + Degarelix Acetate *vs.* Degarelix Acetate Alone in Men With High-risk Localized Prostate Cancer (NCT04301414)	New York, NY, USA	I	-Prostate Cancer (clinical stage T1c-T3b, N0, M0) and shows at least 2 positive cores and a Gleason sum of ≥4+3	- Non-fucosylated Anti-CTLA-4 (BMS-986218) + Degarelix -Degarelix
A Randomized Trial of Cabazitaxel, Docetaxel, Mitoxantrone or Satraplatin (CDMS) Plus Surgery for Prostate Cancer Patients Without Metastasis (NCT03258320)	Qingdao, Shandong, China	I	-cT ≥ 2c -cN0 -cM0	- Cabazitaxel -Docetaxel -Mitoxantrone -Satraplatin -Surgery alone
PROSTVAC in Combination With Nivolumab in Men With Prostate Cancer (NCT02933255)	Bethesda, MD, USA	I/II	-Surgical candidate who has chosen to proceed with prostatectomy	- PROSTVAC-V (vaccinia) + PROSTVAC-F (fowlpox) + Nivolumab

Sonuçlar

- 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 çalışımalarda gösterilmiştir
- Çok sayıda devam eden çalışmalar mevcuttur
- Neoadjuvan tedavi ilerleyen zamanlarda daha çok gündemimize girecek