Non-Metastatik Kastrasyona Dirençli (nmCRP) Prostat Kanseri Tedavisi

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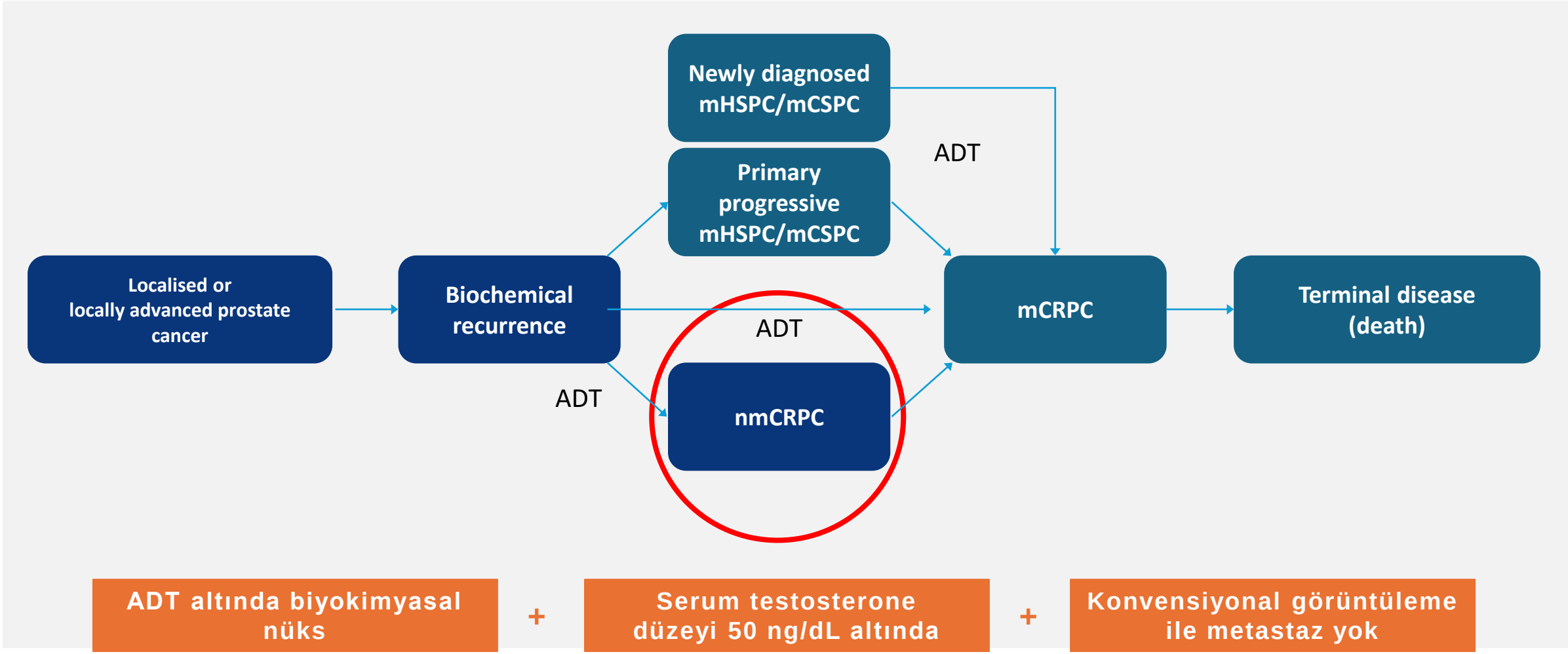
Ders Planı

- ❑Giriş
- ❑PSA double time(PSADT) prognostik ve prediktif
- ❑ARAMIS, PROSPER, SPARTAN benzer sonuç farklı toksisite
- ❑PSMA-PET CT göre çalışmaları yenide okumak
- ❑Gelecek perspektif
- ❑Sonuç

Non-Metastatik Kastrasyona Dirençli (nmCRP) Prostat Kanseri



Kastrasyona Dirençli Metastatik Prostat Kanseri Tedavisinde İlaçların Erkinliği

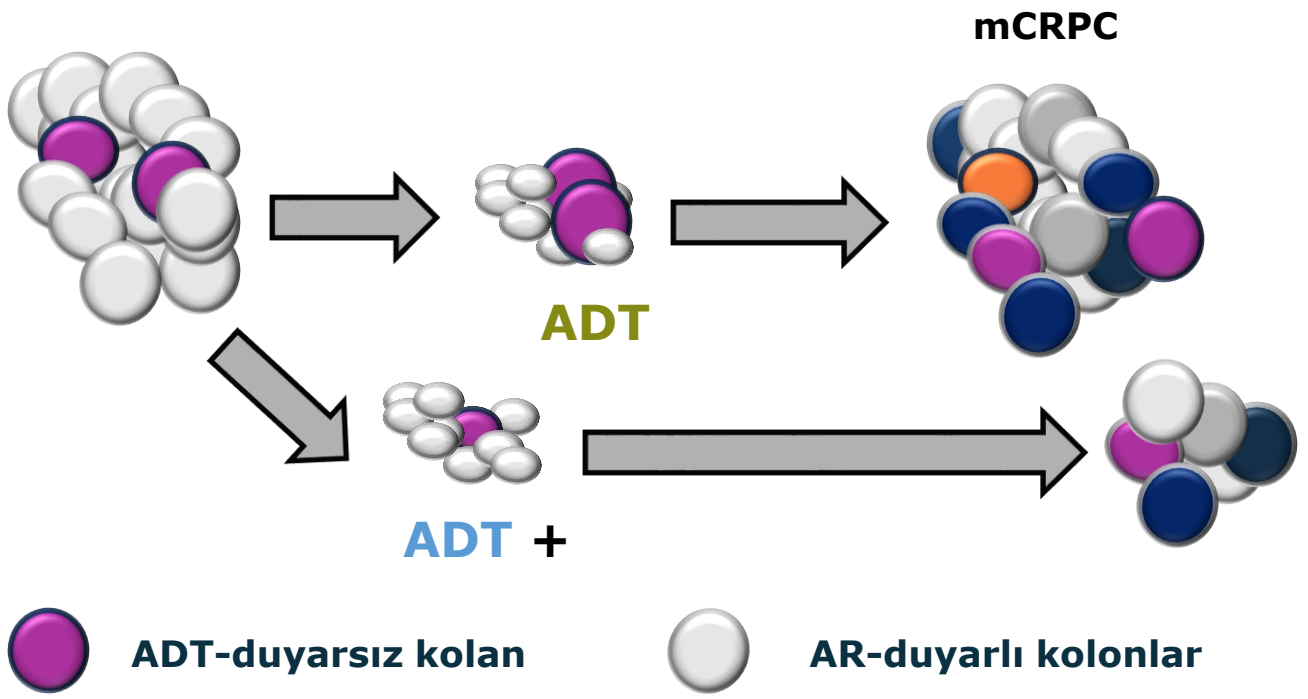
Study	Agents	N	Indication	HR	ΔOS (mo)
TAX-327[1]	DOC/P vs mito/P	1,006	mCRPC, symptomatic or not	0.76	+2.9
COU-AA-302[6]	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms No visceral metastases	0.81	+4.4
COU-AA-301[3]	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74	+4.6
PREVAIL[4]	ENZ vs pbo	1,717	mCRPC (pre-DOC), mild/no symptoms	0.77	+4.0
AFFIRM[5]	ENZ vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63	+4.8
TROPIC[6]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA[7]	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70	+3.6

ABI, abiraterone; CABA, cabazitaxel; DOC, docetaxel; ENZ, enzalutamide; HR, hazard ratio; mito, mitoxantrone; P, prednisone; pbo, placebo; OS, overall survival.

1. Tannock IF *et al. N Engl J Med* 2004; 351:1502–12. **2.** Ryan CJ *et al. Lancet Oncol* 2015;16:152–60. **3.** Rathkopf DE *et al. Eur Urol* 2014;66:815–25. **4.** Beer TM *et al. Eur Urol* 2017;71:151–4.
5. Armstrong AJ *et al. Cancer* 2017;123:2303–11. **6.** de Bono JS *et al. Lancet* 2010;376:1147–54. **7.** Hoskin P *et al. Lancet Oncol* 2014;15:1397–406.

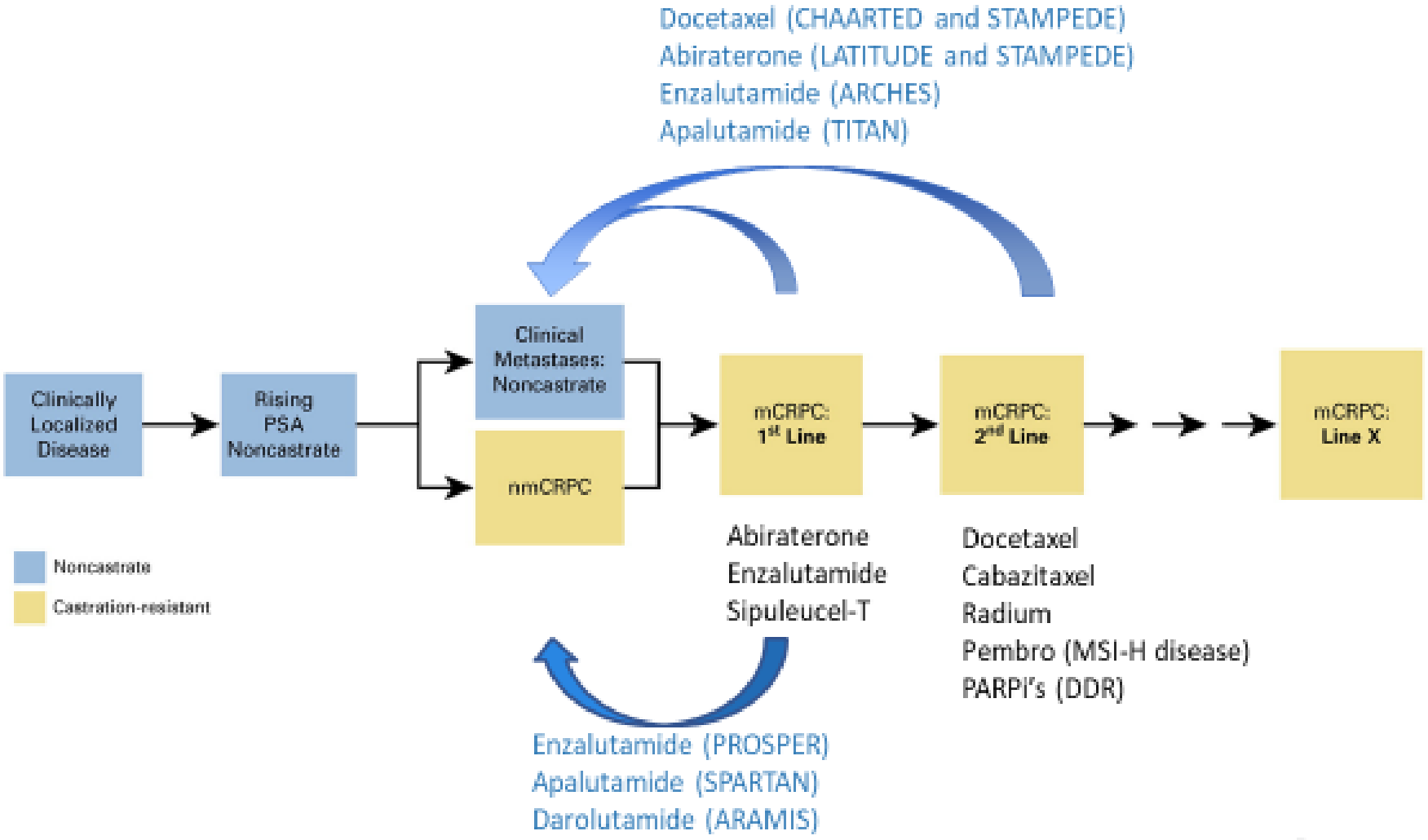
CHUM

Erken Dönem Etkili Tedavi ile Kastrasyona Kadar Geçen Süreyi Uzatmak Sağkalımla İlişkili



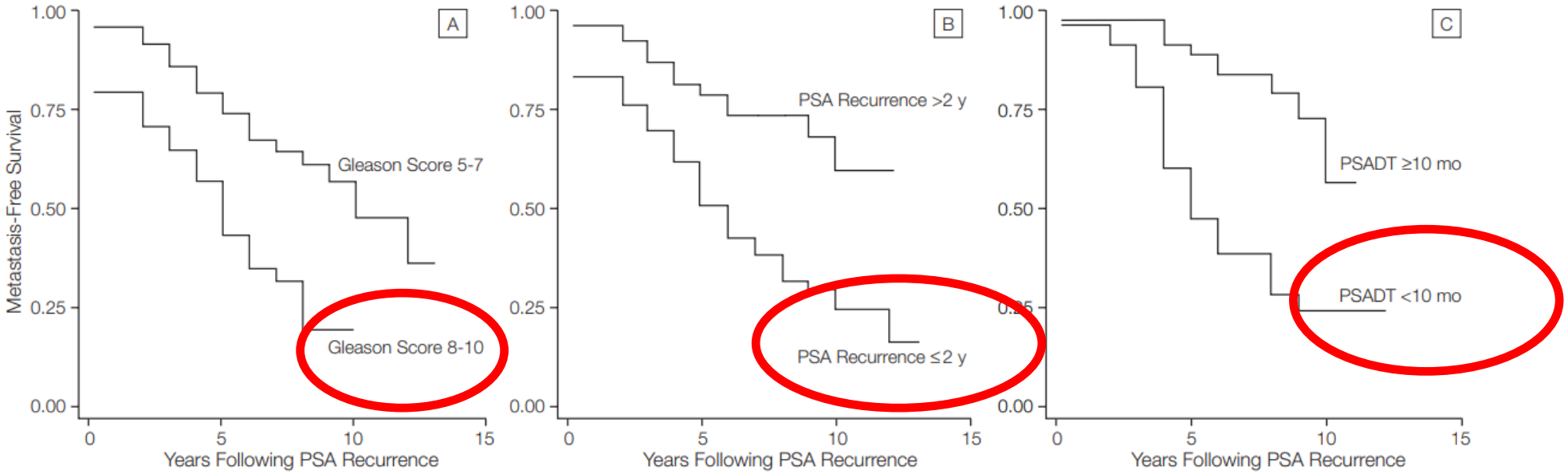
Erken dönem uygun hastaya yoğun tedavi ile kastrasyona kadar geçen süre uzatılabilir ve daha uzun sağkalım iyi yaşam kalitesi elde edilebilir

Prostat Kanserinin ve Tedavisinin Seyri



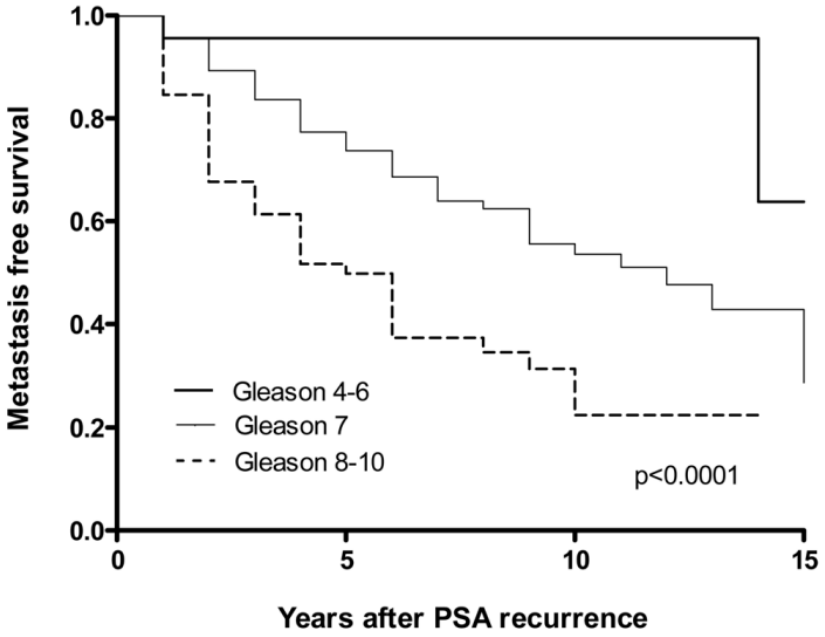
Kastrasyona Duyarlı Prostat kanserinde Biyokimyasal Rekürens Metastaz riski

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

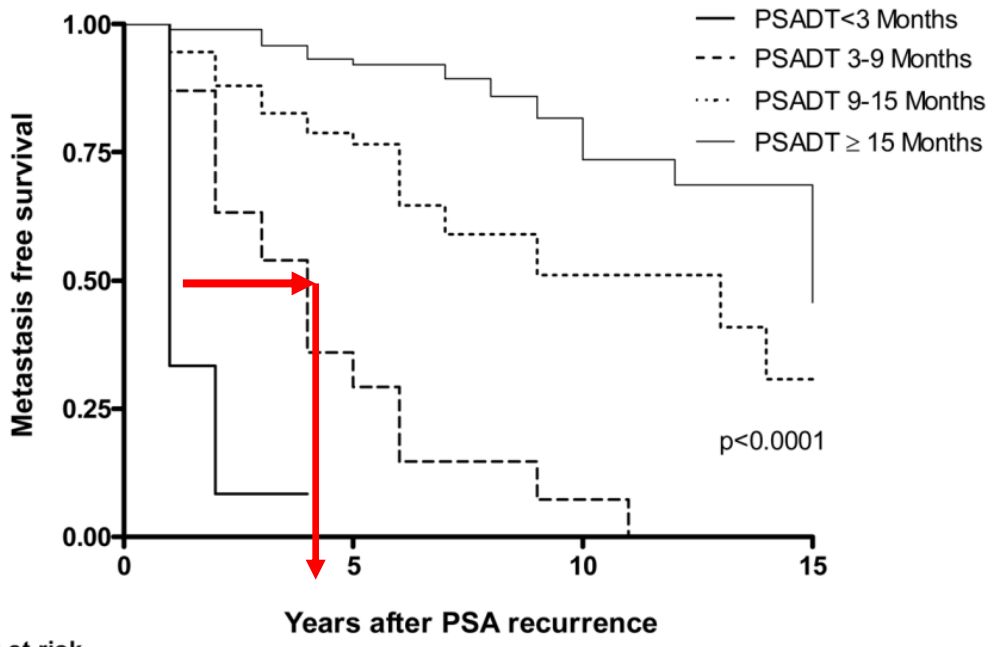


A, Based on Gleason scores in the radical prostatectomy specimen ($P<.001$). B, Based on years until initial biochemical recurrence ($P<.001$). C, Based on prostate-specific antigen doubling time (PSADT) ($P<.001$).

Kastrasyona Duyarlı Prostat kanserinde 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

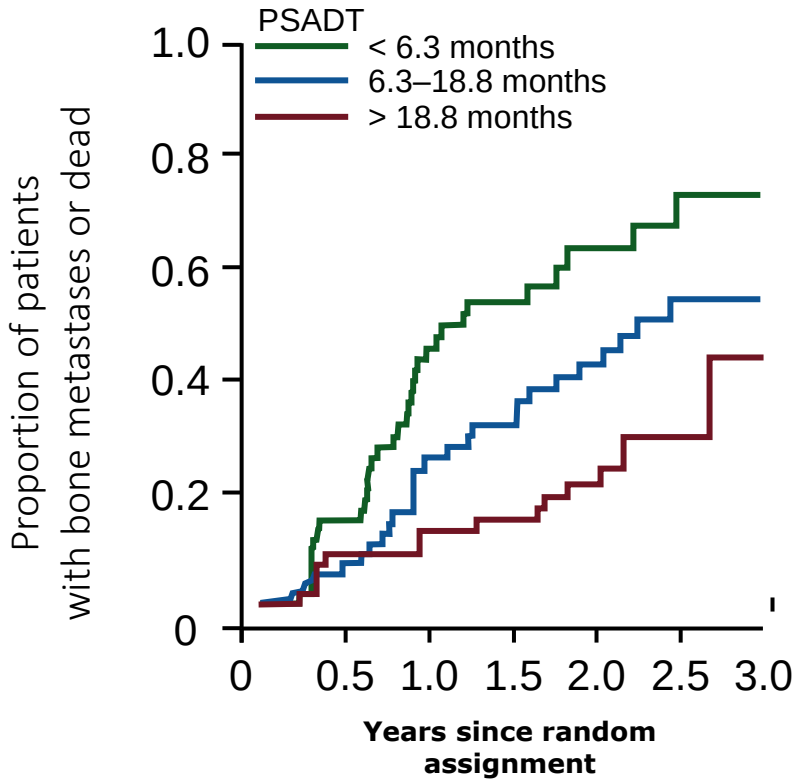


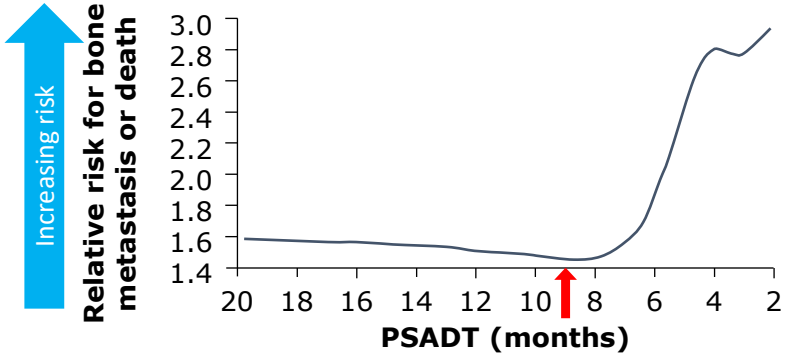
Number at risk				
PSADT < 3 Month	46	0	0	0
PSADT 3-9 Month	106	16	2	0
PSADT 9-15 Month	86	37	11	1
PSADT ≥ 15 Month	212	86	30	3

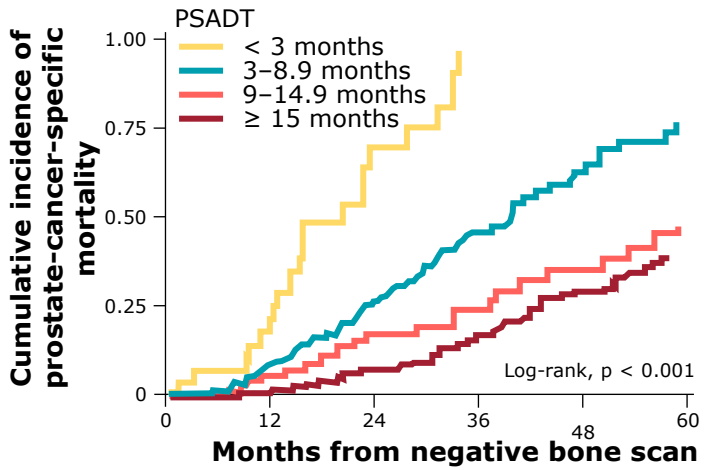
Cerrahi sonrası mediyan 8 yıl takip süresinde, 450 biyokimyasal nüks gelişen ve herhangi bir salvage tedavi almayan hastanın 134'de metastaz görüldü(%29.8).

Emmanuel S. Antonarakis, BJU Int. 2012

nmCRP
PSADT: Metastaz ve hastalığa bağlı ölümü prediktife eder





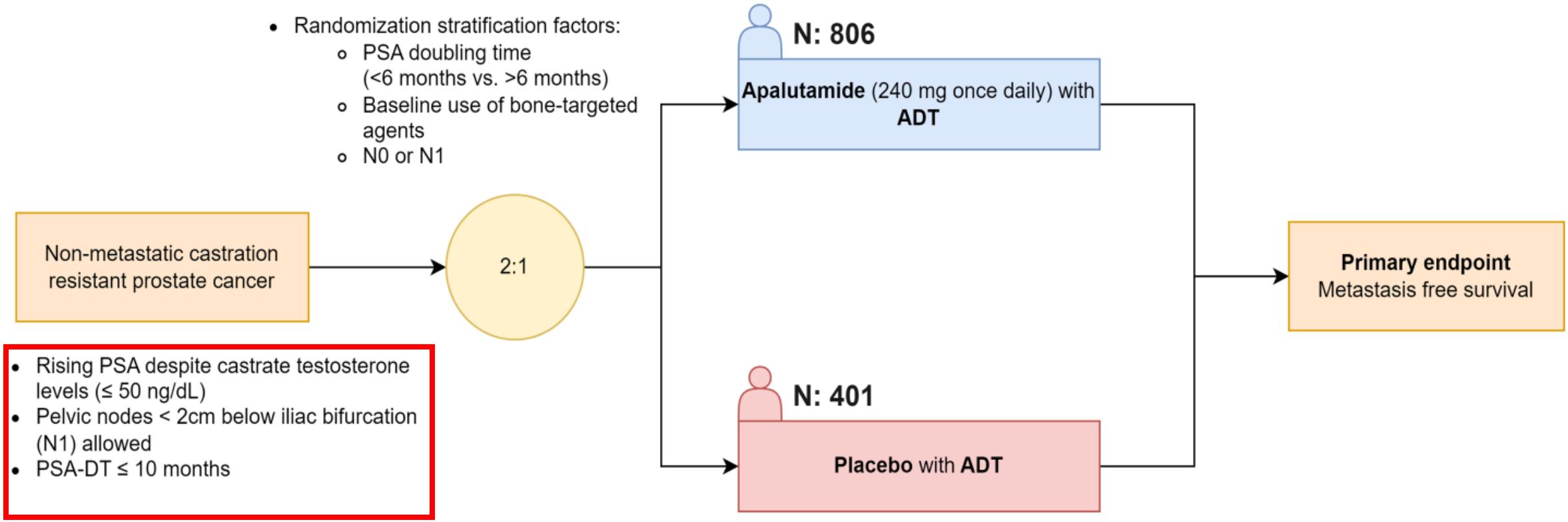


Smith MR, et al. J Clin Oncol. 2005;23:2918-25. Howard LE, et al. BJU Int. 2017;120:E80-6.Smith MR, et al. J Clin Oncol. 2013;31:3800-6.

nmCRP Yoğun Tedavi

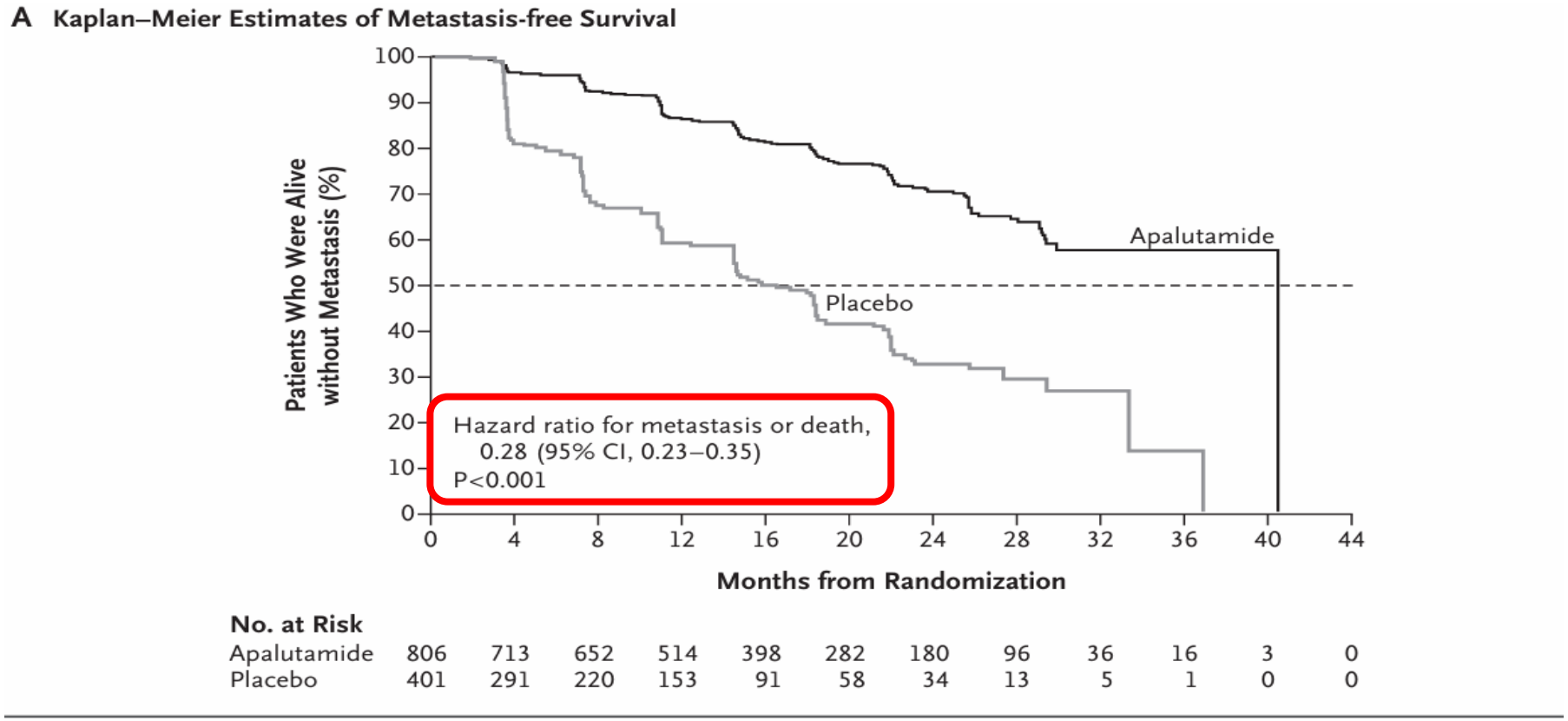
Trial Name	Total Participants	Interventions	Primary Endpoint
PROSPER (NCT02003924)	1560	Enzalutamide 160mg once daily	Metastasis-free survival
SPARTAN (NCT01946204)	1200	Apalutamide 240mg once daily	Metastasis-free survival
ARAMIS (NCT02200614)	1500	Darolutamide 600mg twice daily	Metastasis-free survival

Apalutamide nmCRP etkinliği(SPARTAN)



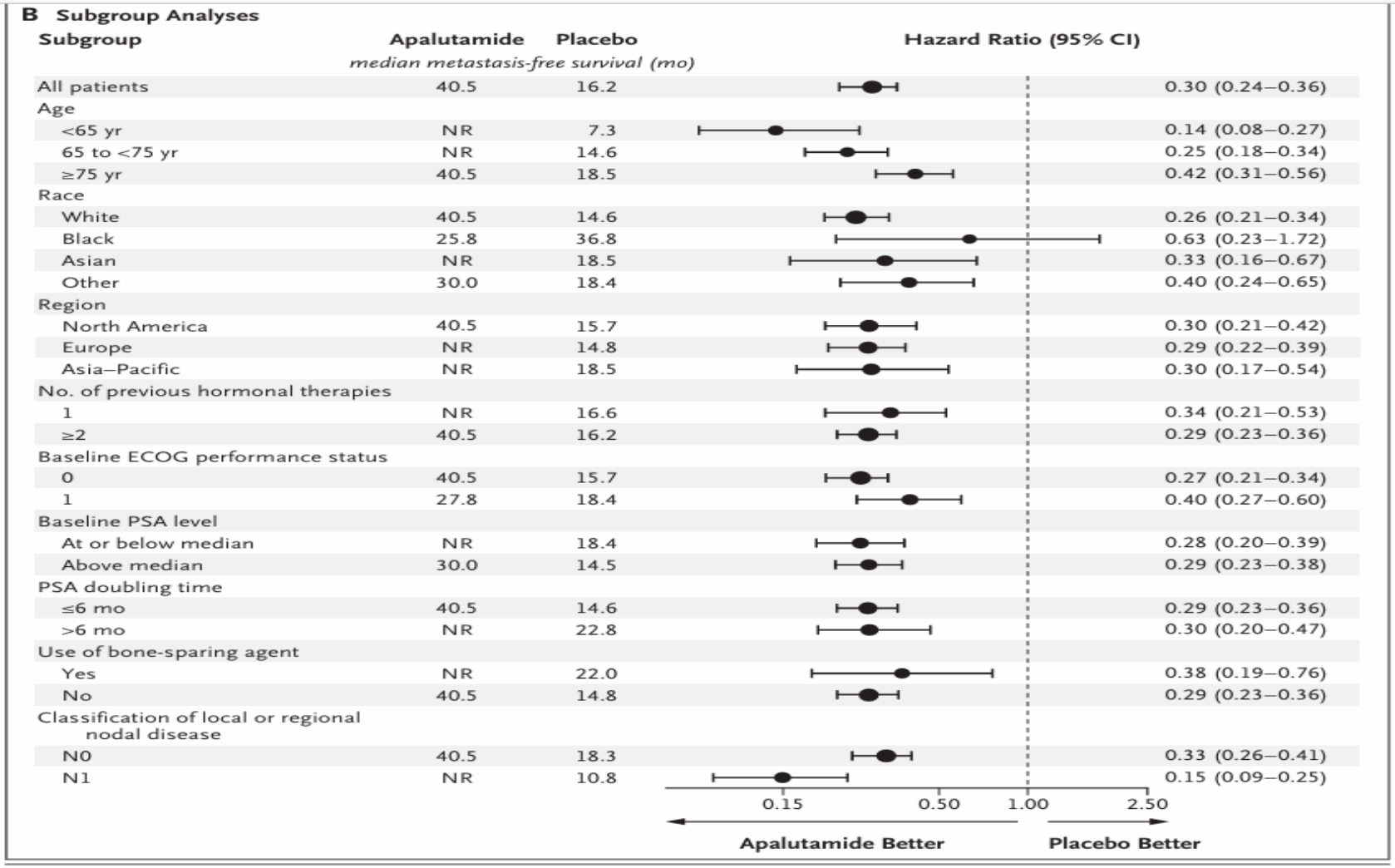
Smith MR et al, NEJM 2018

Apalutamide nmCRP etkinliği(SPARTAN)



Matthew R. Smith at al, NEJM 2018

Apalutamide nmCRP etkinliği(SPARTAN)



Matthew R. Smith at al, NEJM 2018

Apalutamide nmCRP yan etki (SPARTAN)

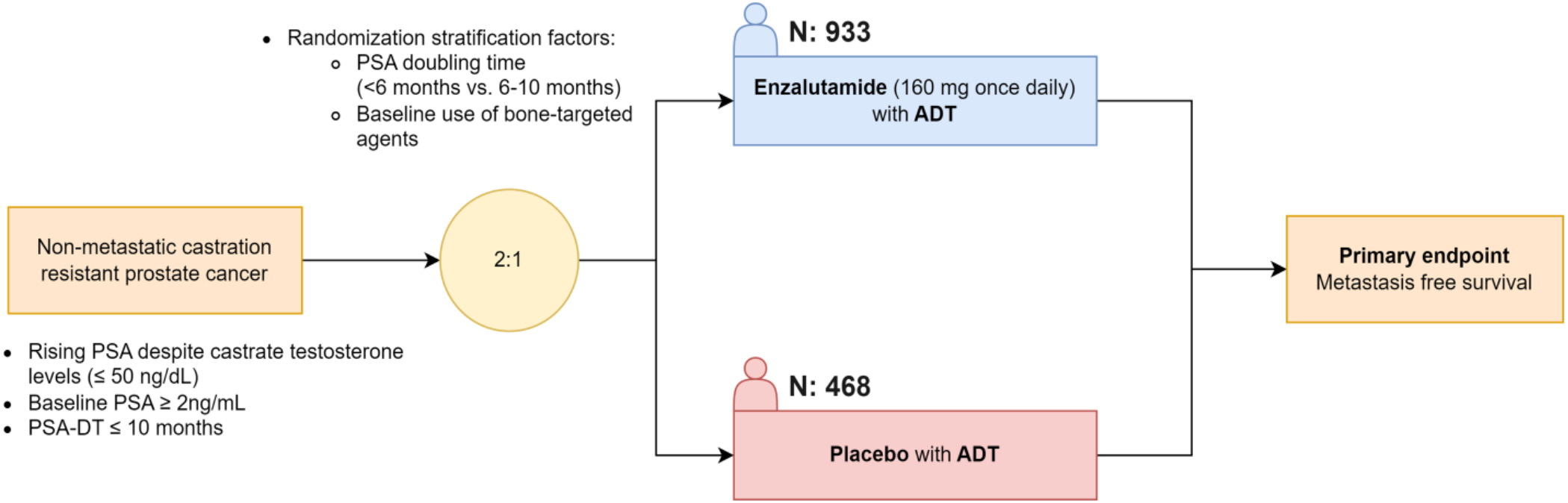
Table 3. Adverse Events.

Adverse Event*	Apalutamide (N=803)		Placebo (N=398)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	—	92 (23.1)	—
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	—	28 (7.0)	—
Adverse event associated with death	10 (1.2)	—	1 (0.3)	—
Adverse events that occurred in ≥15% of patients in either group†				
Fatigue‡	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash‡	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Falls‡	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other adverse events of interest				
Fracture‡	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism‡	65 (8.1)	0	8 (2.0)	0
Mental-impairment disorder§	41 (5.1)	0	12 (3.0)	0
Seizure‡	2 (0.2)	0	0	0

* The incidences of the following adverse events in the apalutamide group versus the placebo group were adjusted for exposure (events per 100 patient-years): fatigue (incidence, 32.3 vs. 27.2), hypertension (36.3 vs. 38.7), rash (29.6 vs. 8.3), diarrhea (21.6 vs. 22.6), nausea (15.8 vs. 20.4), weight loss (18.3 vs. 10.5), arthralgia (14.7 vs. 8.0), falls (13.6 vs. 10.0), fracture (10.5 vs. 7.8), dizziness (7.7 vs. 6.6), hypothyroidism (7.6 vs. 2.2), mental-impairment disorder (3.9 vs. 3.4), and seizure (0.2 vs. 0).
† This category includes adverse events that occurred up to 28 days after the last dose of the trial regimen was administered.
‡ These adverse events were considered by the investigators to be related to the trial regimen.
§ Mental-impairment disorders included the following adverse events: disturbance in attention, memory impairment, cognitive disorder, and amnesia.

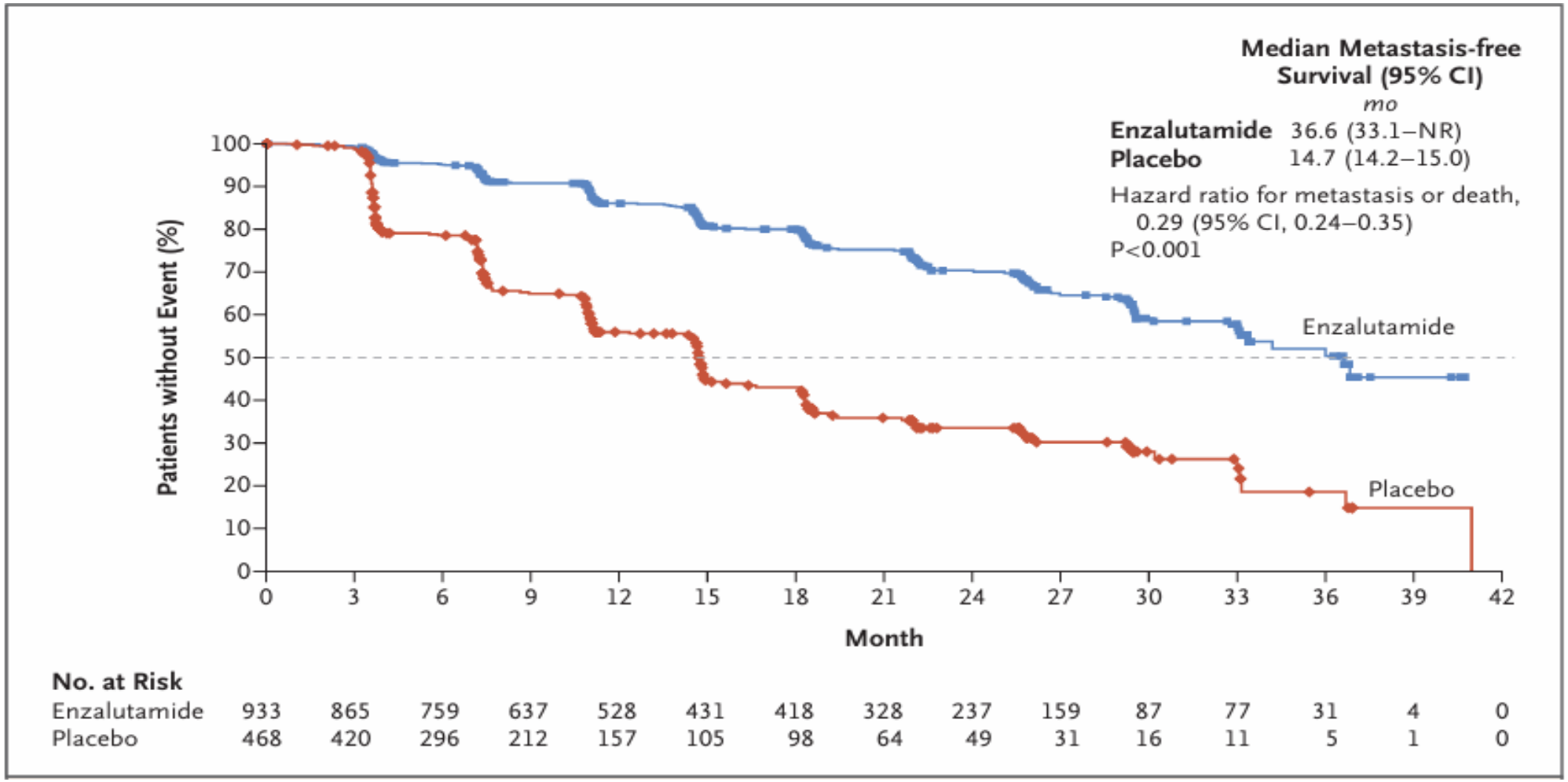
Matthew R. Smith at al, NEJM 2018

Enzalutamide nmCRP etkinliği(PROSPER)



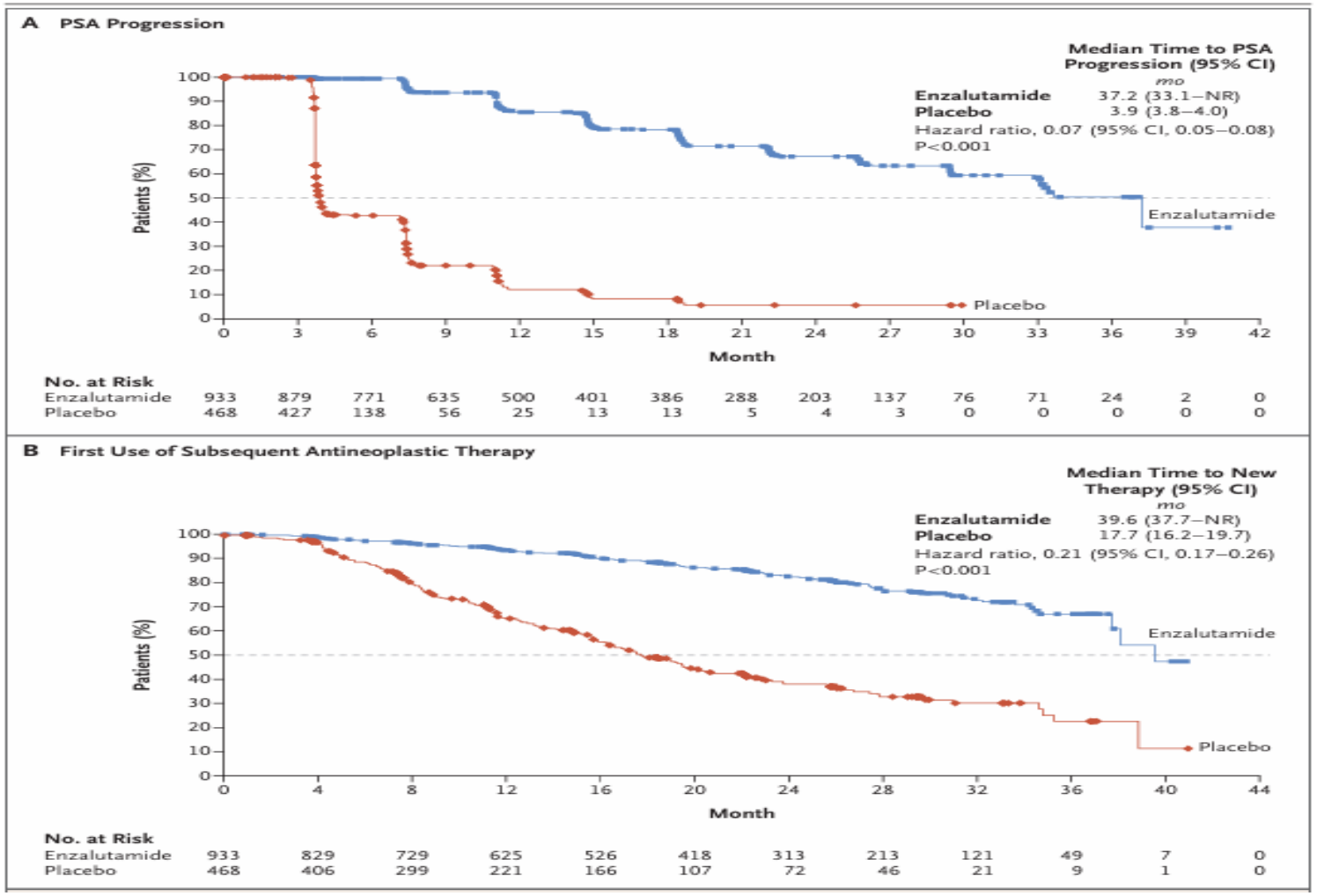
Hussain M et al, NEJM, 2018

Enzalutamide nmCRP etkinliği(PROSPER)



Hussain M at al, NEJM 2018

Enzalutamide nmCRP etkinliği(PROSPER)



Hussain M at al, NEJM 2018

Enzalutamide nmCRP yan etki(PROSPER)

Table 3. Adverse Events.

Event	Enzalutamide Group (N=930)		Placebo Group (N=465)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	808 (87)	292 (31)	360 (77)	109 (23)
Any serious adverse event*	226 (24)	—	85 (18)	—
Adverse event leading to discontinuation of trial regimen	87 (9)	—	28 (6)	—
Adverse event leading to death	32 (3)	—	3 (1)	—
Most common adverse events, occurring in ≥5% of patients†				
Fatigue	303 (33)	27 (3)	64 (14)	3 (1)
Hot flush	121 (13)	1 (<1)	36 (8)	0
Nausea	106 (11)	3 (<1)	40 (9)	0
Diarrhea	91 (10)	3 (<1)	45 (10)	2 (<1)
Hypertension	111 (12)	43 (5)	24 (5)	10 (2)
Fall	106 (11)	12 (1)	19 (4)	3 (1)
Constipation	85 (9)	2 (<1)	32 (7)	2 (<1)
Dizziness	91 (10)	4 (<1)	20 (4)	0
Arthralgia	78 (8)	1 (<1)	32 (7)	1 (<1)
Asthenia	82 (9)	11 (1)	28 (6)	1 (<1)
Decreased appetite	89 (10)	2 (<1)	18 (4)	1 (<1)
Back pain	73 (8)	2 (<1)	33 (7)	1 (<1)
Headache	85 (9)	2 (<1)	21 (5)	0
Hematuria	62 (7)	16 (2)	36 (8)	13 (3)
Urinary tract infection	38 (4)	7 (1)	30 (6)	3 (1)
Weight loss	55 (6)	2 (<1)	7 (2)	0
Urinary retention	20 (2)	4 (<1)	28 (6)	5 (1)
Adverse events of special interest				
Hypertension‡	114 (12)	43 (5)	25 (5)	11 (2)
Major adverse cardiovascular event§	48 (5)	34 (4)	13 (3)	8 (2)
Mental impairment disorders¶	48 (5)	1 (<1)	9 (2)	0
Hepatic impairment	11 (1)	5 (1)	9 (2)	2 (<1)
Neutropenia	9 (1)	5 (1)	1 (<1)	1 (<1)
Convulsion	3 (<1)	2 (<1)	0	0
Posterior reversible encephalopathy syndrome	0	0	0	0

Table 3. Adverse Events of Special Interest, Irrespective of Relationship to Enzalutamide or Placebo.

Adverse Event	Enzalutamide Group (N=930)	Placebo Group (N=465)
	no. of patients (%)	
Fatigue*	424 (46)	103 (22)
Musculoskeletal event†	315 (34)	107 (23)
Fracture‡	168 (18)	29 (6)
Hypertension§	167 (18)	28 (6)
Fall	164 (18)	25 (5)
Cognitive and memory impairment¶	73 (8)	10 (2)
Cardiovascular events‖	60 (6)	11 (2)
Ischemic heart disease**	60 (6)	8 (2)
Second primary cancer	48 (5)	7 (2)
Rash††	38 (4)	13 (3)
Loss of consciousness‡‡	34 (4)	4 (1)
Angioedema§§	20 (2)	4 (1)
Hepatic disorder¶¶	16 (2)	15 (3)
Renal disorder	14 (2)	8 (2)
Thrombocytopenia‖‖	12 (1)	4 (1)
Neutropenia	12 (1)	1 (<1)
Severe cutaneous adverse reaction	1 (<1)	0
Seizure	3 (<1)	0
Posterior reversible encephalopathy syndrome	0	0

* Fatigue events included asthenia.
† Musculoskeletal events included back pain, arthralgia, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal stiffness, muscular weakness, and muscle spasms.
‡ Fracture events included bone and joint injuries.
§ Hypertension events included hypertensive retinopathy, increased blood pressure, systolic hypertension, and hypertensive crisis.
¶ Events of cognitive and memory impairment included disturbance in attention, cognitive disorders, amnesia, Alzheimer's disease, dementia, senile dementia, mental impairment, and vascular dementia.
‖ Cardiovascular events included hemorrhagic central nervous system vascular conditions, ischemic central nervous system vascular conditions, and

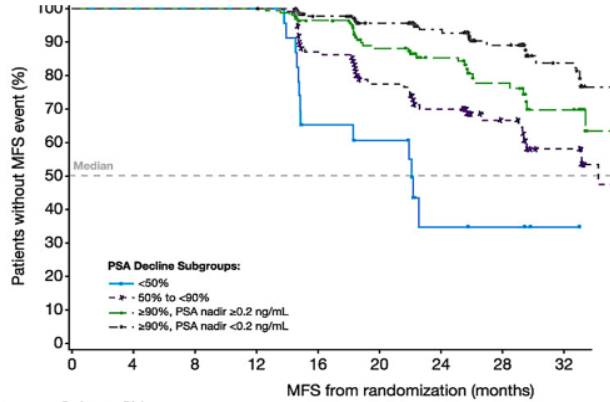
Hussain M at al, NEJM 2018

Enzalutamide nmCRP yan etki(PROSPER)
Nadir PSA ve Derin PSA yanıtı Uzun Sağkalım ile İlişkili

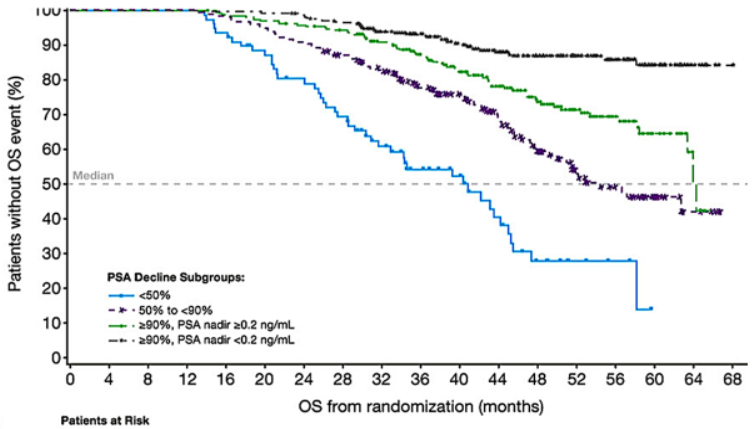
Long-term analysis from PROSPER: PSA nadir associated with benefit

Other nmCRPC trials have also shown this

No known intervention for those with inadequate PSA nadir



Subgroup	Patients at Risk								
<50%:	23	23	23	23	14	12	4	3	1
50% to <90%:	113	113	113	113	90	65	51	34	17
≥90%, PSA nadir ≥0.2 ng/mL:	172	172	172	172	146	107	76	51	27
≥90%, PSA nadir <0.2 ng/mL:	190	190	190	190	151	127	96	67	37



Subgroup	Patients at Risk																	
<50%:	78	78	78	78	73	65	59	51	10	30	25	17	9	6	3	0	0	
50% to <90%:	196	196	196	196	193	186	178	167	151	127	110	87	64	45	35	18	8	
≥90%, PSA nadir ≥0.2 ng/mL:	266	266	266	266	261	257	251	245	225	194	168	141	108	77	53	27	6	
≥90%, PSA nadir <0.2 ng/mL:	287	287	287	287	286	285	281	273	244	224	188	158	128	103	72	39	15	

Hussain M et al. J Urol 2023; 209:532-9

STRIVE çalışması: Faz 2 nmCRP/mCRP Enzalutamide vs Bicalutamide

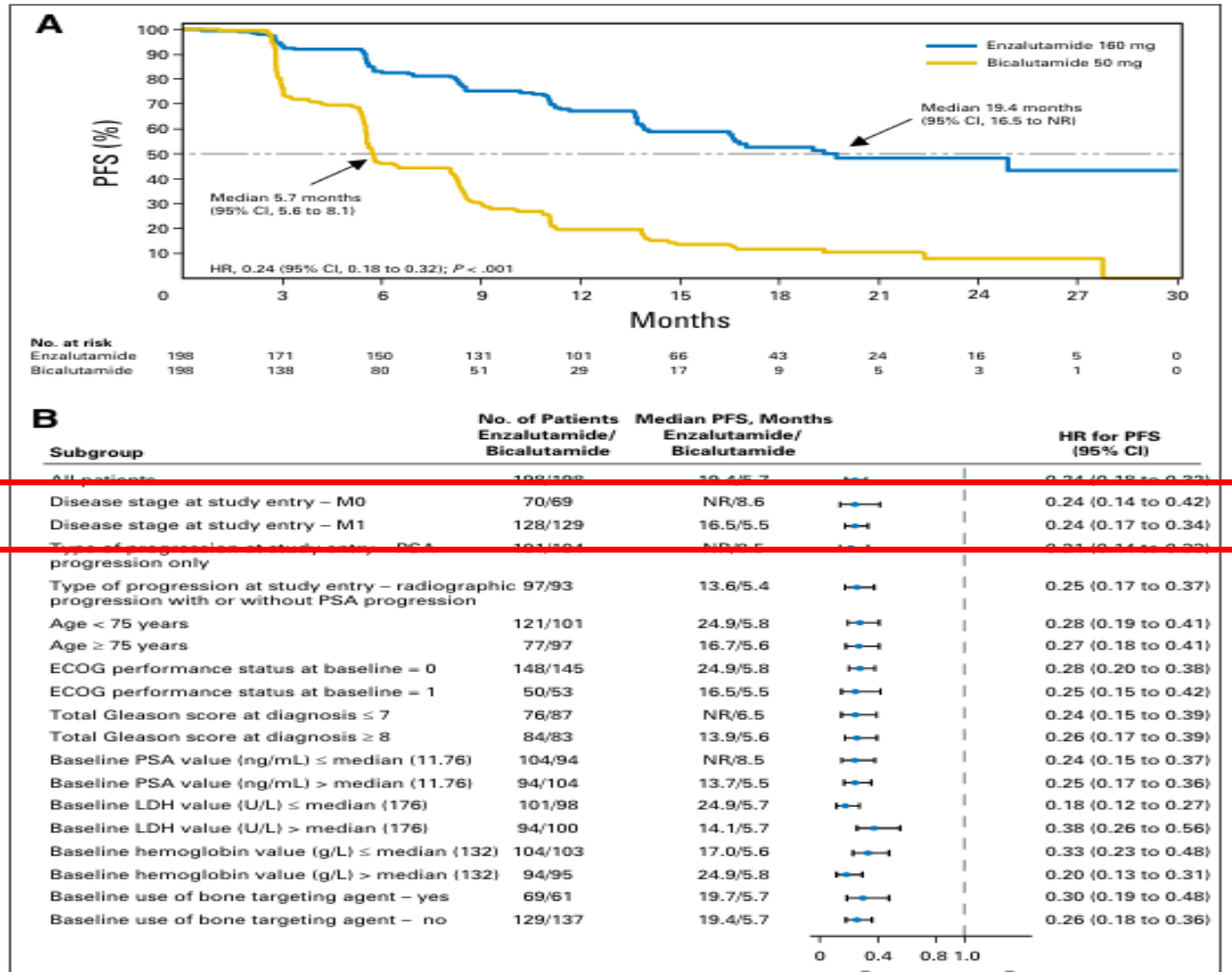
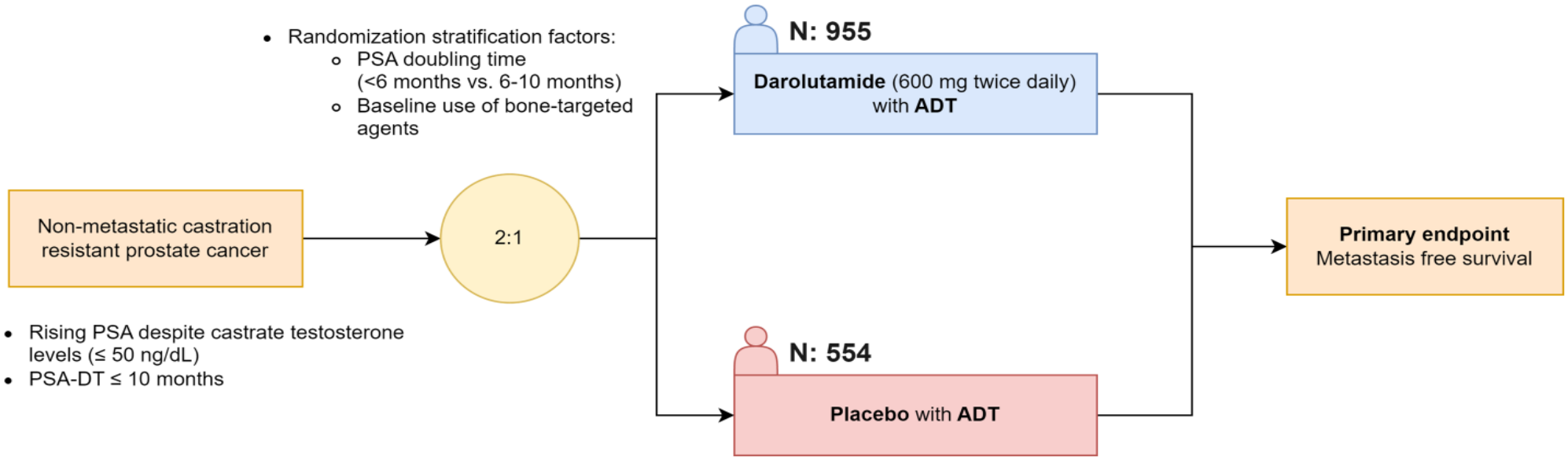


Fig 2. (A) Kaplan-Meier estimates of progression-free survival (PFS); (B) subgroup analyses; (C) Kaplan-Meier estimates of radiographic progression-free survival (rPFS). (A and B) Data for PFS (primary end point). (A) The dashed line indicates the median. (B) Hazard ratios (HRs) are based on a Cox regression model (with treatment as the only covariate) and are relative to bicalutamide, with less than 1.0 favoring enzalutamide. For A and the analysis of all patients in B, the Cox regression model used to estimate the HRs was stratified by disease stage at study entry. (C) Data for the key secondary end point analysis of rPFS in the metastatic subgroup; the dashed line indicates the median. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; M0, nonmetastatic; M1, metastatic; NR, not reached; PSA, prostate-specific antigen.

Enzalutamide nmCRP ve mCRP Benzer etkinliğe sahip

Penson D at al, JCO 2016

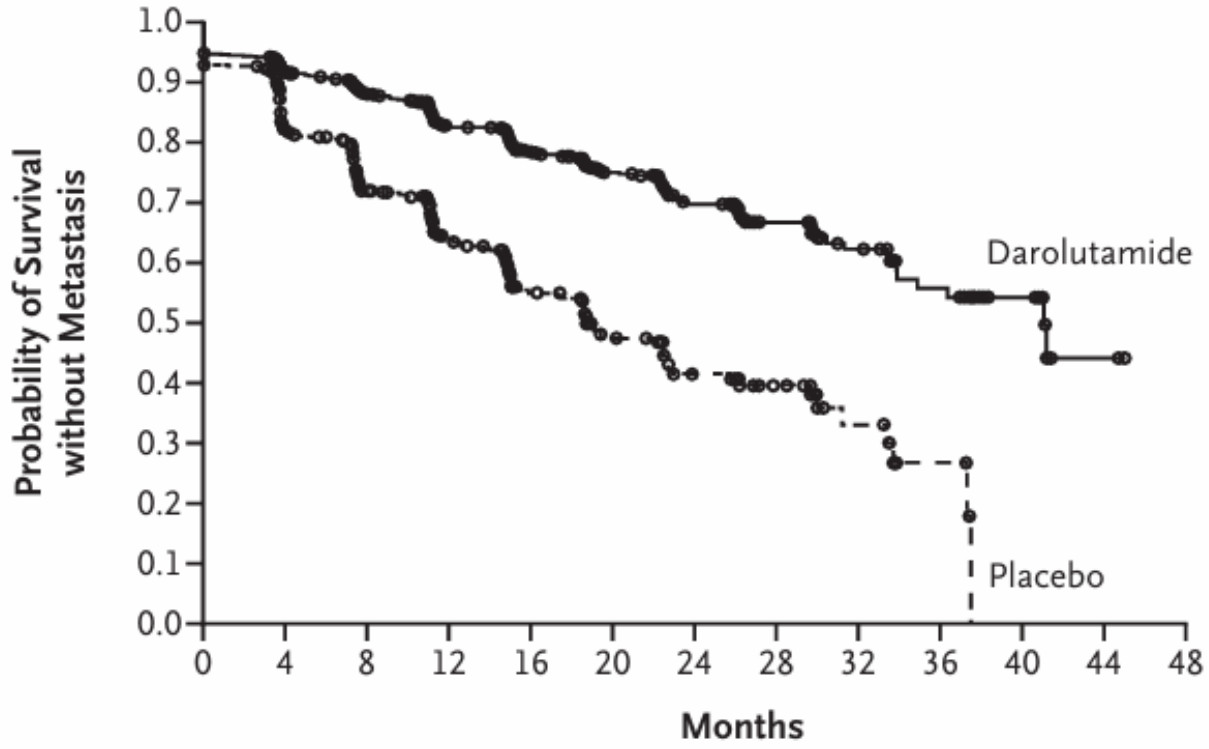
Darolutamide nmCRP etkinliği(ARAMIS)



Fizazi K et al, NEJM 2019

Darolutamide nmCRP etkinliği(ARAMIS)

A Kaplan–Meier Analysis of Metastasis-free Survival



No. at Risk													
Darolutamide	955	817	675	506	377	262	189	116	68	37	18	2	0
Placebo	554	368	275	180	117	75	50	29	12	4	0	0	0

	Median Metastasis-free Survival (95% CI)
	mo
Darolutamide	40.4 (34.3–NR)
Placebo	18.4 (15.5–22.3)

Hazard ratio, 0.41 (95% CI, 0.34–0.50)
P<0.001

Eur Urol 2022 September 8;[Online ahead of print].

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European Association of Urology

Prostate Cancer

Efficacy and Safety of Darolutamide in Patients with Nonmetastatic Castration-resistant Prostate Cancer Stratified by Prostate-specific Antigen Doubling Time: Planned Subgroup Analysis of the Phase 3 ARAMIS Trial

Martin Bögemann[a,*], *Neal D. Shore*[b], *Matthew R. Smith*[c], *Teuvo L.J. Tammela*[d], *Albertas Ulys*[e], *Egils Vjaters*[f], *Sergey Polyakov*[g], *Mindaugas Jievaltas*[h], *Murilo Luz*[i], *Boris Alekseev*[j], *Thierry Lebret*[k], *Martin Schostak*[l], *Frank Verholen*[m], *Marie-Aude Le Berre*[n], *Shankar Srinivasan*[o], *Jorge Ortiz*[o], *Ateesha F. Mohamed*[o], *Toni Sarapohja*[p], *Karim Fizazi*[q]

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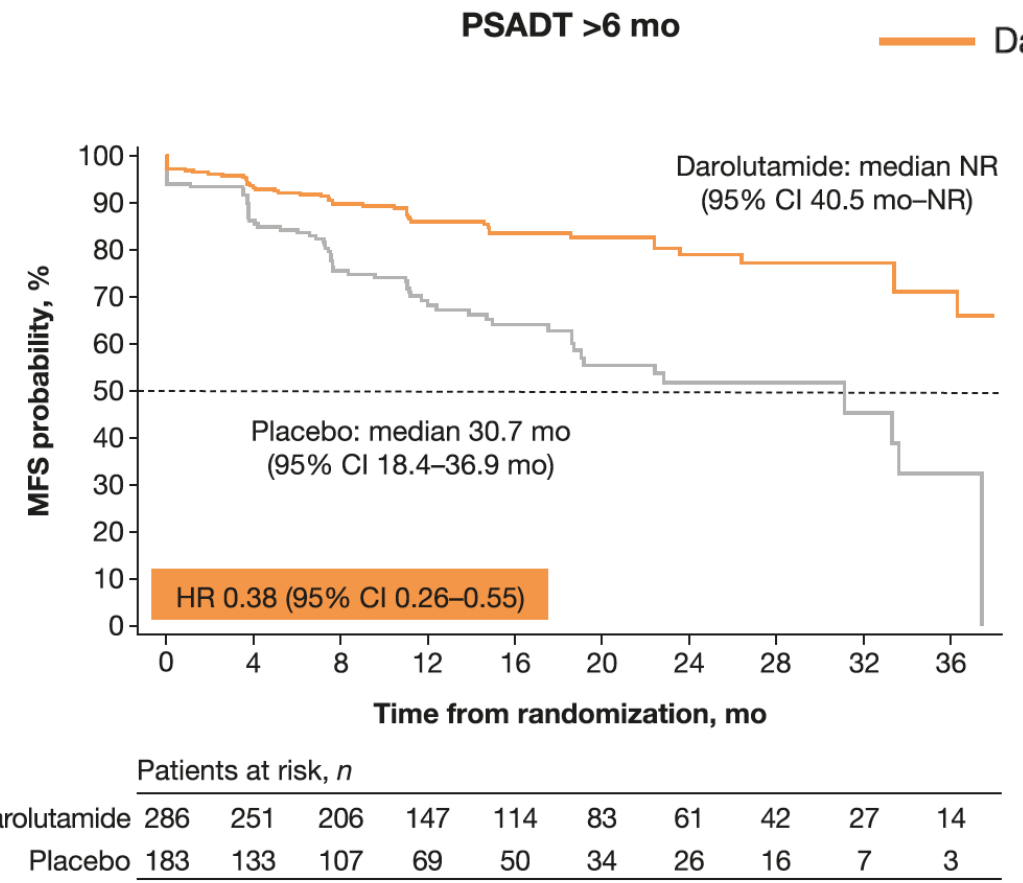
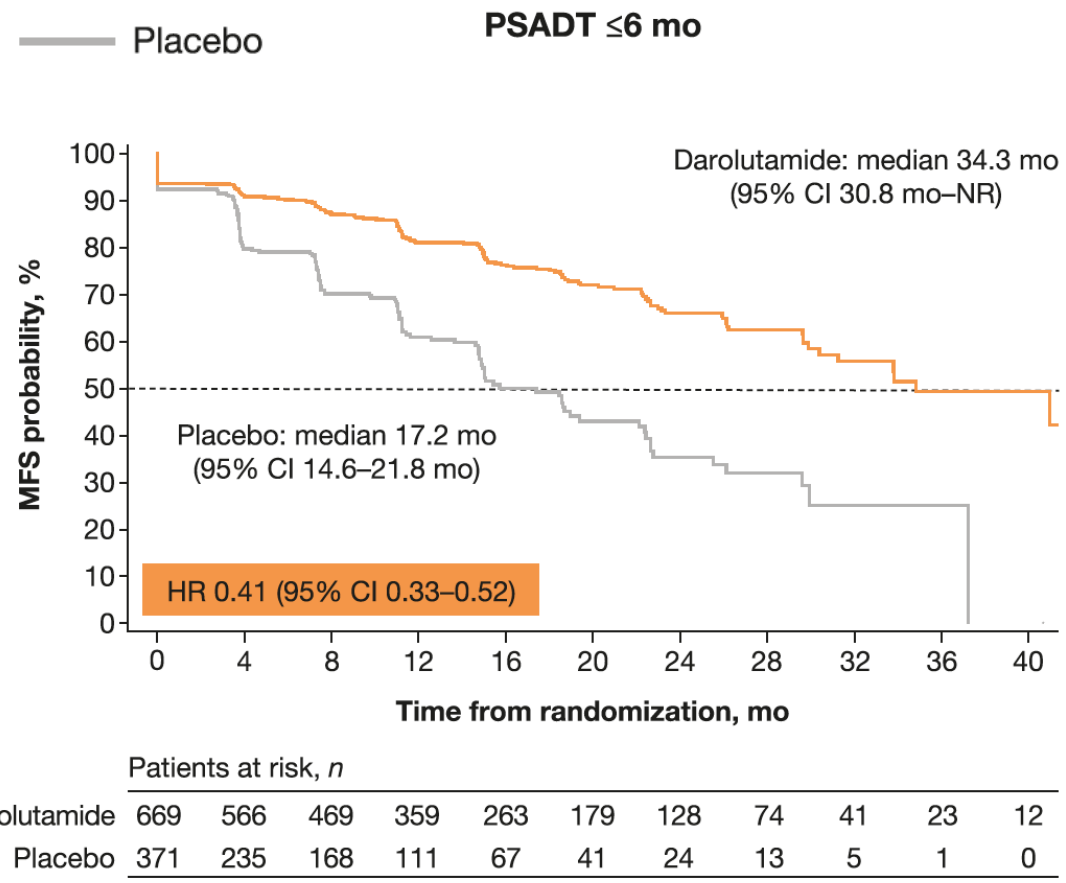
Darolutamide nmCRP PSADT göre etkinliği(ARAMIS)

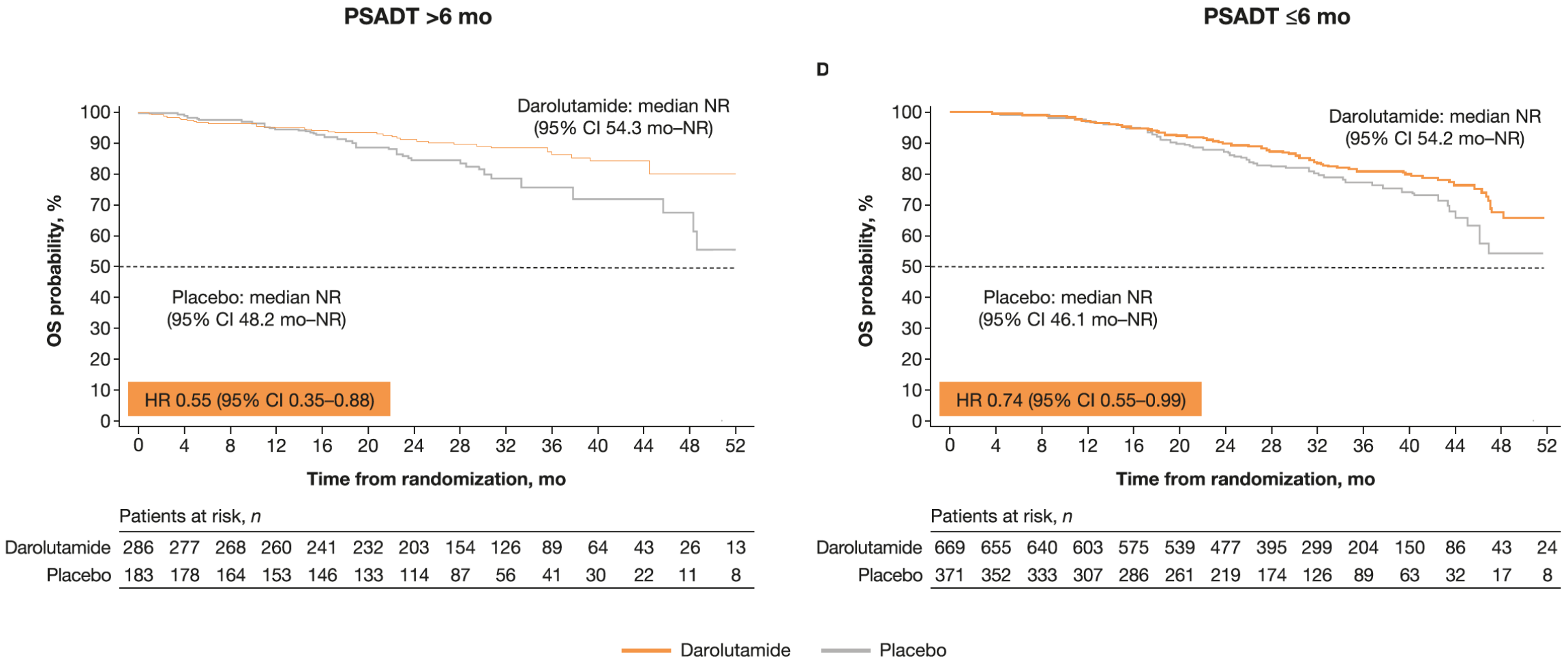




PSADT = prostate-specific antigen doubling time

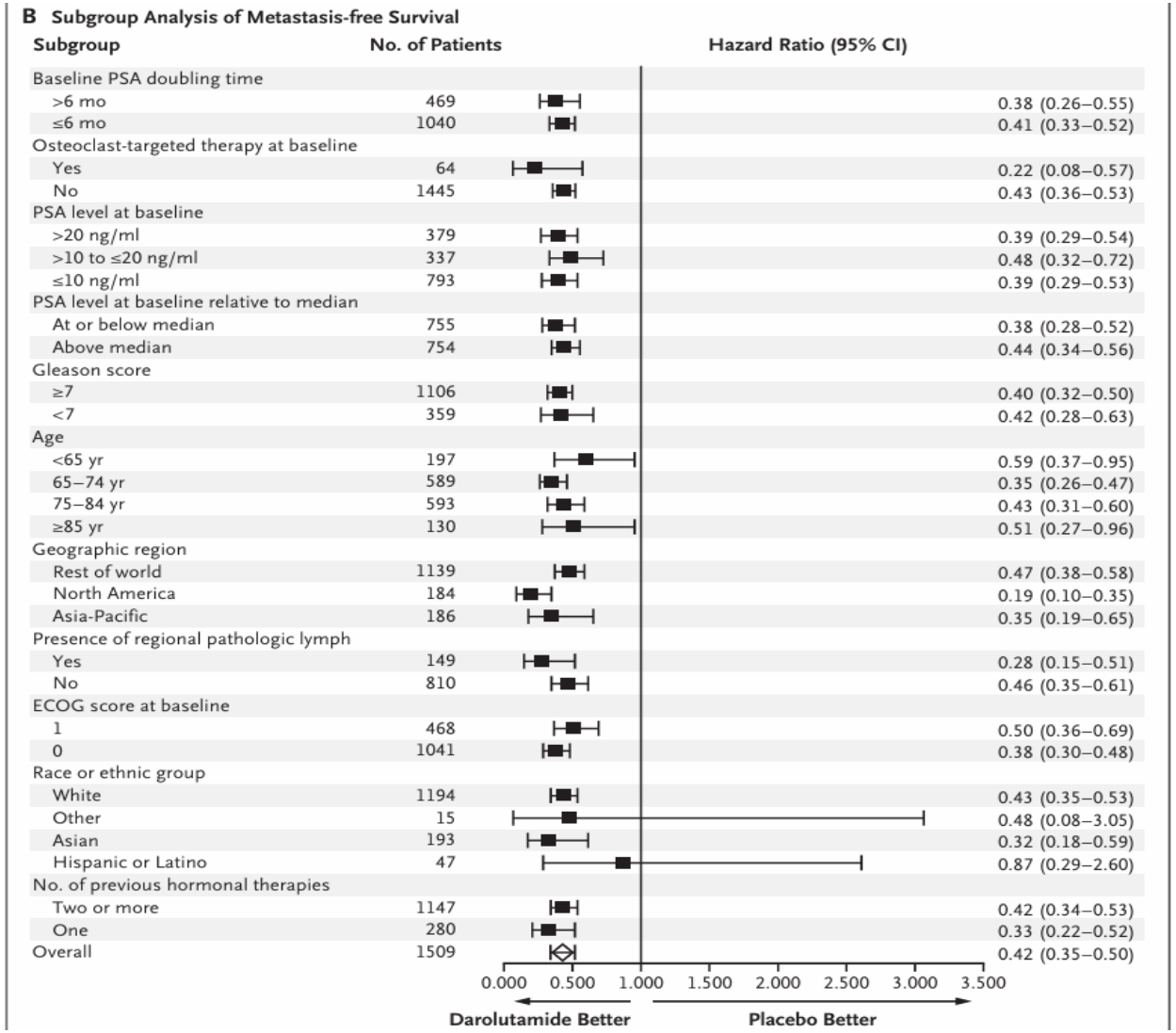
Bogemann M et al. *Eur Urol* 2022 September 8;[Online ahead of print].

Darolutamide nmCRP PSADT göre etkinliği(ARAMIS)



Bogemann M et al. *Eur Urol* 2022 September 8;[Online ahead of print].

Darolutamide nmCRP etkinliği(ARAMIS)



B Subgroup Analysis of Metastasis-free Survival

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Baseline PSA doubling time		
>6 mo	469	0.38 (0.26–0.55)
≤6 mo	1040	0.41 (0.33–0.52)
Osteoclast-targeted therapy at baseline		
Yes	64	0.22 (0.08–0.57)
No	1445	0.43 (0.36–0.53)
PSA level at baseline		
>20 ng/ml	379	0.39 (0.29–0.54)
>10 to ≤20 ng/ml	337	0.48 (0.32–0.72)
≤10 ng/ml	793	0.39 (0.29–0.53)
PSA level at baseline relative to median		
At or below median	755	0.38 (0.28–0.52)
Above median	754	0.44 (0.34–0.56)
Gleason score		
≥7	1106	0.40 (0.32–0.50)
<7	359	0.42 (0.28–0.63)
Age		
<65 yr	197	0.59 (0.37–0.95)
65–74 yr	589	0.35 (0.26–0.47)
75–84 yr	593	0.43 (0.31–0.60)
≥85 yr	130	0.51 (0.27–0.96)
Geographic region		
Rest of world	1139	0.47 (0.38–0.58)
North America	184	0.19 (0.10–0.35)
Asia-Pacific	186	0.35 (0.19–0.65)
Presence of regional pathologic lymph		
Yes	149	0.28 (0.15–0.51)
No	810	0.46 (0.35–0.61)
ECOG score at baseline		
1	468	0.50 (0.36–0.69)
0	1041	0.38 (0.30–0.48)
Race or ethnic group		
White	1194	0.43 (0.35–0.53)
Other	15	0.48 (0.08–3.05)
Asian	193	0.32 (0.18–0.59)
Hispanic or Latino	47	0.87 (0.29–2.60)
No. of previous hormonal therapies		
Two or more	1147	0.42 (0.34–0.53)
One	280	0.33 (0.22–0.52)
Overall	1509	0.42 (0.35–0.50)

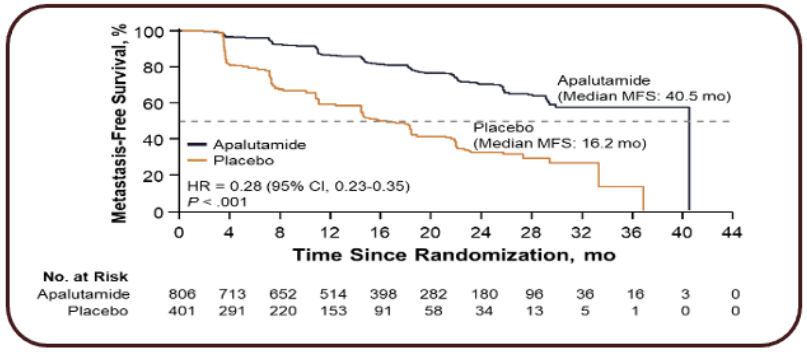
Darolutamide nmCRP yan etki(ARAMIS)

Table 3. Adverse Events.

Adverse Event*	Darolutamide (N=954)		Placebo (N=554)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious adverse event	237 (24.8)	151 (15.8)	111 (20.0)	70 (12.6)
Grade 5 adverse event	37 (3.9)	—	18 (3.2)	—
Adverse event leading to discontinuation of the trial regimen	85 (8.9)	32 (3.4)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhea	66 (6.9)	0	31 (5.6)	1 (0.2)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Constipation	60 (6.3)	0	34 (6.1)	0
Pain in an extremity	55 (5.8)	0	18 (3.2)	1 (0.2)
Anemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0	23 (4.2)	0
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)

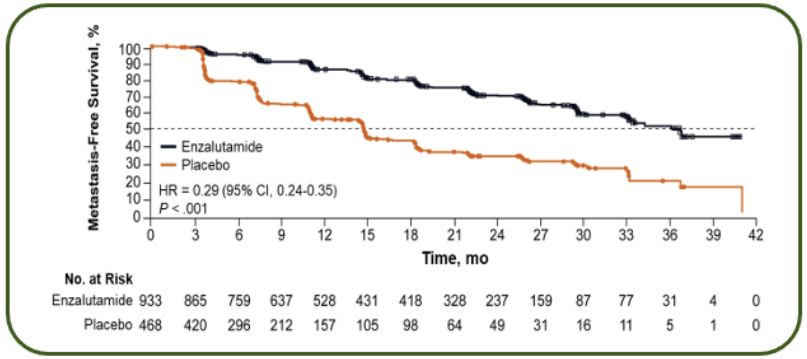
Üç tedavinin: Metastasis Free Survival

SPARTAN
Apalutamide



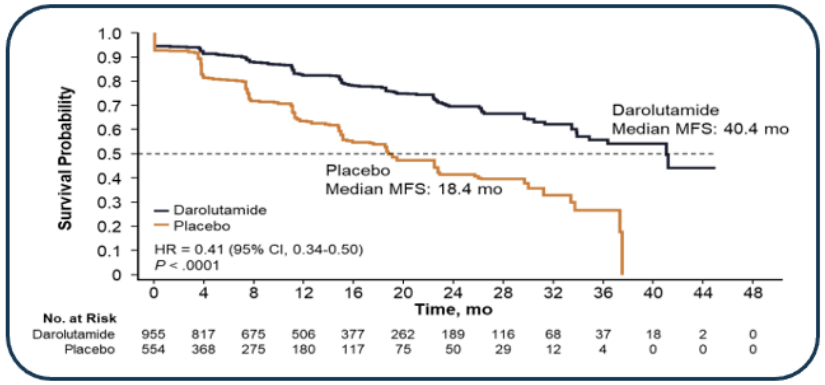
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

PROSPER
Enzalutamide



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 vs PBO 14.7 months
- 22-month MFS benefit

ARAMIS
Darolutamide

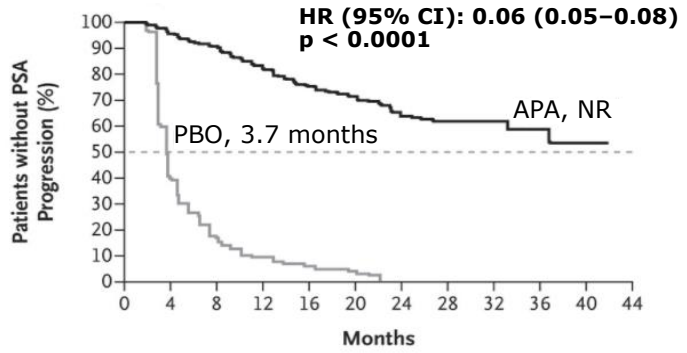


- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

Smith M, et al. *N Engl J Med*. 2018;378:1408-1418. Hussain M, et al. N Engl J Med. 2018;378:2465-2474. Fizazi K, et al. N Engl J Med. 2019;380:1235-1246.

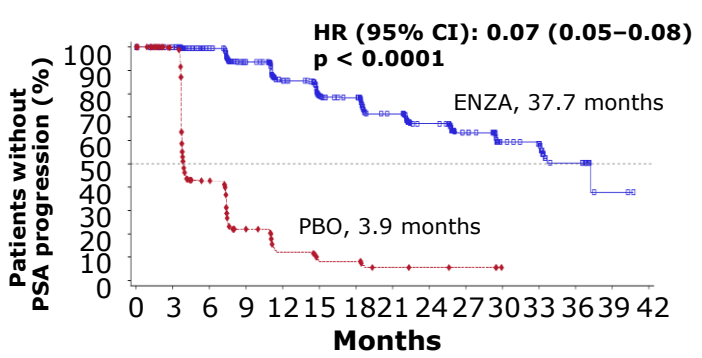
Time to PSA progression (resistance)

SPARTAN[1] (APA)



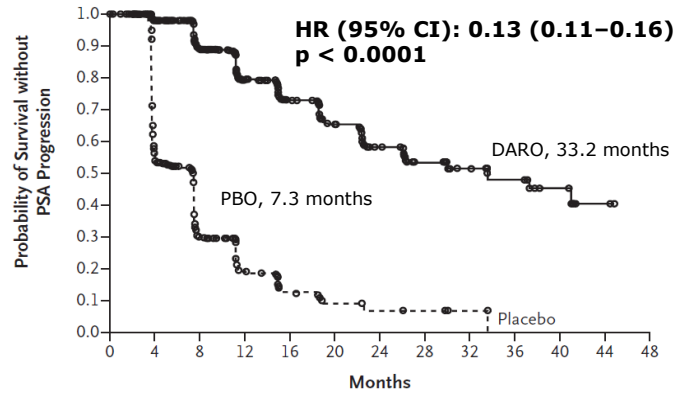
- 94% risk reduction in PSA progression
- TTPP: PBO 3.9 vs APA NR months

PROSPER[2] (ENZA)



- 93% risk reduction in PSA progression
- TTPP: PBO 3.9 vs ENZA 37.7 months

ARAMIS[3] (DARO)



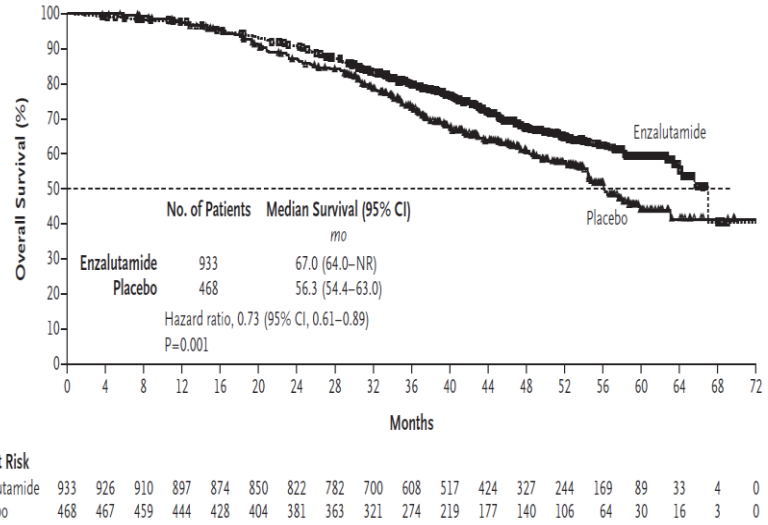
- 87% risk reduction in PSA progression
- TTPP: PBO 7.3 vs DARO 33.2 months

Resistance to therapy much longer than in mCRPC

1. Smith MR, *et al. N Engl J Med.* 2018;378:1408-18. **2.** Hussain M, *et al. N Engl J Med.* 2018;378:2465-74. **3.** Fizazi K, *et al. N Engl J Med.* 2019 Feb 14 [Epub ahead of print].

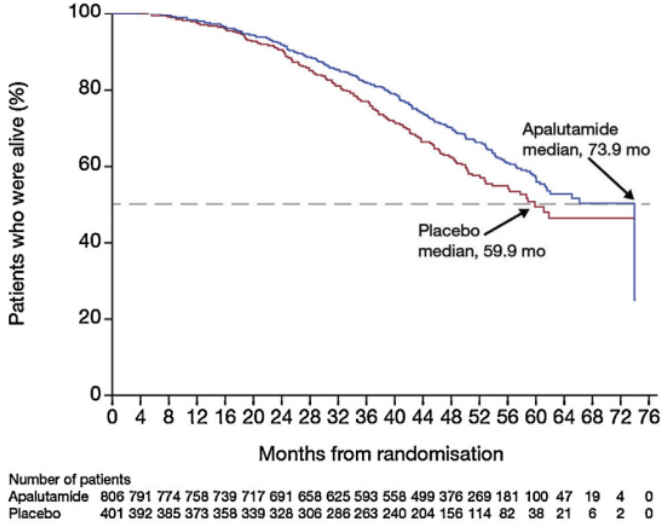
ÜÇ TEDAVİ: UZUN DÖNEM OS SONUÇLARI

PROSPER



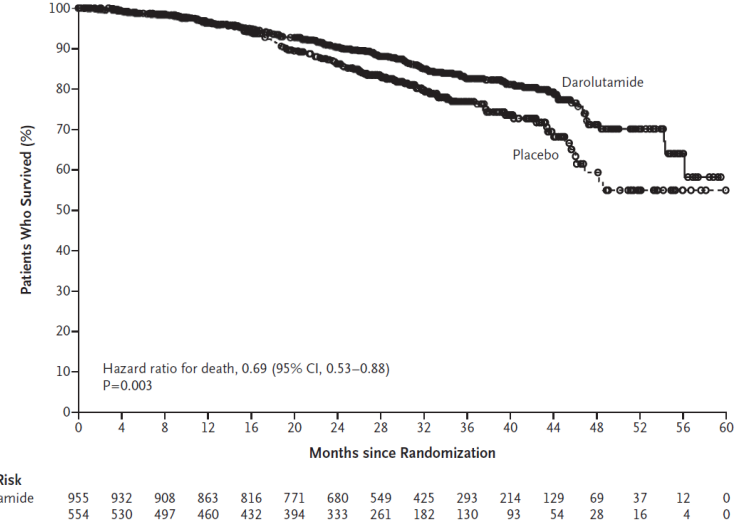
Arms	Overall survival	
	Median OS	HR (95% CI)
Treatment: Enzalutamide Control: ADT	67.0 vs. 56.3 (months)	0.73 (0.61-0.89)
Median Follow up: **48.0 months**		

SPARTAN



Arms	Overall survival	
	Median OS	HR (95% CI)
Treatment: Apalutamide Control: ADT	73.9 vs. 59.9 (months)	0.78 (0.64–0.96)
Median Follow up: **52.0 months**		

ARAMIS



Arms	Overall survival	
	Median OS	HR (95% CI)
Treatment: Darolutamide Control: ADT	NR vs. NR (months)	0.69 (0.53-0.88)
Median Follow up: **29.0 months**		

Sternberg CJ et al, NEJM 2020; Smith MR et al, Eur Urol 2021; Fizazi K et al, NEJM 2020

Recent FDA Approvals of Next-Generation Antiandrogens for Nonmetastatic Castration-Resistant Prostate Cancer

Agent	Approval date	Pivotal study
Darolutamide	July 30, 2020	ARAMIS
Enzalutamide	July 12, 2018	PROSPER
Apalutamide	February 14, 2018	SPARTAN

https://www.fda.gov/drugs/resources-information-approved-drugs/

nmCRP hangi hastalara yoğun tedavi gerekir

Study Name Agent	SPARTAN Apalutamide 240 mg daily	PROSPER Enzalutamide 160 mg daily	ARAMIS Darolutamide 600 mg BID
Design	2:1 apa/placebo	2:1 enza/placebo	2:1 daro/placebo
Number of pts	1207	1401	1509
Inclusion:	PSA DT <10 mo Pelvic LN <2 cm OK	PSA DT ≤10 mo -- bPSA ≥2	PSA DT ≤10 mo Pelvic LN <2cm OK bPSA ≥2
Met Free Surv	40.5 mo vs 16.2 placebo (HR 0.28)	36.6 mo vs 14.7 placebo (HR 0.29)	40.4 mo vs 18.4 placebo (HR 0.41)
Discontinuation	10.6% apa, 7.0% placebo	9% enza, 6% placebo	8.9% daro, 8.7% placebo

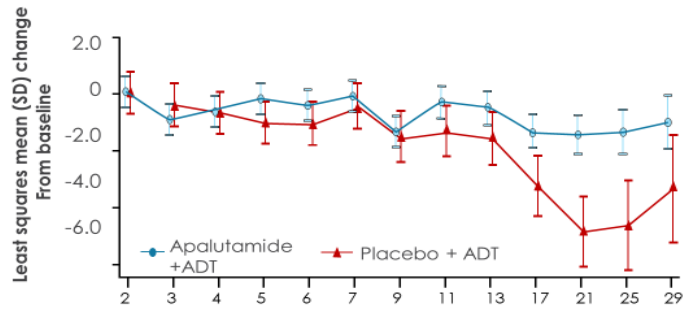
1. Smith MR et al. NEJM 2018; 378:1408-1418
2. Hussain M et al. NEJM 2018; 378:2465-74
3. Fizazi K et al. NEJM 2019; 380:1235-46

Kastrasyona Dirençli nmCRP Yoğun Tedavi Yaşam Kalitesi Sonuçları

Health-Related QoL is Maintained

SPARTAN

FACT-P total score (treatment difference in least squares mean change from baseline)

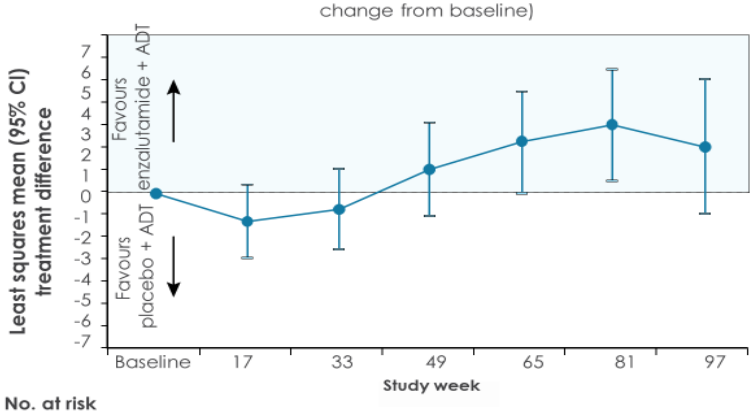


No. of patients in each cycle

APA + ADT	787	769	750	732	707	689	657	631	598	486	373	274	179
PBO + ADT	390	382	376	358	339	289	276	255	208	181	99	62	44

PROSPER

FACT-P total score (treatment difference in least squares mean change from baseline)

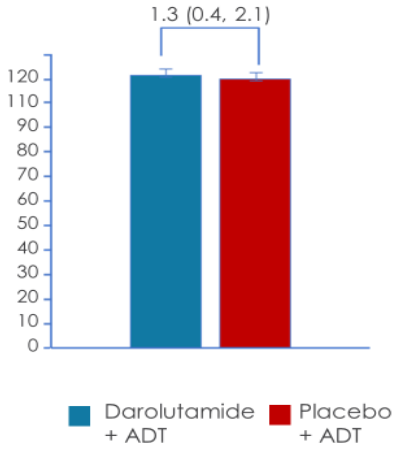


No. at risk

ENZA + ADT	...	815	718	621	522	427	354
PBO + ADT	...	403	329	239	183	139	90

ARAMIS

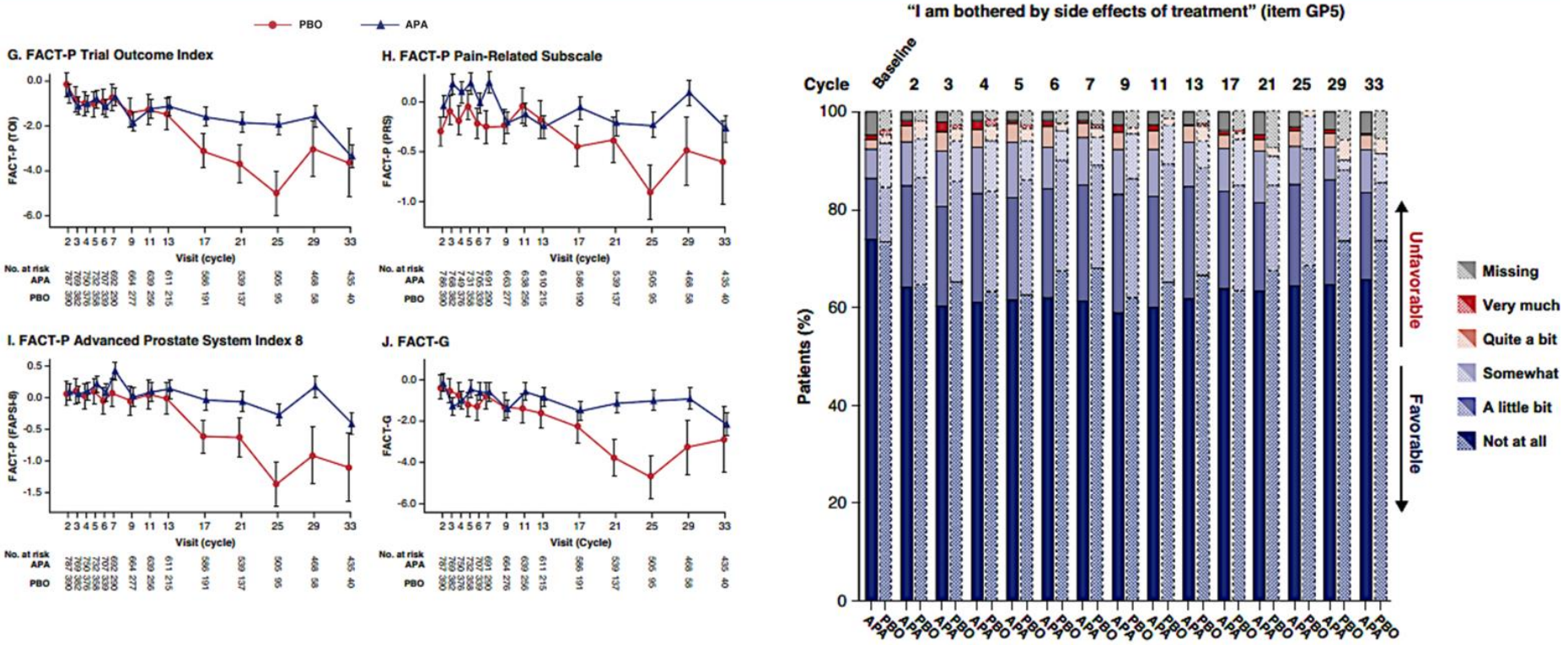
FACT-P total score (difference with placebo)



Saad F, et al. *Lancet Oncol* 2018;19:1404-1416;
Tombal B, et al. *Lancet Oncol* 2019;20:556-559;
Fizazi K, et al. *N Engl J Med* 2019;380:1235-1246. [Epub ahead of print](Supplement Appendix)

Apalutamide nmCRP etkinliği(SPARTAN)
Yaşam kalitesi sonuçları

Long-term results from nmCRPC trials: SPARTAN (apalutamide)



Oudard S et al. Eur Urol Focus 2022; 8:958-67

Darolutamide nmCRP etkinliği(ARAMIS)
Yaşam Kalitesi Sonuçları

Long-term safety and tolerability of darolutamide: ARAMIS

Table 1. Treatment-emergent adverse events during long-term darolutamide treatment.

Treatment-emergent adverse events (TEAEs),[a] *n* (%)	Total: Darolutamide >2 years (*n* = 13)	Darolutamide >2 and ≤4 years (*n* = 7)	Darolutamide >4 years (*n* = 6)
Any TEAE	13 (100)	7 (100)	6 (100)
Worst grade			
1 or 2	7 (54)	6 (86)	1 (17)
3	6 (46)	1 (14)	5 (83)
Serious TEAE	6 (46)	2 (29)	4 (67)
TEAE leading to discontinuation of darolutamide	1 (8)	1 (14)	0
Any drug-related TEAE	5 (38)	3 (43)	2 (33)
Worst grade			
1 or 2	5 (38)	3 (43)	2 (33)
3	0	0	0
Serious drug-related TEAE	0	0	0
Drug-related TEAE leading to discontinuation of darolutamide	0	0	0
Most common TEAEs (occurring in ≥3 patients)[b]			
Diarrhea	5 (38)	2 (29)	3 (50)
Abdominal pain	4 (31)	2 (29)	2 (33)
Nausea	4 (31)	2 (29)	2 (33)
Arthralgia	3 (23)	1 (14)	2 (33)
Fatigue	3 (23)	2 (29)	1 (17)
Hematuria	3 (23)	1 (14)	2 (33)
Influenza	3 (23)	1 (14)	2 (33)

[a]Treatment-emergent adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[b]All TEAEs were grade 1 or 2 except 1 event each of grade 3 nausea and grade 3 hematuria.

Very small subset of patients

No new safety signals emerged

No DEXA data

Jones RH et al. Prost Ca Prost Dis 2023; 1-4

ÜÇ TEDAVİNİN YAN ETKİLERİ

Safety	SPARTAN[1,2,3]		PROSPER[4]		ARAMIS[5]	
	APA (n = 803)	PBO (n = 398)	ENZA (n = 930)	PBO (n = 465)	DARO (n = 954)	PBO (n = 554)
Any AE, n (%)	781 (97)	373 (94)	876 (94)	380 (82)	818 (85.7)	439 (79.2)
Any serious AE, n (%)	290 (36)	99 (25)	372 (40)	100 (22)	249 (26.1)	121 (21.8)
AE leading to discontinuation, %	15.0	7.3	17.0	9.0	8.9	8.7
AE leading to death, n (%)	24 (3.0)	2 (0.5)	51 (5.0)	3 (1.0)	38 (4.0)	19 (3.4)
AE (all grades), %						
Fatigue	31.9†	21.4†	37	16	13.2	8.3
Hypertension	27.6†	20.9†	18.0	6.0	7.8	6.5
Rash	26.0	6.3	4	3	3.1	1.1
Falls	22.0	9.5	18.0	5.0	5.2	4.9
Fractures	18.0	7.5	18	6	5.5	3.6
Mental impairment disorder#	5.1§	3.0§	8.0	2.0	2.0	1.8

#SPARTAN: disturbance in attention, memory impairment, cognitive disorder and amnesia; PROSPER: as per SPARTAN trial with the addition of Alzheimer's disease, mental impairment, vascular dementia and senile dementia; ARAMIS trial: cognitive disorder, memory impairment and change in mental status; § Data taken from first interim analysis as placebo group not reported in final analysis[1] ; † Data taken from second interim analysis as placebo group not reported in final analysis[2]

AE, adverse event; APA, apalutamide; DARO, darolutamide; ENZA, enzalutamide; NA, not available; PBO, placebo

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Small EJ, et al. Annals of Oncology 2019; 30: 1813-1820; 3. Smith MR, et al. Eur Urol. 2020; https://doi.org/10.1016/j.eururo.2020.08.011; 4. Sternberg CN, et al. N Engl J Med. 2020;382: 2197-206; 5. Fizazi K, et al. N Engl J Med. 2020; 383: 1040-1049

Courtesy of Tanya B Dorff, MD

ÜÇ TEDAVİNİN YAN ETKİLERİ

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Courtesy of Tanya B Dorff, MD

Kastrasyona Dirençli nmCRP Yoğun Tedavi İskelet İlişkili Olaylar

Table 1 Falls, fractures, and other bone-related AEs in phase 3 trials for ARIs.

Study	Drug	Treatment arm			Placebo arm		
		Falls[a] *n* (%)	Fractures *n* (%)	Other[b] *n* (%)	Falls[a] *n* (%)	Fractures *n* (%)	Other[b] *n* (%)
SPARTAN (*N* = 1207) [15]	Apalutamide	125 (15.6)	94 (11.7)	NR	36 (9.0)	26 (6.5)	NR
ARAMIS (*N* = 1509) [17]	Darolutamide	40 (4.2)	40 (4.2)	139 (14.6)	26 (4.7)	20 (3.6)	68 (12.2)
PROSPER (*N* = 1401) [16, 28]	Enzalutamide	106 (11)	91 (10)	73 (8)	19 (4)	23 (5)	33 (7)

AE adverse event, *ARI* androgen receptor inhibitor, *NR* not reported.

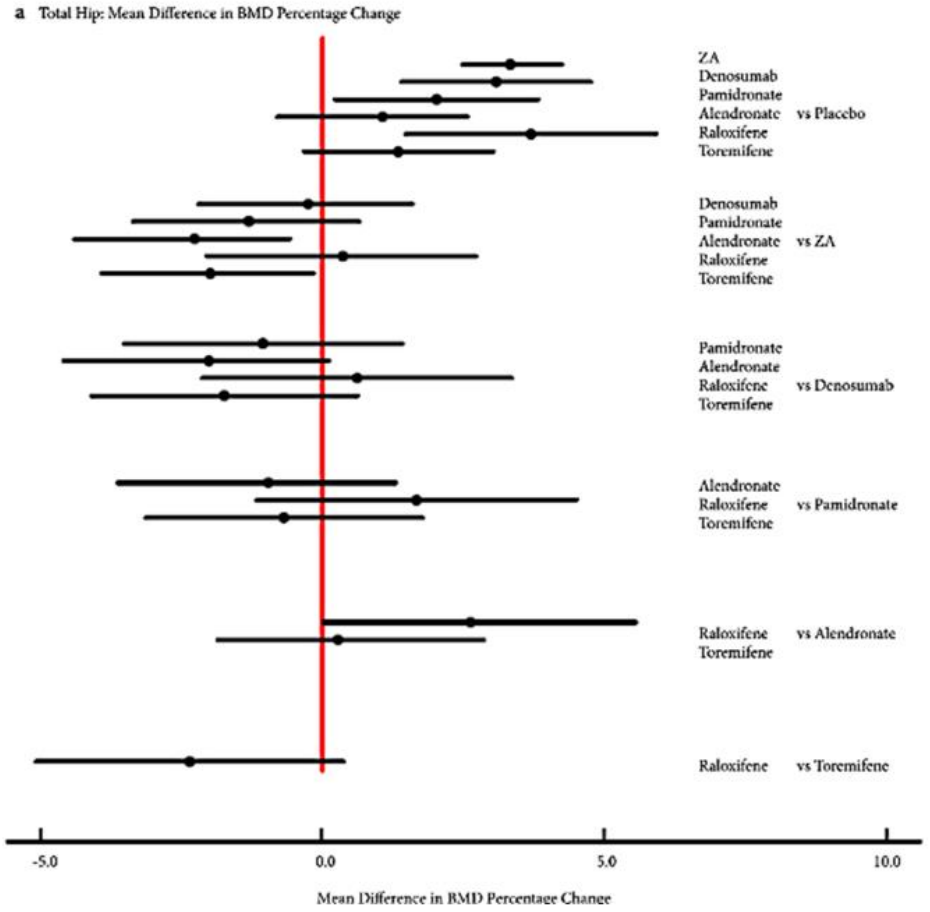
[a]In SPARTAN, falls were deemed treatment-related by the investigators. In ARAMIS, falls included events recorded as accidents, and were determined to have been accidental falls.

[b]Other includes back pain in PROSPER, and back pain or pain in an extremity in ARAMIS.

Management strategies:

- Vitamin D +/- Calcium
- Exercise
- Regular screening by DEXA
- Bone support agents

Hussain A et al. PCAN 2021; 24:290-300



Poon Y et al. BJUI 2018; 121:17-28

Prostate Cancer and Prostatic Diseases www.nature.com/pcan

Prostate Cancer Prostatic Dis 2022 October 8;[Online ahead of print].

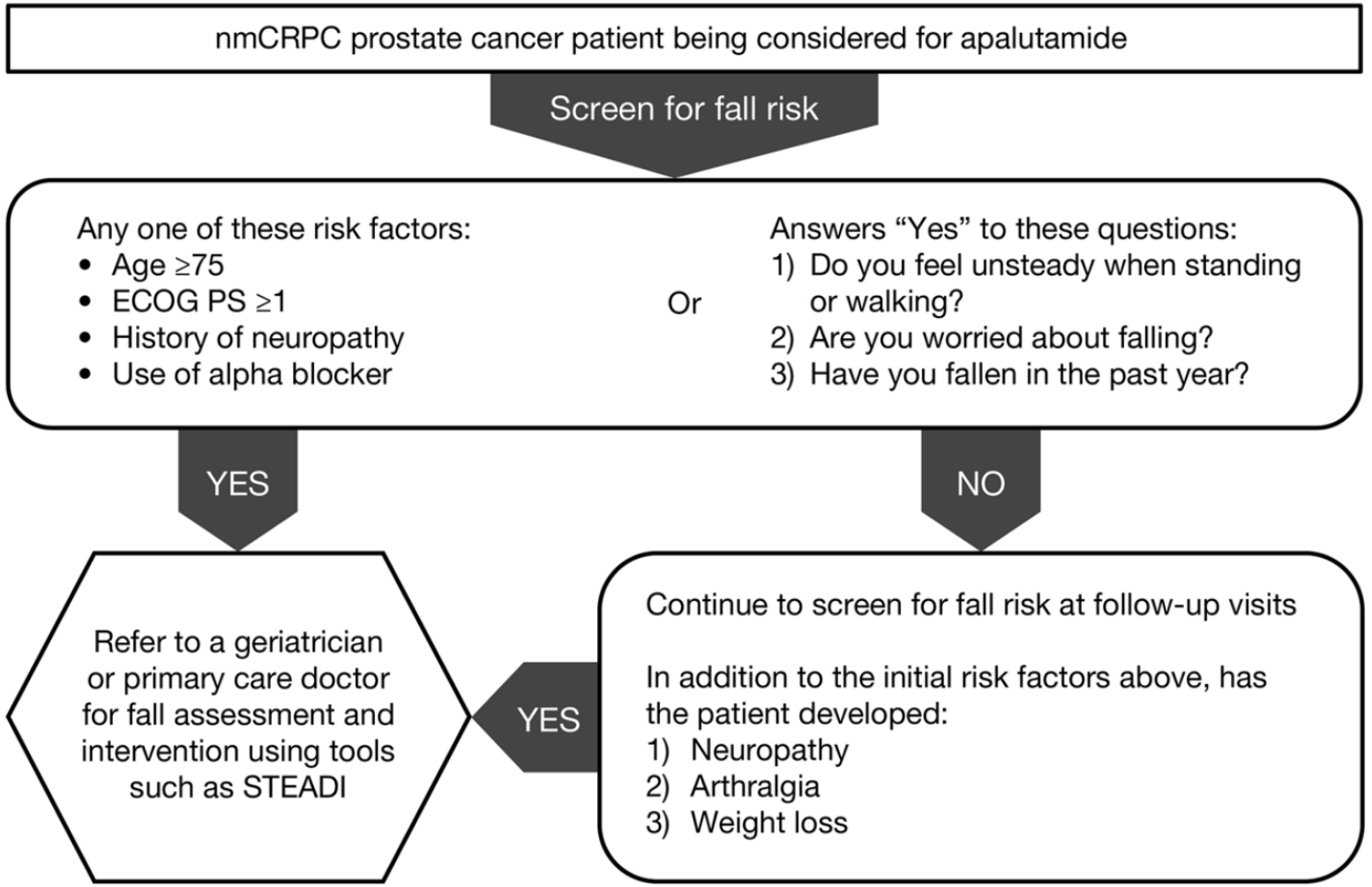
ARTICLE

Clinical Research

Clinical characteristics associated with falls in patients with non-metastatic castration-resistant prostate cancer treated with apalutamide

YaoYao Pollock[1,16]✉, Matthew R. Smith[2], Fred Saad[3], Simon Chowdhury[4], Stéphane Oudard[5], Boris Hadaschik[6], David Olmos[7], Ji Youl Lee[8], Hiroji Uemura[9], Amitabha Bhaumik[10], Anil Londhe[10], Brendan Rooney[11], Sabine D. Brookman-May[12,13], Peter De Porre[14], Suneel D. Mundle[15] and Eric J. Small[1]

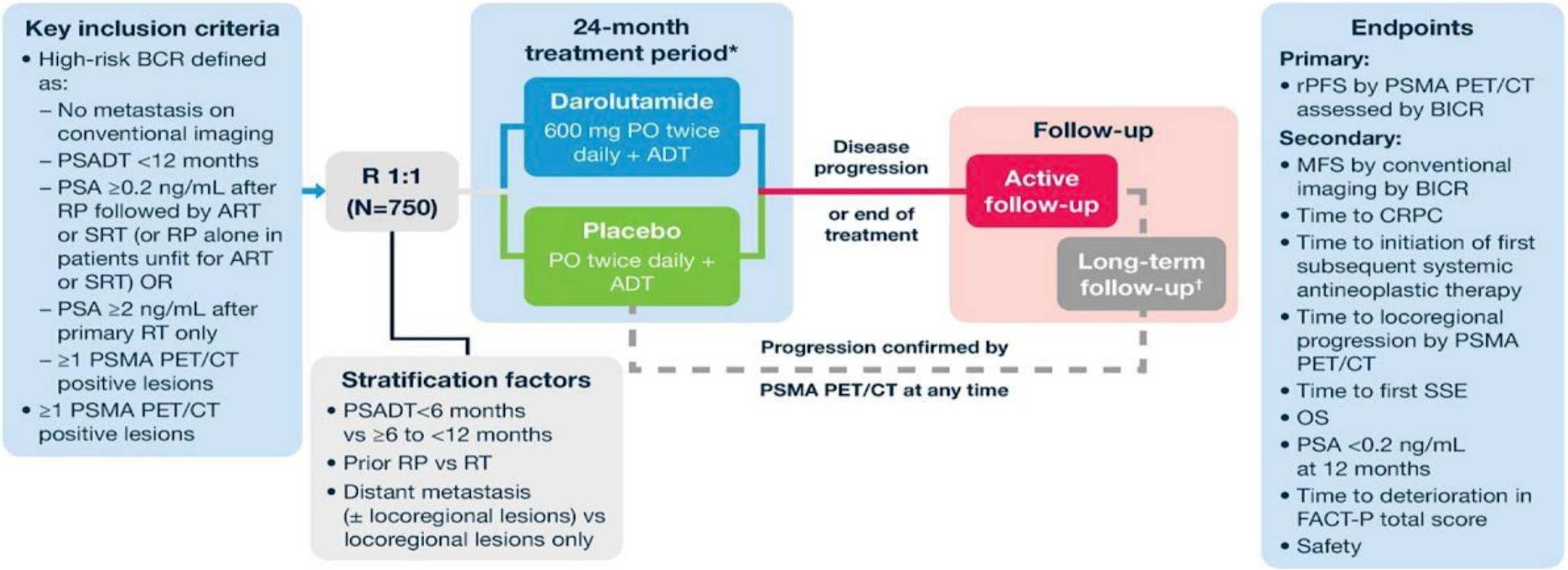
Fall Risk Screening Diagram



Pollock YY et al. *Prostate Cancer Prostatic Dis* 2022 October 8;[Online ahead of print].

Gelecek Perspektif

ARASTEP: Phase 3 Trial of Darolutamide in nmCSPC

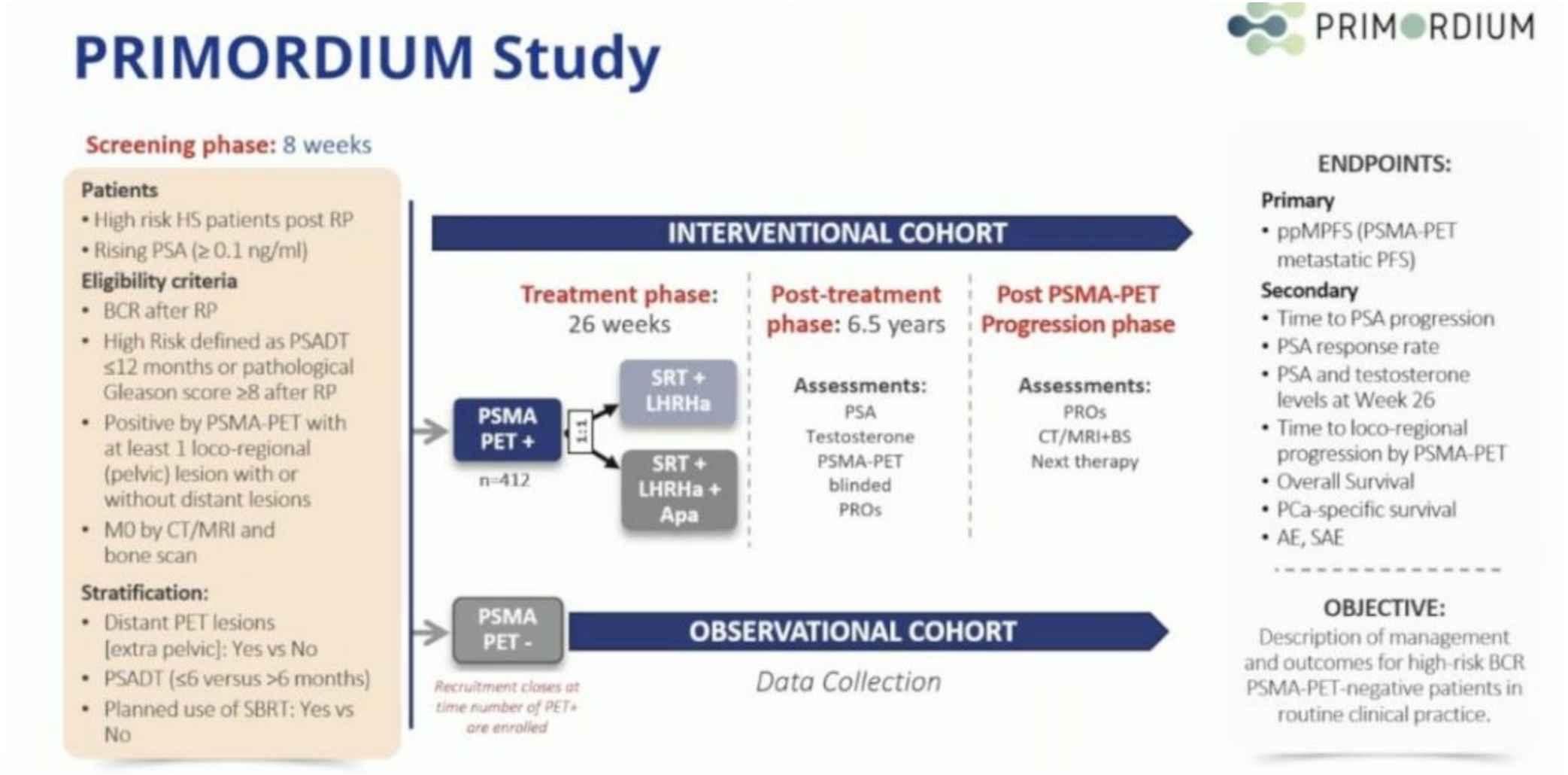


Gelecek Perspektif
Kastrasyona Duyarlı Lokalize Yüksek Riskli PSA Nüksü

EMBARK and PRESTO at a glance

	EMBARK (n=1068)	PRESTO (n=503)
Inclusion	PSA DT ≤9 mo PSA ≥2 post RT or ≥1 post RRP	PSA DT ≤9 months PSA >0.5
Arms	A) Leuprolide B) Leuprolide + Enzalutamide C) Enzalutamide	A) Degarelix (or LHRH agonist) B) Degarelix + Apalutamide C) Degarelix + Apalutamide + Abiraterone
Treatmt duration	36 weeks (stop if PSA <0.2)	1 year
Baseline PSA	Median 5-5.5 (1-308) 50% had RRP + salvage RT 30% had prior ADT	Median 1.8 (1-3.6) 100% had RRP, 85% salvage RT 42% had prior ADT
Primary Endpt result	5 year MFS (A vs B) 87.3% vs 71.4% HR 0.42 (0.30-0.61)	PSA PFS (incr by 25%, >2 ng/dL) A vs B 24.9 mo vs 20.3 HR 0.52 (0.35-0.77)

Gelecek Perspektif
Kastrasyona Duyarlı Yüksek Riskli PSA Nüksü



PSMA-PET nmCRP tedavisini nasıl değiştirir

Precision Medicine and Imaging

Clinical Cancer Research

Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose: Systemic androgen-signaling inhibition added to ongoing androgen-deprivation therapy (ADT) improved clinical outcomes in patients with nonmetastatic castration-resistant prostate cancer without detectable metastases by conventional imaging (nmCRPC). Prostate-specific membrane antigen ligand positron emission tomography (PSMA-PET) detects prostate cancer with superior sensitivity to conventional imaging, but its performance in nmCRPC remains largely unknown. We characterized cancer burden in high-risk patients with nmCRPC using PSMA-PET.

Experimental Design: We retrospectively included 200 patients with nmCRPC, prostate-specific antigen (PSA) >2 ng/mL, and high risk for metastatic disease [PSA doubling time (PSADT) of ≤10 months and/or Gleason score of ≥8] from six high-volume PET centers. We centrally reviewed PSMA-PET detection rate for pelvic disease and distant metastases (M1). We further evaluated SPARTAN patients stratified by risk factors for PSMA-PET-detected M1 disease.

Results: PSMA-PET was positive in 196 of 200 patients. Overall, 44% had pelvic diseases, including 24% with local prostate bed recurrence, and 55% had M1 disease despite negative conventional imaging. Interobserver agreement was very high (κ: 0.81–0.91). PSA ≥ 5.5 ng/mL, locoregional nodal involvement determined by pathology (pN1), prior primary radiation, and prior salvage radiotherapy independently predicted M1 disease (all $P < 0.05$).

Conclusions: PSMA-PET detected any disease in nearly all patients and M1 disease in 55% of patients previously diagnosed with nmCRPC, including subgroups with PSADT of ≤10 months and Gleason score of ≥8. The value of PSMA-PET imaging for treatment guidance should be tested in future studies.

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Table 1. Patient characteristics

	All PSMA-PET patients ($N = 200$)	PSADT of ≤10 months ($n = 115$)	Gleason score ≥8 only ($n = 85$)	SPARTAN ($N = 1,207$)
Age (years)				
Median (range)	71 (46–94)	71 (46–94)	73 (48–86)	74 (48–97)
Prostate-specific antigen (ng/mL)				
Median (range)	5.3 (1.3[a]–263.8)	5.2 (1.3[a]–263.8)	5.4 (2.0–99.1)	7.8 (0.1–294.8)
Prostate-specific antigen doubling time (months)	$n = 132$		$n = 17$	
Median (range)	4.0 (0.0–90.0)	3.6 (0.0–10.0)	Not applicable	4.4 (0.7–10.0)
≤6	85 (64)	85 (74)	Unknown	860 (71)
>6	47 (36)	30 (26)	17 (100)	347 (29)
Gleason score	$n = 193$	$n = 108$		$n = 1171$
<8	42 (22)	42 (39)	0 (0)	661 (56)
≥8	151 (78)	66 (61)	85 (100)	510 (44)
Prior therapy				
Prior prostate cancer–related surgery	130 (65)	79 (69)	51 (60)	682 (57)
Prior prostate cancer–related radiotherapy	104 (52)	69 (60)	35 (41)	696 (58)

NOTE: Data are number of patients (%) unless otherwise indicated.

[a]Two eligible patients had prostate-specific antigen ≤2 ng/mL at time of PSMA-PET.

SPARTAN, PROSPER, ARAMIS benzer hasta özeliklerine sahip 200 hastanın verileri ; hastaların %55 metastatik

SPARTAN, PROSPER, ARAMIS benzer hasta özeliklerine sahip 200 hastanın verileri ; hastaların %55 metastatik

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Table 2. Stage categorized by PSMA-PET PROMISE criteria (16)

miTNM stage, *n* (%)	All patients (*N* = 200)	PSADT of ≤10 months (*n* = 115)	Gleason score of ≥8 only (*n* = 85)
M0	**91 (46)**	**48 (42)**	**43 (51)**
T0N0M0	4 (2)	4 (3)	0 (0)
TrN0M0	48 (24)	22 (19)	26 (31)
T0N1M0	13 (7)	11 (10)	2 (2)
TrN1M0	26 (13)	11 (10)	15 (18)
M1	**109 (55)**	**67 (58)**	**42 (49)**
T0N0M1	31 (16)	15 (13)	16 (19)
TrN0M1	9 (5)	6 (5)	3 (4)
T0N1M1	42 (21)	30 (26)	12 (14)
TrN1M1	27 (14)	16 (14)	11 (13)
Extrapelvic disease[a]			
M1a (lymph node)	77 (39)	51 (44)	26 (31)
M1b (bone)	47 (24)	26 (23)	21 (25)
M1c[b] (visceral)	12[b] (6)	8 (7)	4 (5)
N/M disease extent			
Unifocal (1)	29 (15)	19 (17)	10 (12)
Oligometastatic (2–3)	28 (14)	16 (14)	12 (14)
Multiple/disseminated (≥4)	91 (46)	54 (47)	37 (44)

NOTE: Numbers in boldface represent the total.
Abbreviations: miTNM, molecular imaging TNM; TNM, tumor, nodes, metastases; Tr, local recurrence in the prostate bed.
[a]PROMISE allows patients to be counted under multiple M1 categories.
[b]Lung (*n* = 4), liver (*n* = 5), peritoneum (*n* = 4), and connective tissue (*n* = 1) with overlap.

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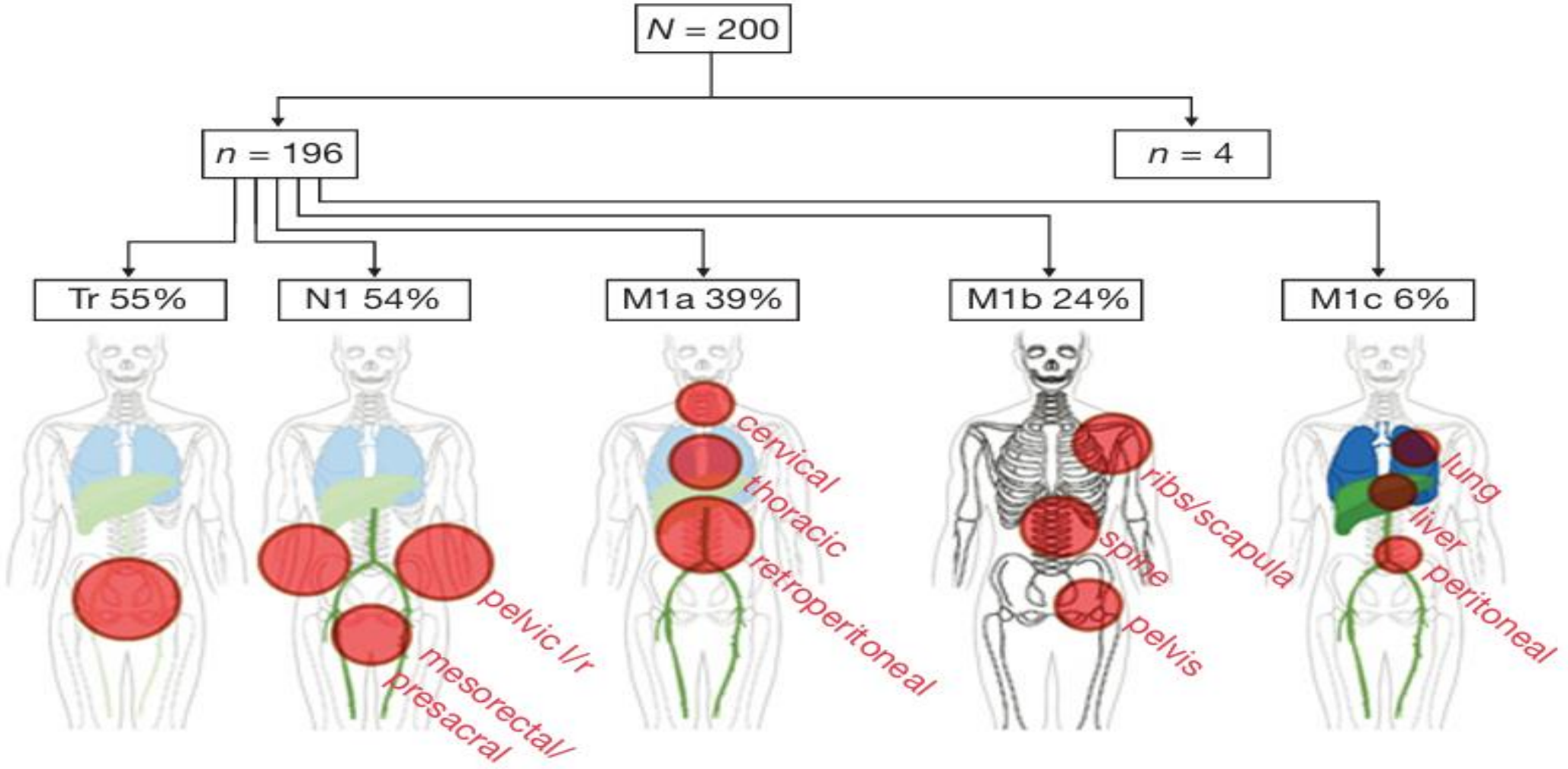
PSMA-PET nmCRP tedavisini nasıl değiştirir



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PSMA-PET nmCRP tedavisini nasıl değiştirir

Table 4. Multivariable analysis of odds for PSMA-PET M1 disease ($n = 200$)

Variable	*n* (%)	OR	95% CI	*P*
Age ≥65 years	151 (76)	0.6	0.3–1.3	0.23
Gleason score of ≥8	151 (76)	1.1	0.5–2.3	0.80
PSA ≥5.5 ng/mL	97 (49)	2.0	1.1–3.6	0.03[a]
PSADT of ≤6 months ($n = 132$[b])	85 (43)	1.6	0.8–3.3	0.22
Locoregional disease pN1	45 (23)	2.7	1.3–6.0	0.01[a]
RPE and SRT	40 (20)	4.6	2.0–11.0	<0.01[a]
PRT	64 (32)	3.1	1.5–6.1	0.02[a]

Abbreviations: PRT, primary radiotherapy; RPE, radical prostatectomy; SRT, salvage radiotherapy.

[a]$P < 0.05$.

[b]On the basis of univariate analysis.

Nüks ile ilişkili parametreler: PSA düzeyi, PSADT, Lokal hastalık için aldığı tedaviler

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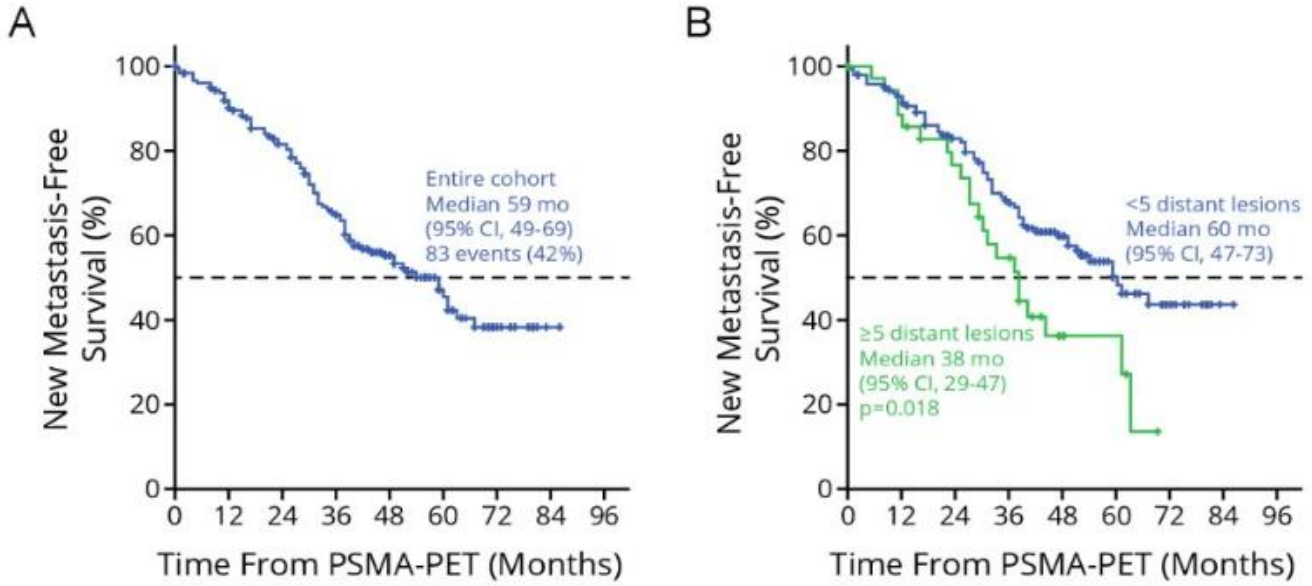
The median new metastases-free survival was significantly shorter in patients with polymetastatic disease (5+ lesions: 38 months versus <5 lesions: 60 months):

FIGURE 2: nMFS in the entire cohort (A) and in patients stratified by number of extrapelvic metastases by PSMA-PET (B)



SPARTAN, PROSPER, ARAMIS benzer hasta özeliklerine sahip 200 hastanın verileri ; hastaların %55 metastatik, polimetastaz olanlar daha kötü seyirli

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PSMA-PET nmCRP tedavisini nasıl değiştirir

Subgroup (N=200)	N (%)	OS	
		HR (95% CI)	p
Age <65 y	49 (25)	0.97 (0.52-1.81)	0.92
Gleason grade ≥8	151 (76)	1.41 (1.77-2.58)	0.27
pN1	45 (23)	2.01 (1.17-3.45)	**0.012***
Prior definitive RT	64 (32)	1.58 (0.93-2.70)	0.092
Prior salvage RT	40 (20)	0.64 (0.31-1.31)	0.22
PSA ≥5.5 mg/dL	97 (49)	1.29 (0.76-2.19)	0.34
PSADT ≤6	85[a] (64)	0.87 (0.45-1.66)	0.66
Extrapelvic disease, any	109 (55)	1.41 (0.83-2.40)	0.21
Extrapelvic disease, ≥5 lesions	37 (19)	1.93 (1.08-3.46)	**0.027***

[a]n=132, *p<0.05.

SPARTAN, PROSPER, ARAMIS benzer hasta özeliklerine sahip 200 hastanın verileri ; pN1 ve extrapelvik ≥ 5 lezyon kötü gidişle ilişkili

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Sonuç

- nmCRP sağkalım sonuçları Kastrasyona duyarlı metastatik prostat ca ile benzer
- nmCRP kanserinde yoğun tedavi için primer prognostik ve prediktif faktör PSDBT 10 ay ≤
- ARAMIS, PROSPER, SPARTAN benzer MFS ve OS
- Tedavi kararında etkili faktör hasta özeliklerine bağlı uzun dönem kulanım ile ilişkili toksisite
- PSMA-PET CT ile aynı grup hastaları > %50 fazlasında metastaz
- Klinik lenf nodu pozitifliği, bazal PSA değerinin yüksek olması, PSA double time ≤ 6 ay olanlarda metastaz oranı yüksek
- PSA nüksü olan kastrasyona duyarlı yüksek riskli grupta EMBARK, PRESTO çalışmaları ile yeni nesil AR yolağı inhibitörleri bu evreye taşımıştır.