

Prostate-Specific Antigen Response and Long-Term Outcomes in PROTEUS: Perioperative Apalutamide Plus Androgen Deprivation Therapy in Patients With High-Risk Localized/ Locally Advanced Prostate Cancer

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Key Takeaway

Perioperative APA + ADT resulted in high rates of ultra-low (<0.02 ng/mL) PSA response. In patients receiving APA + ADT, ultra-low PSA at 3 months post EOT was significantly associated with improved long-term outcomes, including a 67% reduced risk of metastasis or death, a 50% lower risk of BCF, recurrence, metastasis, or death. Ultra-low PSA at Cycle 9 (3 months after surgery) delayed initiation of subsequent therapy by 32 months

Conclusions

Perioperative APA + ADT resulted in high rates of ultra-low PSA post RP + PLND

In patients receiving perioperative APA + ADT, ultra-low PSA post RP and at EOT was significantly associated with improved long-term outcomes

Patients without BCF at 3 years had clinically meaningful improvement in oncologic outcomes, including MFS and TTDM



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Introduction

- PROTEUS demonstrated enhanced curative success of radical prostatectomy with pelvic lymph node dissection (RP + PLND) with perioperative apalutamide (APA) + androgen deprivation therapy (ADT) versus placebo (PBO) + ADT in high-risk localized/locally advanced prostate cancer (HR-LPC/LAPC):
 - 6-cycle neoadjuvant APA + ADT resulted in 9-fold improvement in pathological complete response/minimal residual disease at RP (odds ratio [OR], 10.17 [95% confidence interval (CI), 5.27-19.64]; p<0.001)
 - 1-year perioperative APA + ADT resulted in 20% reduction in the risk of metastasis or death by blinded independent central review at 5 years (hazard ratio [HR], 0.80; 95% CI, 0.67-0.96; p=0.02)
- Achievement of a deep (≤0.2 ng/mL) prostate-specific antigen (PSA) response with APA + ADT is associated with improved outcomes in metastatic castration-sensitive prostate cancer^{2,3}
- To better understand how PSA response is associated with long-term outcomes, we conducted a post hoc analysis of PSA response in this perioperative disease setting

Results

Patients

- Of patients with PSA values at Cycle 9, 89.3% (1634/1830) had ultra-low PSA (<0.02 ng/mL) post RP (Table 1)
- Patients with non-ultra-low PSA (≥0.02 ng/mL) had higher median PSA at baseline and initial diagnosis, higher tumor stage at diagnosis, and higher percentage of N1 disease compared with patients with ultra-low PSA

Table 1: Baseline demographics and disease characteristics in patients with ultra-low/non-ultra-low PSA at Cycle 9		
	Ultra-low PSA (n=1634)	Non-ultra-low PSA (n=196)
Age, median (range), years	66 (41-84)	66 (49-82)
Time from initial diagnosis to randomization, median (range), months	2.3 (0.5-245.5)	2.1 (0.6-17.6)
PSA at baseline, median (range), ng/mL	14.1 (0.0-2798.0)	29.0 (0.3-328.0)
PSA at initial diagnosis, median (range), ng/mL	13.1 (1.1-1800.0)	25.0 (2.4-306.1)
Cumulative ADT duration between informed consent and treatment start, median (range), months	0.6 (0.1-1.6)	0.6 (0.1-1.2)
Tumor stage at initial diagnosis, n (%)		
T1	333 (20.4)	21 (10.7)
T2	738 (45.2)	70 (35.7)
T3	519 (31.8)	83 (42.3)
T4	36 (2.2)	20 (10.2)
TX	8 (0.5)	2 (1.0)
Regional lymph node stage at initial diagnosis, n (%) ^a		
N0	1467 (89.8)	146 (74.5)
N1	167 (10.2)	50 (25.5)
Gleason total score at initial diagnosis, median (min, max)	9 (7, 10)	9 (7, 10)
ECOG performance status at baseline, median (min, max)	0 (0, 1)	0 (0, 1)
ACCI total score at baseline, median (min, max)	2 (0, 7)	2 (0, 7)

ACCI, Age-adjusted Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group.
^aClinical diagnoses based on conventional imaging.

PSA over time

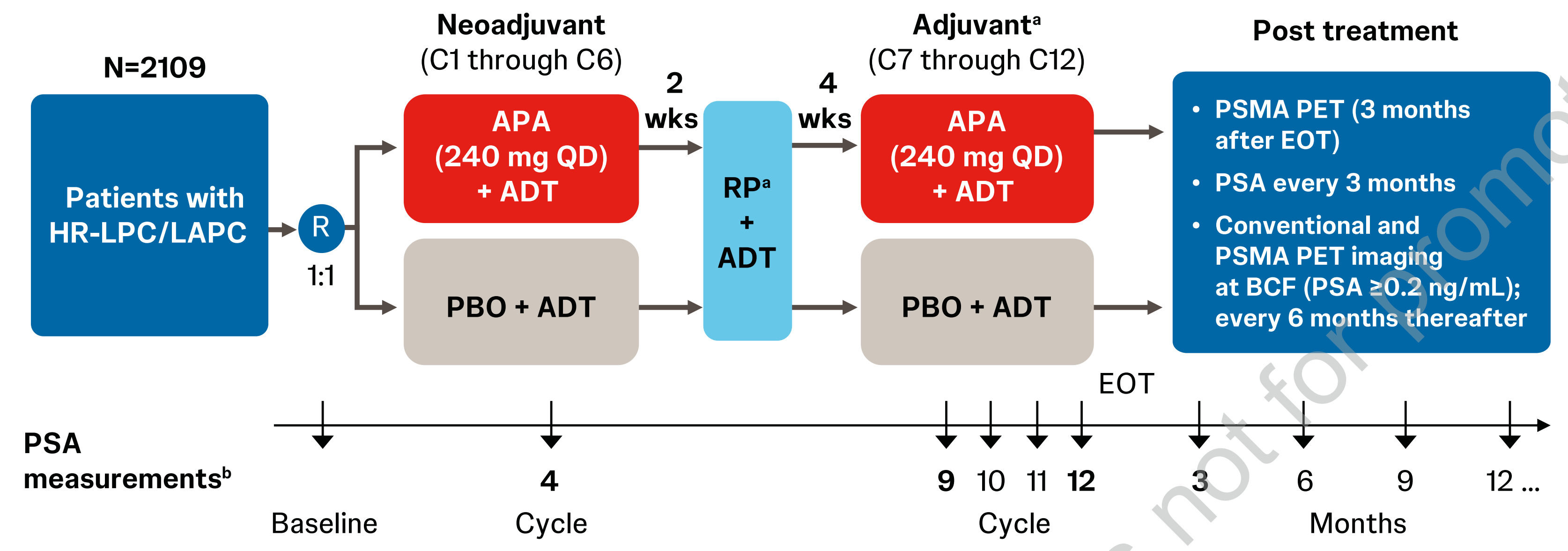
- Neoadjuvant APA + ADT reduced PSA levels pre-surgery (Cycle 4), with most patients experiencing ultra-low PSA levels post surgery (Cycle 9; Figure 2). Ultra-low PSA was maintained through EOT and follow-up
- Median duration of ultra-low PSA was 13.6 (Q1, Q3: 6.3, 32.3) months with APA + ADT versus 10.9 (2.8, 27.1) months with PBO + ADT
- Median time to nadir was 8.1 (7.0, 8.8) months and 8.7 (8.0, 9.0) months, respectively
- Time to BCF (which represents PSA progression) was significantly longer among patients who achieved ultra-low PSA (Figure 3)

References

1. Taplin M, et al. *N Engl J Med*. 2026;395(6):546-560. 2. Merseburger AS, et al. *BJU Int*. 2024;134(6):982-991. 3. Chowdhury S, et al. *Ann Oncol*. 2023;34(5):477-485.

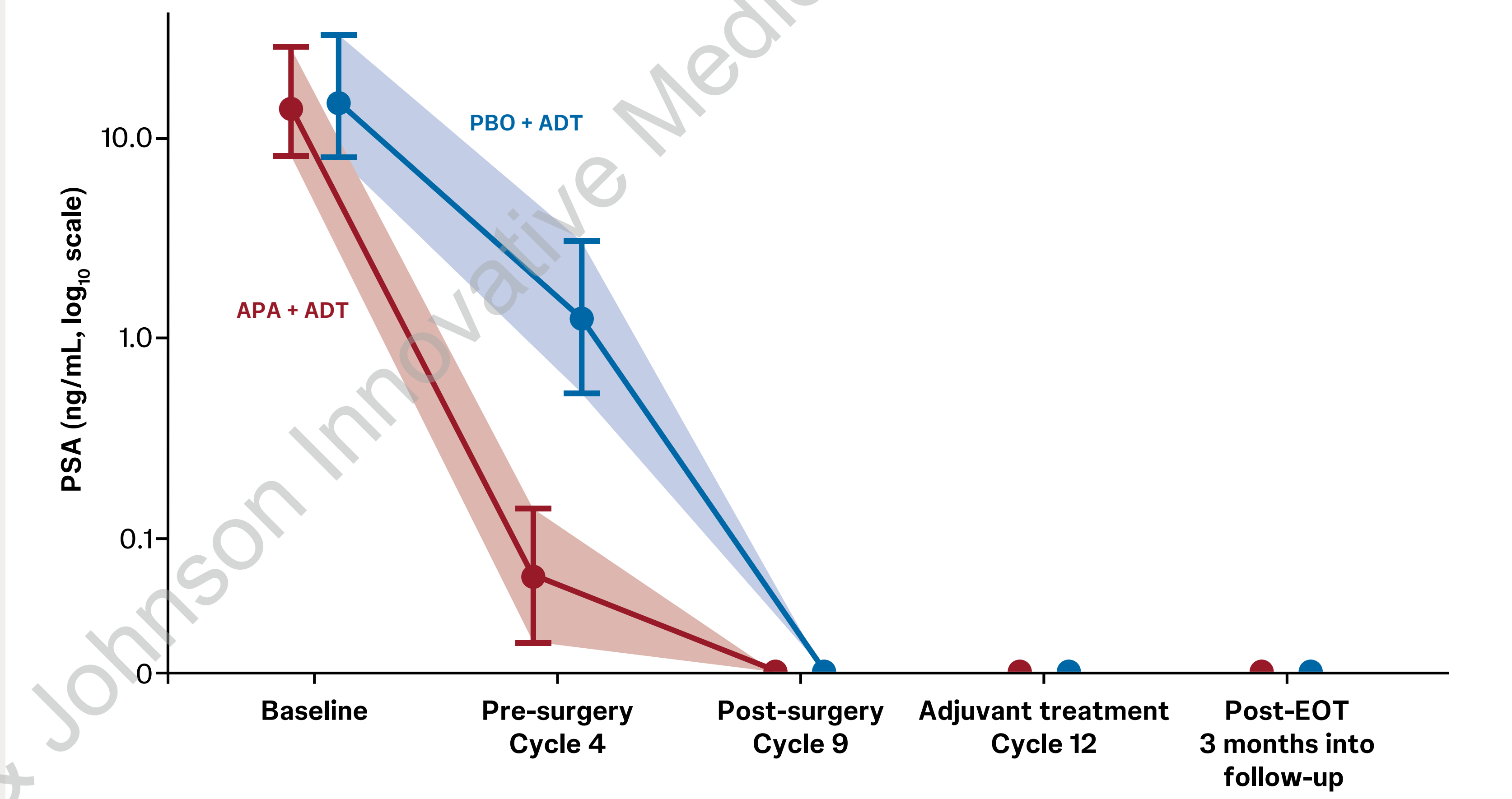
Methods

Figure 1: PROTEUS, phase 3, double-blind, placebo-controlled randomized study



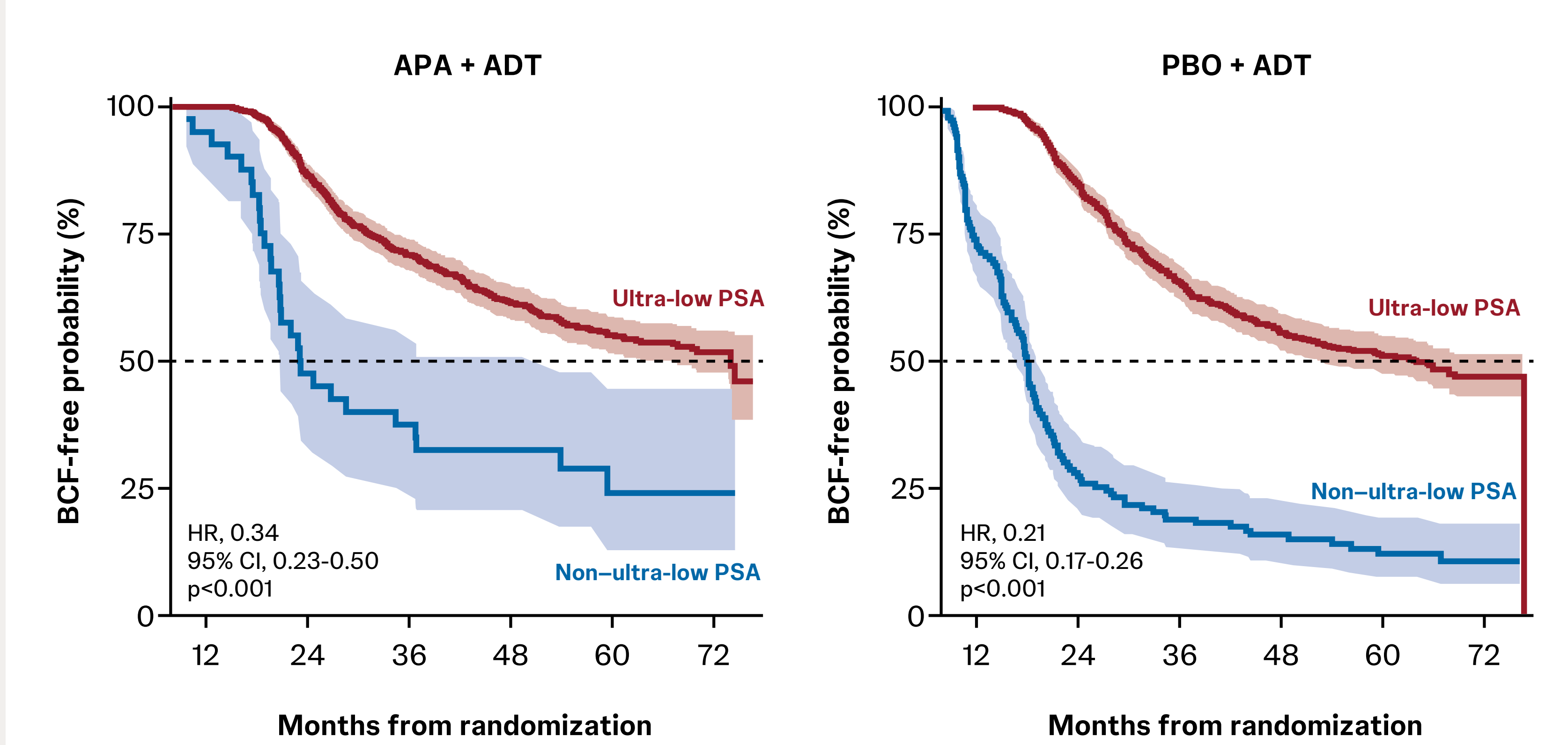
BCF, biochemical failure (PSA progression); C, cycle; EOT, end of treatment; PSMA PET, prostate-specific membrane antigen positron emission tomography; R, randomization; RT, radiotherapy. Each treatment cycle was 28 days; following EOT, PSA assessments were conducted at monthly intervals.
^aAdjuvant or salvage RT post RP at investigator's discretion. ^bPSA was measured on day 1 of indicated cycles.

Figure 2: Median PSA levels with IQR at key visits



IQR, interquartile range. Data points are staggered around the time points for visual clarity and to minimize overlap of error bars.

Figure 3: Time to BCF with 95% CI by ultra-low PSA at Cycle 9



Long-term outcomes

- Patients in the APA + ADT arm who had ultra-low PSA had significantly improved long-term outcomes compared with those who had non-ultra-low PSA (Table 2)

BCF at 3 years

- Patients without BCF at 3 years had significantly improved MFS (median: not reached [NR] vs 68.3 months) and TTDM (median: NR vs 71.3 months) versus those with BCF (Figures 4 and 5)

Post hoc analysis

Stratification	Outcomes with APA + ADT
Ultra-low (also referred to as undetectable) PSA <0.02 ng/mL vs non-ultra-low ≥0.02 ng/mL at Cycle 9	MFS, ^a EFS, ^b TTDM, ^c TTFST ^d
Ultra-low PSA <0.02 ng/mL vs non-ultra-low at 3 months post EOT	MFS, ^a EFS, ^b TTDM, ^c TTFST ^d
With or without BCF ^e	MFS, ^a TTDM ^c

MFS, metastasis-free survival; TTDM, time to distant metastasis; TTFST, time to first systemic or local therapy.
^aTime to first occurrence of radiographic distant metastasis based on conventional or PSMA PET imaging, pathologic finding of distant metastasis, or death from any cause. ^bTime to first of BCF (PSA progression) or local or regional recurrences or distant metastasis, or death by any cause. ^cTime to first distant metastasis by conventional or PSMA PET imaging, or pathologic finding of distant metastasis. ^dTime to local, regional, or systemic therapy, including reinitiation of ADT. ^eBCF was defined by 2 consecutive increases in the PSA level, measured at least 1 week apart, with the second PSA level ≥0.2 ng/mL.

Table 2: Long-term outcomes by ultra-low PSA and BCF at Cycle 9 and EOT in the perioperative APA + ADT arm

	Cycle 9		Post EOT 3 months into follow-up	
	Ultra-low PSA (n=860)	Non-ultra-low PSA (n=197)	Ultra-low PSA (n=778)	Non-ultra-low PSA (n=279)
MFS				
25th percentile	72.7 (71.3-NE)	25.9 (22.0-35.9)	72.8 (71.5-NE)	28.6 (23.5-35.9)
Median	NR (NE-NE)	NR (62.5-NE)	NR (NE-NE)	73.9 (62.4-NE)
75th percentile	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)	NR (73.9-NE)
HR (95% CI) ^a	0.34 (0.25-0.46)		0.33 (0.24-0.43)	
p Value ^b	<0.0001		<0.0001	
EFS				
Median	61.4 (53.6-73.9)	35.9 (28.1-53.9)	69.4 (57.5-NE)	31.6 (24.6-38.0)
HR (95% CI) ^a	0.60 (0.48-0.76)		0.50 (0.41-0.61)	
p Value ^b	<0.0001		<0.0001	
TTDM				
25th percentile	NR (72.7-NE)	59.4 (28.3-NE)	NR (72.7-NE)	53.6 (31.9-NE)
Median	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
75th percentile	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
HR (95% CI) ^a	0.51 (0.34-0.76)		0.45 (0.31-0.63)	
p Value ^b	0.0009		<0.0001	
TTFST				
25th percentile	30.4 (28.0-33.4)	18.0 (12.7-22.4)	32.9 (29.7-35.8)	19.5 (17.1-21.4)
Median	74.2 (70.4-NE)	41.8 (31.9-NE)	NR (72.9-NE)	38.9 (28.0-59.9)
75th percentile	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)	NR (NE-NE)
HR (95% CI) ^a	0.57 (0.45-0.74)		0.56 (0.45-0.69)	
p Value ^b	<0.0001		<0.0001	

NE, not estimable. Median, 25th, and 75th percentiles reported in months. 25th and 75th percentiles were included where median was not reached.
^aHR is from stratified proportional hazards model. HR <1 favors ultra-low PSA group. ^bp Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (NO, N1), geographic region (North America, Europe, rest of the world).

Figure 4: MFS by BCF at 3 years with APA + ADT

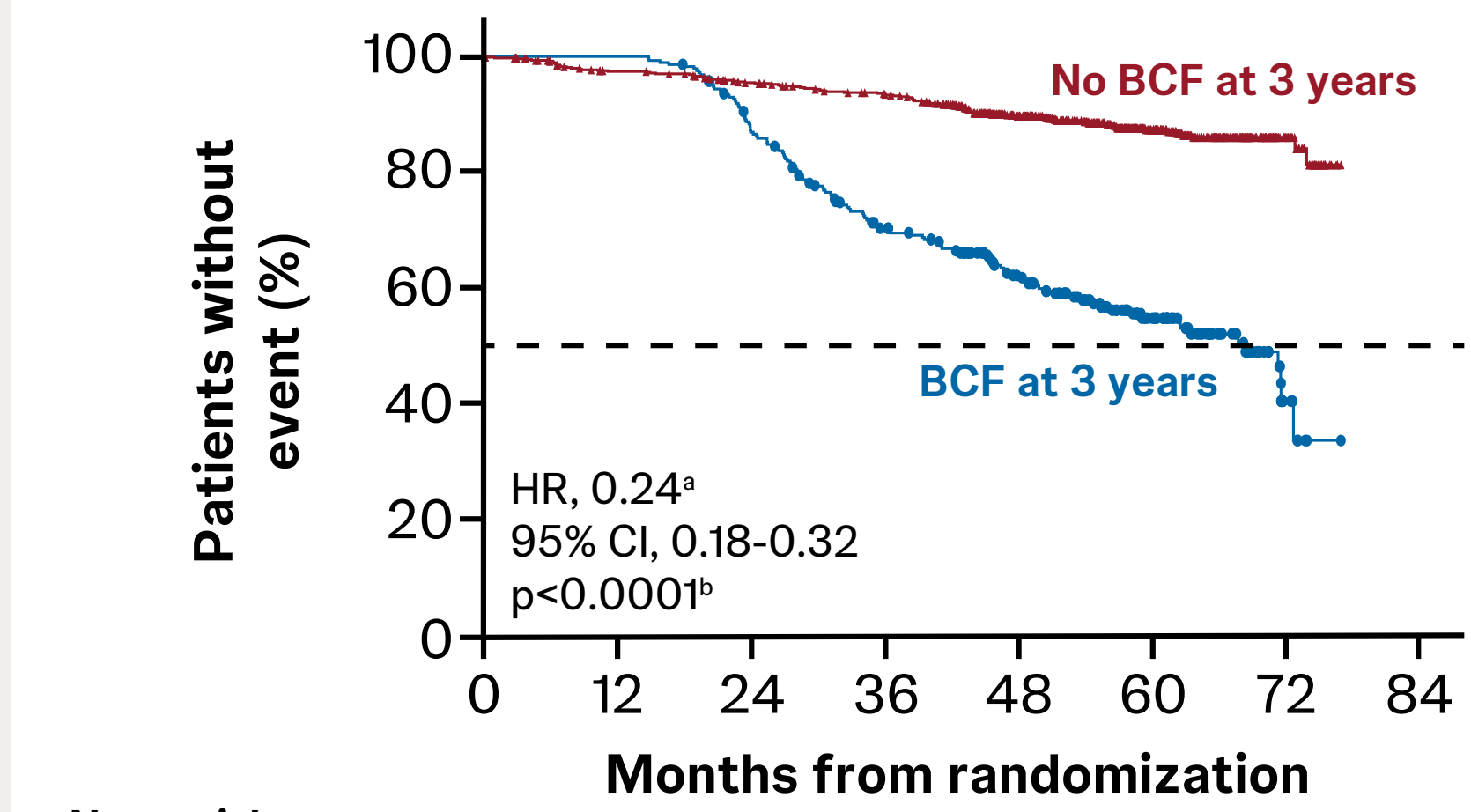
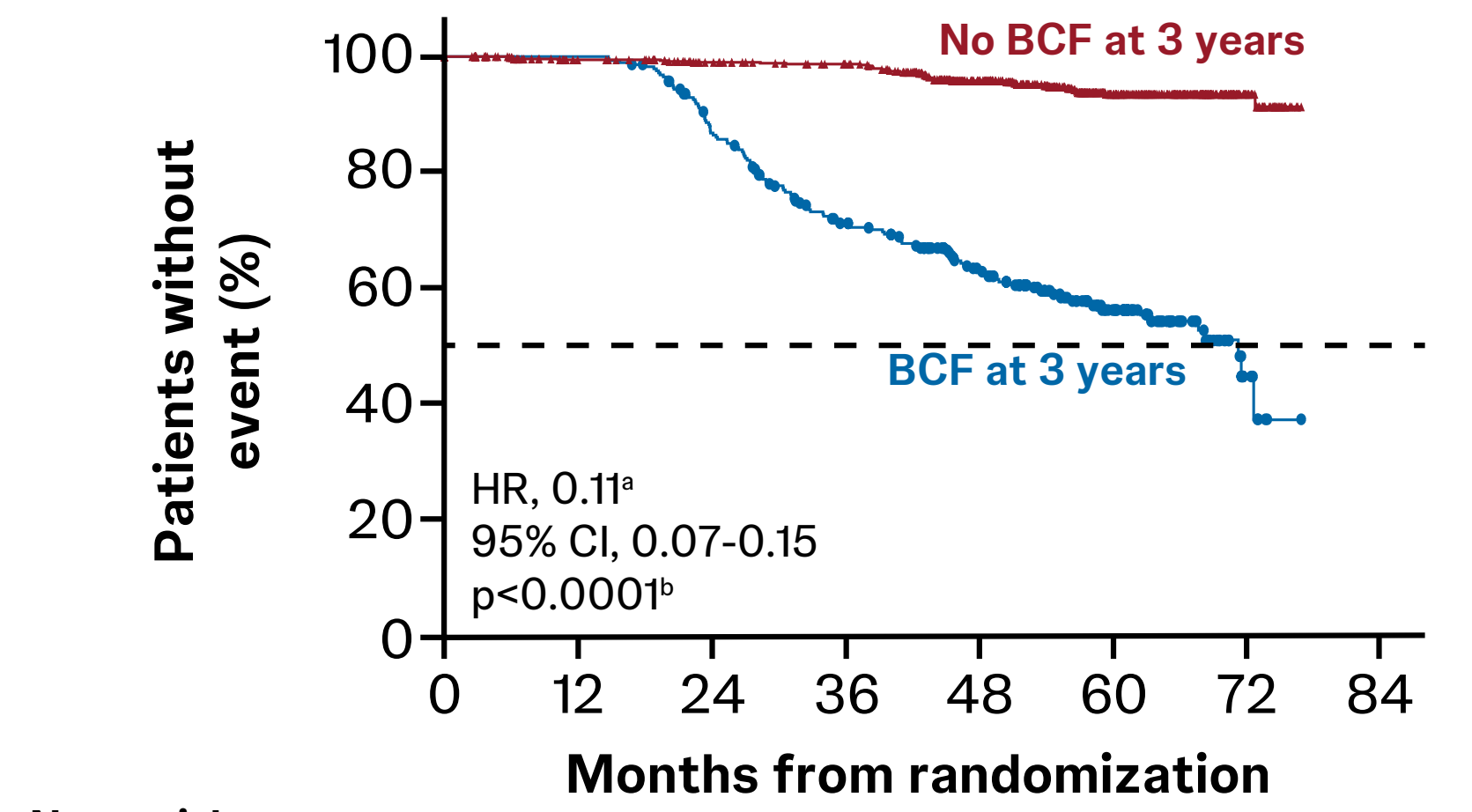


Figure 5: TTDM by BCF at 3 years with APA + ADT



^aHR is from stratified proportional hazards model. HR >1 favors BCF at 3 years group. ^bp Value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (NO, N1), geographic region (North America, Europe, rest of the world).

