

Perioperative Apalutamide Plus Androgen Deprivation Therapy With Radical Prostatectomy Plus Pelvic Lymph Node Dissection (RP + PLND) vs RP + PLND Alone in Patients With High-Risk Localized or Locally Advanced Prostate Cancer (HR LPC/LAPC): PROTEUS Substudy

Alberto Briganti¹, Thomas Steuber², Neal D Shore³, Martin Gleave⁴, Alexander Kretschmer⁵, Lisa Wetherhold⁵, Eleni Efstathiou⁶, David J Cahn⁷, Ronaldo Damião⁸, Alexandre De La Taille⁹, Boris A Hadaschik¹⁰, Bernardo Herrera Imbroda¹¹, Álvaro Juárez Soto¹², Giuseppe Simone¹³, Zhuokai Li¹⁴, Sharon A McCarthy¹⁵, Mark Wildgust¹⁶, Suneel D Mundle¹⁶, Adam S Kibel¹⁷, Mary-Ellen Taplin¹⁸

¹Division of Experimental Oncology/Unit of Urology, Urological Research Institute (URI), Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; ²Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany; ³Urology, START Carolinas/Carolina Urologic Research Center, Myrtle Beach, SC, USA; ⁴Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; ⁵Innovative Medicine R&D Oncology, Johnson & Johnson, Spring House, PA, USA; ⁶Department of Genitourinary Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; ⁷Colorado Clinical Research, Colorado Urology, Lakewood, CO, USA; ⁸Department of Surgery (Urology), Universidade do Estado do Rio de Janeiro, Rio de Janeiro; ⁹Department of Urology, Centre Hospitalier Universitaire Henri Mondor, Créteil, France; ¹⁰Department of Urology, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany; ¹¹Urology Department, Hospital Universitario Virgen de la Victoria, IBIMA-Plataforma BIONAND, Málaga, Spain; ¹²Urology Department, Hospital Universitario de Jerez de la Frontera, Cadiz, Spain; ¹³Department of Urology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; ¹⁴Statistics & Decision Science SH, Johnson & Johnson, Shanghai, China; ¹⁵Clinical Research Oncology, Johnson & Johnson, Spring House, PA, USA; ¹⁶Global Medical Affairs, Johnson & Johnson, Raritan, NJ, USA; ¹⁷Department of Urology, Mass General Brigham and Harvard Medical School, Boston, MA, USA; ¹⁸Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

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Declaration of Interests

Alberto Briganti reports advisory/advisory board roles with Astellas Pharma, Johnson & Johnson, MDx Health, Bayer, A3P Biomedical, MSD/AstraZeneca, Ferring, Pfizer, Sandoz -Novartis, and Telix Pharmaceuticals.

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PROTEUS: A Significant Advance in Surgery Outcomes in HR LPC/LAPC but No Surgery-Alone Comparator

- In HR LPC/LAPC, despite refinement of prostatectomy as an SOC,¹ the frequency of disease recurrence is high and patients may be subject to additional morbidity from subsequent therapy^{2,3}
- The PROTEUS main study, with a blinded design, demonstrated superior efficacy of 1-year perioperative apalutamide plus ADT compared with an active comparator⁴:

Unprecedented Study Design

- Largest size to date
- Novel end points
- PSMA PET inclusion

Enhanced Disease Control With Perioperative Apalutamide + ADT

Significant benefit:

- 9× greater pCR/MRD
- 20% lower hazard for metastasis or death
- 29% lower risk of recurrence or death
- ~3 years longer time to next treatment

Limitation

Control group did not receive SOC (surgery alone)

The PROTEUS Substudy was designed to compare perioperative apalutamide + ADT with RP + PLND versus SOC (surgery alone)

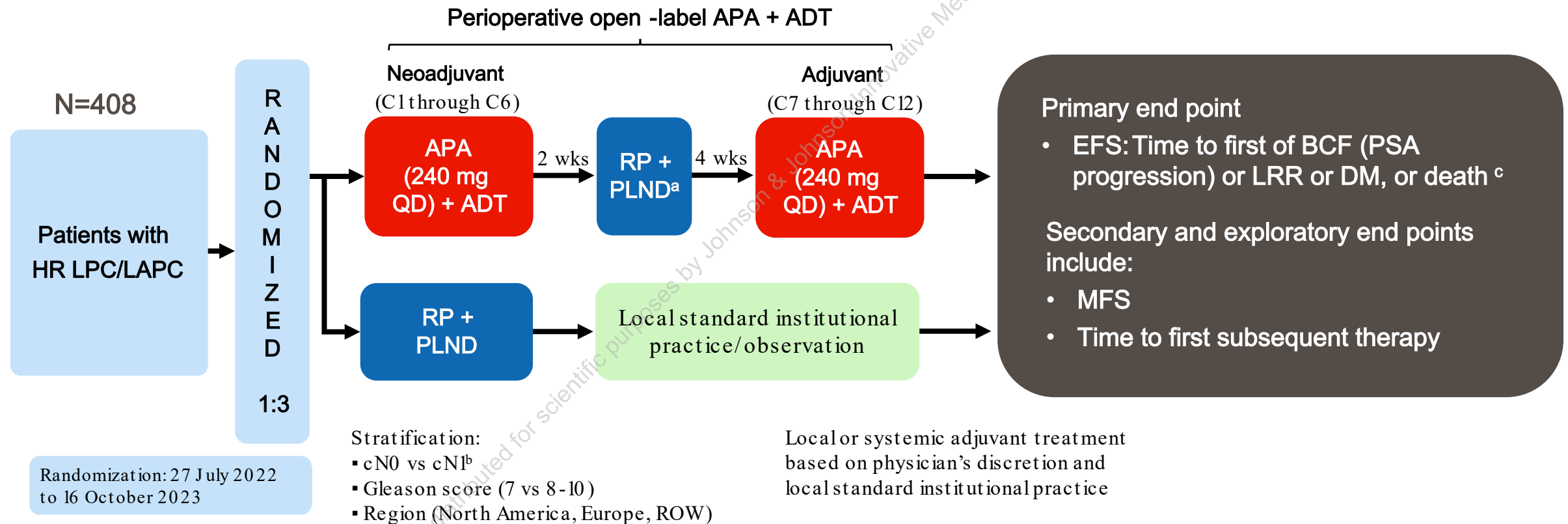
ADT, androgen deprivation therapy; HR LPC/LAPC, high-risk localized/locally advanced prostate cancer; pCR/MRD, pathologic complete response/minimal residual disease; PLND, pelvic lymph node dissection; PSMA PET, prostate-specific membrane antigen positron emission tomography; RP, radical prostatectomy; SOC, standard of care.

1. Cooley LF, Shore ND. *Transl Androl Urol* 2025;14:493-495. 2. Eiber M, et al. *J Clin Oncol* 2024;42:5027. 3. Stattin P, et al. *BJU Int* 2024;134:96-102. 4. Taplin ME, et al. *N Engl J Med* 2026;395:546-560.



The PROTEUS Substudy Compared APA + ADT With RP + PLND vs RP + PLND Alone

- Immediate RP + PLND without neoadjuvant treatment, followed by subsequent adjuvant treatment based on physician's discretion, is used to reflect SOC based on current guideline recommendations¹



APA, apalutamide; BCF, biochemical failure; BICR, blinded independent central review; C, cycle; DM, distant metastases; EFS, event-free survival; LRR, local or regional recurrence; PSA, prostate-specific antigen; QD, daily; ROW, rest of the world.

^aAPA + ADT is stopped 2 weeks prior to planned RP and then resumed 4 weeks after RP. Cardiovascular risk prophylaxis and venous thromboembolism prophylaxis given based on risk.

^bBased on conventional imaging.

^cBCF defined as 2 consecutive PSA rises ≥ 1 week apart, with the second test resulting in an absolute PSA ≥ 0.2 ng/mL following RP; LRR and DM based on PSMA PET or conventional imaging, both by BICR, or histopathology.

1. Cornford P, et al. *Eur Urol* 2026;S0302-2838(26)02114.

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PROTEUS Substudy Statistical Analysis Plan

- The final analysis of the primary end point was conducted after at least 120 EFS events were observed or the median follow-up reached 3 years, whichever occurred later^a
- p Values were nominal for secondary and exploratory end points

Final analysis	Primary end point of EFS
Alpha (2 sided)	0.05
Power	80%
Assumption: HR of perioperative APA + ADT vs RP + PLND alone	0.6
Final analysis	408 patients

HR, hazard ratio.

^aFinal analysis was triggered by reaching median follow-up of 3 years.



Baseline Characteristics Were Well Balanced

ITT population		Perioperative APA + ADT (n=102)	RP + PLND alone (n=306)
Median age (range), years		66.0 (51-82)	66.0 (45-84)
≥75, n (%)		9 (8.8)	31 (10.1)
Gleason score at initial diagnosis, n (%)	7	4 (3.9)	8 (2.6)
	≥8	98 (96.1)	298 (97.4)
Baseline PSA ^a	Median (range), ng/mL	14.1 (1.4-422.6) ^b	14.2 (1.5-384.3) ^c
	<20, n (%)	66 (65.3)	183 (64.0)
	≥20, n (%)	35 (34.7)	103 (36.0)
Tumor stage at diagnosis, n (%) ^d	≤cT2	69 (67.6)	217 (70.9)
	≥cT3	31 (30.4)	86 (28.1)
Regional lymph node stage at diagnosis, n (%)	cN0	94 (92.2)	285 (93.1)
	cN1	8 (7.8)	21 (6.9)

- At clinical cutoff on 13 July 2026:
 - Median follow -up - 37.8 months
 - Patients still on the study - 94% (perioperative APA + ADT, n=96) and 89% (RP + PLND alone, n=306)

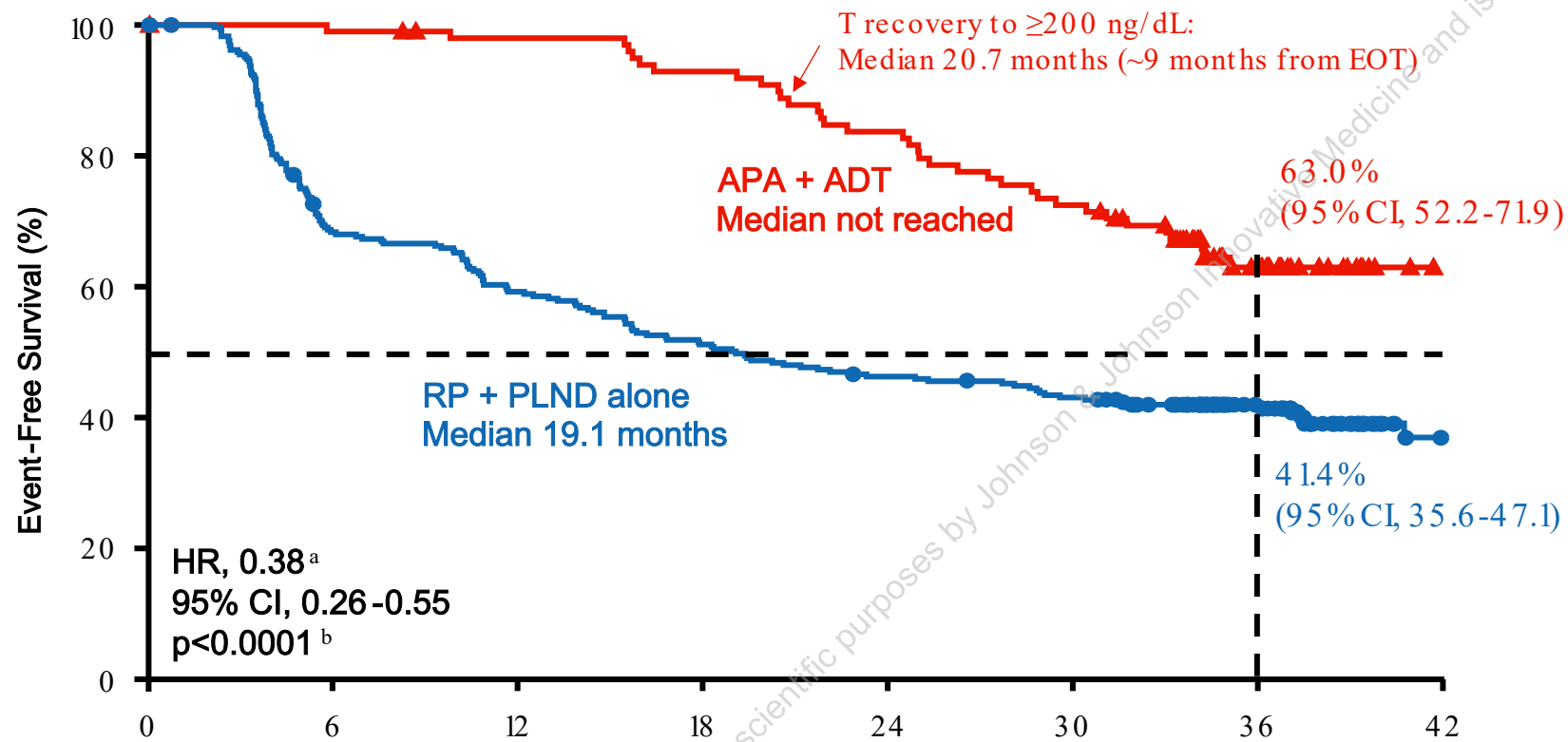
ITT, intent to treat.

^aPSA before first dose was the closest value assessment on or prior to the start date for ADT or APA and the closest value assessment on or prior to the date of randomization for the RP + PLND alone group.

^bn101. ^cn=286. ^dTX n=2 (APA + ADT); n=3 (RP + PLND alone).



PROTEUS Substudy Met Primary End Point: EFS Significantly Improved



- 62% reduction in risk of oncologic event or death
- Median 19.1 months EFS with SOC highlights the unmet need

No. at risk	0	6	12	18	24	30	36	42
APA + ADT	102	99	96	91	82	71	38	10
RP + PLND alone	306	195	169	146	131	121	74	15

EFS: Time to first of BCF (PSA progression) or LRR or DM, or death by any cause. LRR and DM based on PSMA PET or conventional imaging, both by BICR, or histopathology.

CI, confidence interval.

^aHR is from stratified proportional hazards model; HR <1 favors APA + ADT.

^bp Value is from a log-rank test stratified by Gleason score (7, ≥ 8), nodal status (N0, N1), and geographic region (North America, Europe, and ROW).

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Treatment Benefit for EFS Was Consistent Over Time With Perioperative APA + ADT, Even After T Recovery

- T recovery to ≥ 200 ng/dL with perioperative APA + ADT: Median 20.7 months (~9 months from EOT)

Time after randomization	EFS rate, % (95% CI)		EFS rate difference, % (95% CI)	Nominal p value
	Perioperative APA + ADT (n=102)	RP + PLND alone (n=306)		
20 months	91 (85-97)	49 (43-55)	42 (33-51)	<0.001
24 months	84 (75-90)	46 (40-52)	37 (27-47)	<0.001
36 months	63 (52-72)	41 (36-47)	22 (10-33)	<0.001

EFS: Time to first of BCF (PSA progression) or LRR or DM, or death by any cause. LRR and DM based on PSMA PET or conventional imaging, both by BICR, or histopathology.

EOT, end of treatment; T, testosterone.



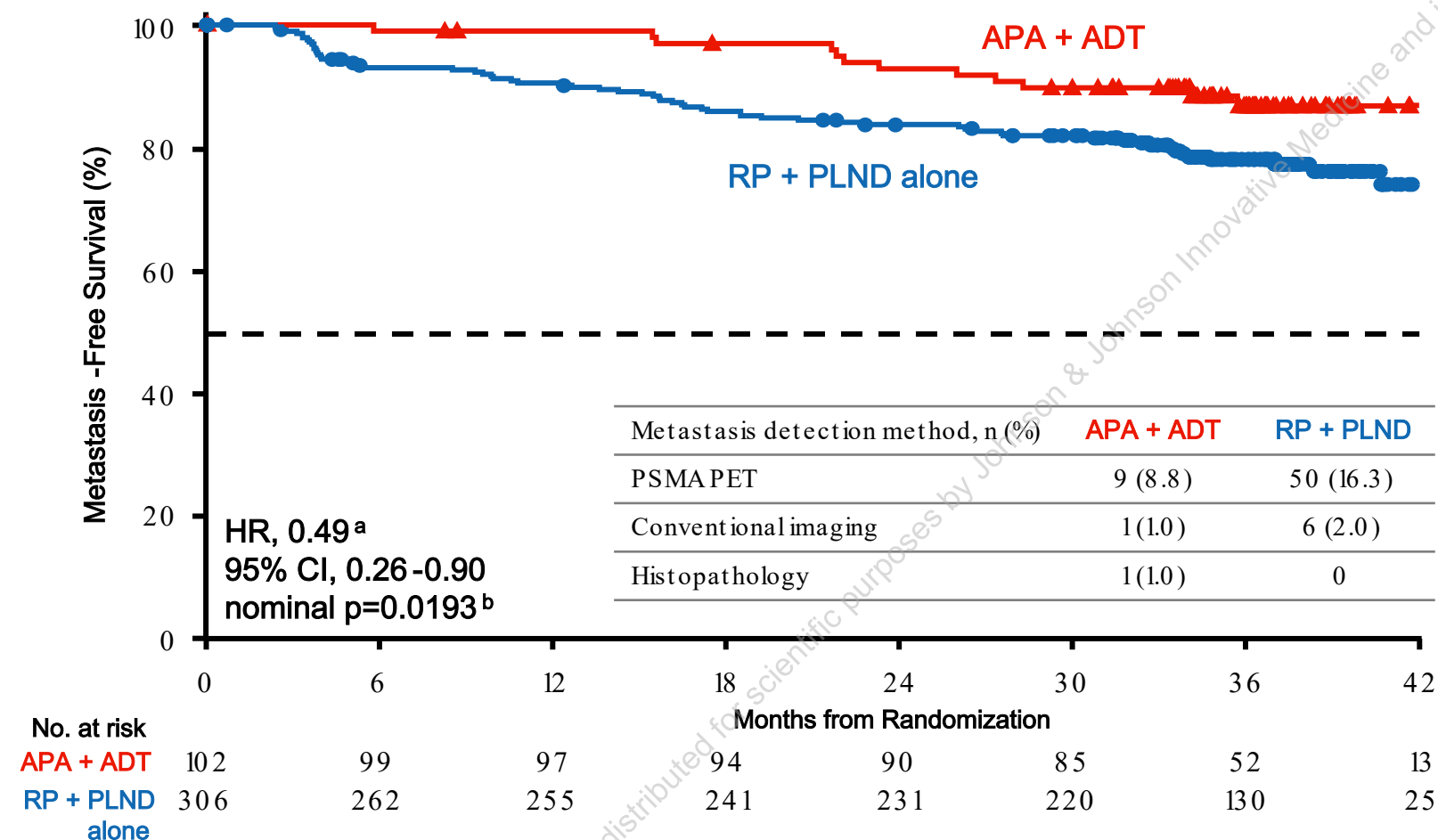
Fewer Local/Regional Recurrence or Distant Metastasis Events With Perioperative APA + ADT

	Perioperative APA + ADT (n=102)	RP + PLND alone (n=306)
First event (denominator for events below), n (%)	35/102 (34.3)	172/306 (56.2)
Biochemical failure (BCF)	27 (77.1)	92 (53.5)
Local or regional recurrence by PSMA PET/conventional imaging	4 (11.4)	51 (29.7)
LRR by PSMA PET	4 (11.4)	50 (29.1)
LRR by PSMA PET without BCF	4 (11.4)	48 (27.9)
LRR by conventional imaging	0	1 (0.6)
Distant metastasis by PSMA PET/conventional imaging/histopathology	4 (11.4)	28 (16.3)
DM by PSMA PET	2 (5.7)	24 (14.0)
DM by PSMA PET without BCF	2 (5.7)	23 (13.4)
DM by conventional imaging/histopathology	2 (5.7)	4 (2.3)
Death	0	1 (0.6)
Censored, n (%)	67/102 (65.7)	134/306 (43.8)

- ~70 % of PSMA PET-detected LRR/DM without BCF in the RP group were associated with PSA persistence (PSA $\geq$ 0.1 ng/mL) 3 months after RP
- Excluding patients (both arms) with PSMA PET-detected events (LRR or DM) without prior BCF: HR, 0.50; 95% CI, 0.33-0.76; p=0.001



Perioperative APA + ADT Improved MFS by Conventional or PSMA PET Imaging (BICR)



- 51% reduction in risk of metastasis or death
- MFS by local investigator assessment:
 - HR, 0.38^a
 - 95% CI, 0.22-0.66
 - nominal p=0.0004^b

MFS: Time to first occurrence of distant metastasis on PSMA PET or conventional imaging by BICR, pathologic finding of distant

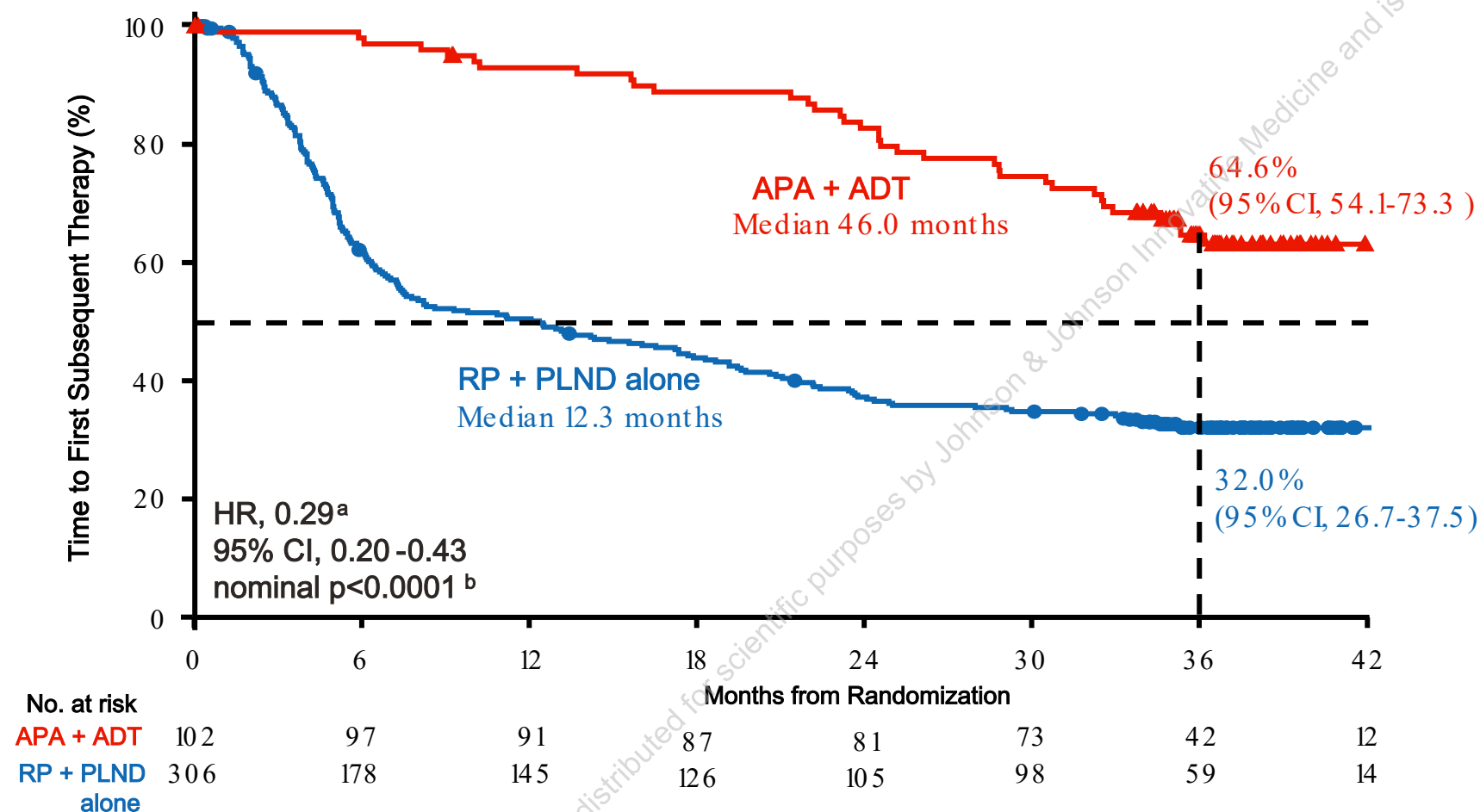
metastasis, or death from any cause.

^aHR is from stratified proportional hazards model; HR <1 favors APA + ADT.

^bNominal p value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), and geographic region (North America, Europe, and ROW).



Time to First Subsequent Therapy Was Prolonged by ~3 Years With Perioperative APA + ADT



- 71% reduced risk of starting subsequent therapy
- ~50 % fewer patients started subsequent therapy by 3 years

Time to first subsequent therapy: Time from randomization to first local, regional, or systemic therapy, including reinitiation of ADT.

^aHR is from stratified proportional hazards model; HR <1 favors APA + ADT.

^bNominal p value is from a log-rank test stratified by Gleason score (7, ≥8), nodal status (N0, N1), and geographic region (North America, Europe, and ROW).



Subsequent Therapy

ITT population	Perioperative APA + ADT (n=102)	RP + PLND alone (n=306)
Subsequent therapy/surgery/procedure, n (%)	36 (35)	197 (64)
Systemic anticancer therapy	28 (27)	175 (57)
Hormonal	28 (27)	175 (57)
Postoperative radiotherapy	20 (20)	131 (43)
Adjuvant radiotherapy +/- ADT	4 (3.9)	44 (14)
Salvage radiotherapy +/- ADT	16 (16)	85 (28)
Both settings	0	2 (0.65)
Other radiotherapy	5 (4.9)	18 (5.9)
Surgery/procedure	0	0

Nearly half as many patients needed salvage radiotherapy when perioperative APA + ADT was added to RP + PLND



Treatment -Related Adverse Events

	Safety population, n (%)	Perioperative APA + ADT (n=101) ^a		RP + PLND alone ^b (n=286)
		Related to APA + ADT	Related to RP + PLND	
All grades	Treatment-related AE	77 (76.2)	83 (82.2)	265 (92.7)
Grade 3/4	Treatment-related AEs	11 (10.9)	17 (16.8)	42 (14.7)
All grades	Treatment-related AEs leading to dose reduction ^c	5 (5.0)	0	na
	Treatment-related AEs leading to dose interruption ^c	5 (5.0)	1 (1.0)	na
	Treatment-related AEs leading to death ^d	0	0	0

Perioperative APA + ADT did not worsen treatment -related AEs related to surgery

AE, adverse event; na, not applicable.

Treatment-related AEs are those that occurred on or after the first dose of study drug through the last dose of study treatment + 30 days or prior to the start of subsequent therapy, whichever is earlier, or any AE that is considered treatment related regardless of the start date of the event. An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study drug (apalutamide), ADT, or RP.

^aPatients may have experienced an AE from both APA + ADT and RP. ^bAEs were collected during the treatment phase and for 30 days prior to the start of subsequent therapy, whichever was earlier. ^cAEs leading to treatment interruption or dose reduction are based on AE action taken. ^dIncludes grade 5 events; AEs leading to death are based on AE outcome of fatal.



Cumulative Most Common Treatment -Emergent AEs (>10% Incidence)

Safety population, n (%)	Perioperative APA + ADT (n=101)		RP + PLND alone (n=286)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
≥ 1 TEAE, n (%)	99 (98)	31 (31)	271 (95)	62 (22)
Urinary incontinence	64 (63)	0	190 (66)	6 (2.1)
Erectile dysfunction	57 (56)	6 (5.9)	176 (62)	15 (5.2)
Urinary tract infection	23 (23)	4 (4.0)	36 (13)	3 (1.0)
Hot flush	65 (64)	0	2 (0.70)	0
Fatigue	22 (22)	0	8 (2.8)	0
Rash	16 (16)	3 (3.0)	2 (0.70)	0
Arthralgia	15 (15)	1 (1.0)	10 (3.5)	0
Pruritus	13 (13)	0	1 (0.35)	0

Most common APA + ADT related treatment -emergent AE was hot flush



Limitations and Planned Analyses

PROTEUS Substudy Limitations

- **PSMA PET**
 - Not performed at screening to maintain consistency with main study protocol and planned pooling analyses
- **Open-label design**
- **3-Year duration of follow -up not sufficient for overall survival assessment**
- **Patient enrollment was not enriched using biomarker profiling**

Planned Future Analyses

- **Pathology correlates**
- **Surgical and patient -reported outcomes**
- **Biomarker assessment**



PROTEUS Substudy Conclusions

- Together with the PROTEUS main study, the PROTEUS Substudy supports 1 -year perioperative APA + ADT as a treatment option for patients with HR LPC/LAPC fit for surgery and systemic therapy
- Perioperative APA + ADT improves disease control and gives patients a longer time before starting subsequent therapy

Enhanced Disease Control With Perioperative APA + ADT

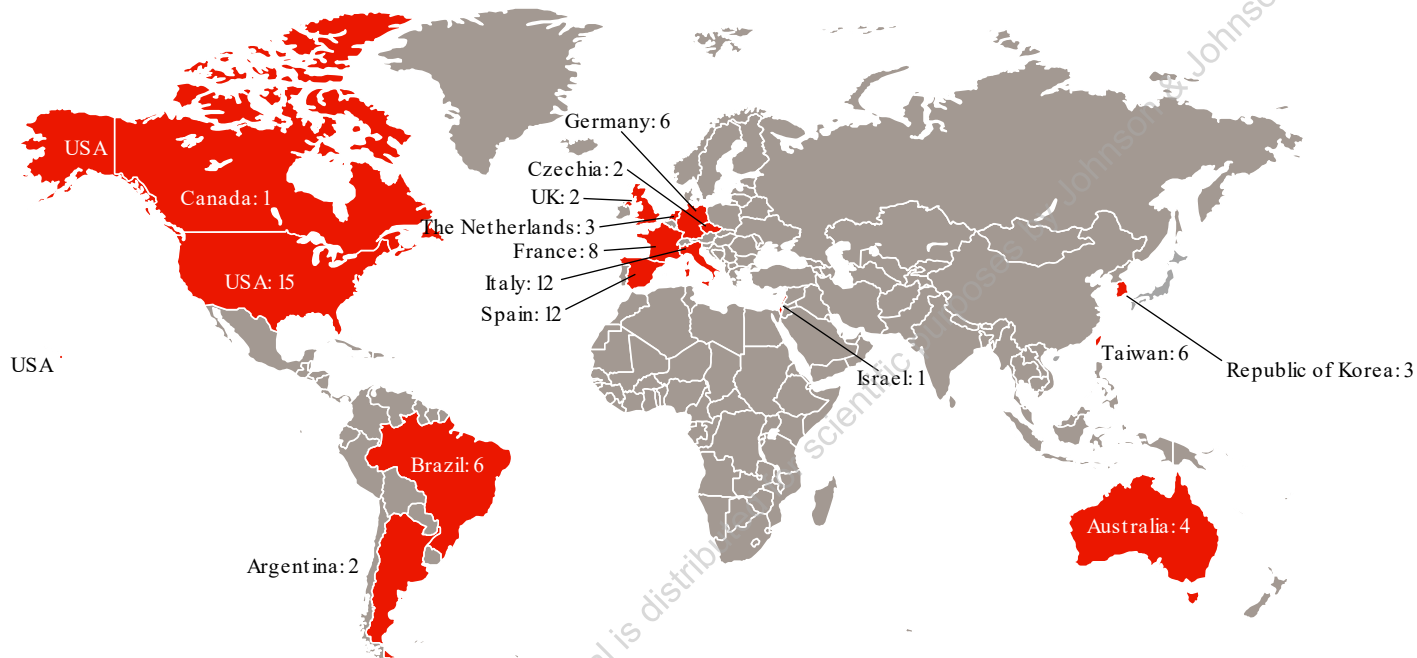
- 62% lower risk of recurrence or death
- 51% lower risk of death or developing metastases over time
- ~50% fewer patients starting subsequent therapy by ~3 years
- >3× longer time to first subsequent therapy



Acknowledgments

Thank you to our patients, their families and caregivers, PROTEUS Substudy investigators, site staff, and clinical teams

A total of 408 patients from 83 sites in 15 countries/regions were randomized in the PROTEUS Substudy



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Treatment Effect of Perioperative (Neoadjuvant and Adjuvant) Apalutamide plus Androgen-deprivation Therapy Versus Radical Prostatectomy Alone in Patients with High-risk Localized or Locally Advanced Prostate Cancer from the PROTEUS Substudy

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