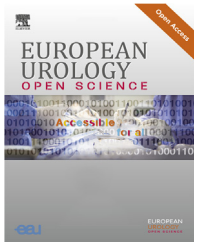
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Ultralow Prostate-specific Antigen Nadir After Apalutamide: Outcomes in Synchronous Versus Metachronous Metastatic Hormone-sensitive Prostate Cancer

Mike Wenzel[a,*], *Thomas Steuber*[b], *Carolin Siech*[a], *Maximilian Kriegmair*[b,c], *Benedikt Hoeh*[a], *Derya Tilki*[d,e,f], *Axel S. Merseburger*[g], *Felix K.H. Chun*[a], *Philipp Mandel*[a,d]

[a] *Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Frankfurt, Germany;* [b] *Urologische Klinik München Planegg, Planegg, Germany;* [c] *Department of Urology and Urosurgery, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany;* [d] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [e] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [f] *Department of Urology, Koc University Hospital, Istanbul, Turkey;* [g] *Department of Urology, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany*

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Abstract

As an ultralow prostate-specific antigen (PSA) nadir (≤0.02 ng/ml) after apalutamide treatment for metastatic hormone-sensitive prostate cancer (mHSPC) was associated with the best oncological outcomes, the question arises as to whether this holds true for both synchronous and metachronous mHSPC. We addressed this knowledge gap using data from the FRAMCAP (Frankfurt Metastatic Cancer of the Prostate) database. In a cohort of 75 patients with synchronous mHSPC treated with apalutamide, 35% experienced a PSA decline to ≤0.02 ng/ml. Analysis of time to castration-resistant prostate cancer (CRPC) and overall survival (OS) revealed significant differences by PSA nadir category ($p < 0.01$). In a cohort of 33 patients with metachronous mHSPC treated with apalutamide, 52% experienced a PSA decline to ≤0.02 ng/ml. Analysis of CRPC revealed significant differences by PSA nadir category ($p = 0.02$). Although there were no significant differences in OS among the PSA nadir categories ($p = 0.3$), the best numerical OS outcome was observed for PSA ≤0.02 ng/ml. For the overall group of patients achieving PSA ≤0.02 ng/ml, there were no significant difference in time to CRPC and OS between synchronous and metachronous mHSPC.

Patient summary: Apalutamide is a drug for treatment of metastatic prostate cancer that is sensitive to hormone treatment. We found that a decrease in PSA (prostate-specific antigen) to a very low level of ≤0.02 ng/ml after apalutamide treatment

* Corresponding author. Department of Urology, University Hospital Frankfurt, Goethe University Frankfurt am Main, Frankfurt, Germany. Tel: +49 69 630 183 147; Fax: +49 69 630 180 069.
E-mail address: mikewenzel91@aol.com (M. Wenzel).

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can predict good cancer control. This applies to patients with metastasis when they are first diagnosed and to patients who develop metastasis after their diagnosis of prostate cancer. This level of ≤0.02 ng/ml can be used in discussing prognosis and treatment options with these patients.

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Addition of an androgen receptor pathway inhibitor (ARPI) to androgen deprivation therapy (ADT) is the current standard of care for metastatic hormone-sensitive prostate cancer (mHSPC) [1–3]. Novel ARPIs such as apalutamide extend the time to metastatic castration-resistant prostate cancer (ttCRPC) and overall survival (OS), and also achieve very low prostate-specific antigen (PSA) levels [4]. The introduction of a novel ultralow PSA nadir (PSA-N) cutoff of ≤0.02 ng/ml for stratification of patient prognosis was recently suggested on the basis of post hoc analyses of the TITAN trial and validation in contemporary real-world scenarios for apalutamide and other treatment options [5–8]. This raises the question of whether this new cutoff and its prognostic value hold true for both synchronous and metachronous mHSPC, as PSA values before treatment initiation differ significantly in absolute value between these settings and there may be differences in both tumor biology and treatment outcomes [9].

We addressed this knowledge gap using data from the FRAMCAP (Frankfurt Metastatic Cancer of the Prostate) database to expand the initial cohort analysis already published [9]. We hypothesized that the proportion of patients with mHSPC achieving an ultralow PSA-N after apalutamide treatment may differ between synchronous and metachronous mHSPC, in line with the differences in ttCRPC and OS outcomes between these settings [9]. After approval from the local ethics committee, we tested this hypothesis in a study conducted in accordance with the Declaration of Helsinki.

Inclusion criteria for the current study were patients with apalutamide-treated mHSPC with data available for the PSA-N after treatment, synchronous versus metachronous status for metastasis, and follow-up. A total of 75 patients with synchronous mHSPC and 32 with metachronous mHSPC treated with apalutamide were eligible for analyses.

For analyses of progression-free survival and OS, published PSA-N cutoffs were applied in Kaplan-Meier estimates assessed via log-rank tests [5]: ≤0.02 ng/ml (PSA-$N_{\leq 0.02}$) versus >0.02–0.2 ng/ml (PSA-$N_{0.02–0.2}$) versus >0.2 ng/ml (PSA-$N_{>0.2}$). Follow-up started from initiation of systemic treatment for mHSPC and was performed in accordance with the European Association of Urology guidelines at 3-mo intervals or according to the discretion of individual physicians. Multivariable Cox regression models were tested, with adjustment for CHAARTED high-volume disease (and PSA at mHSPC). Wald interaction tests were used for between-group analyses for the PSA-N groups and synchronous versus metachronous mHSPC. All tests were two-sided, with the level of significance set at $p < 0.05$. R version 3.4.3 (R Foundation for Statistical Analysis, Vienna, Austria) was used for all analyses.

Baseline characteristics were similar for the synchronous and metachronous mHSPC cohorts, despite a significant difference in median PSA at mHSPC (4.5 vs 54.9 ng/ml; $p < 0.001$). Differences in baseline patient and tumor characteristics by PSA-N category were previously reported for this mHSPC apalutamide cohort [8].

Of 75 patients with synchronous mHSPC, the post-apalutamide PSA-N was ≤0.02 ng/ml in 35%, >0.02–0.2 ng/ml in 25%, and >0.2 ng/ml in 40%. Median follow-up for patients alive was 21 mo (interquartile range [IQR] 10–37). The rate of high-volume mHSPC was 51% in the overall cohort and was lower in the PSA-$N_{\leq 0.02}$ group (22% vs 39% for PSA-$N_{0.02–0.2}$ vs 82% for PSA-$N_{>0.2}$; $p < 0.001$). There were significant differences in median PSA at mHSPC for the three PSA-N groups: 42 ng/ml for PSA-$N_{\leq 0.02}$ versus 70 ng/ml for PSA-$N_{0.02–0.2}$ and 87 ng/ml for PSA-$N_{>0.2}$ ($p = 0.035$). In total, 98.5% of patients experienced a PSA decrease of at least ≥90%. Rates of local therapy to the prostate were 50% in the PSA-$N_{\leq 0.02}$ group versus 26% in the PSA-$N_{0.02–0.2}$ group and 20% in the PSA-$N_{>0.2}$ group ($p = 0.046$). No further significant differences in baseline characteristics were observed.

Analysis of ttCRPC revealed significant differences between the three PSA nadir groups, with median ttCRPC of not reached (NR) for PSA-$N_{\leq 0.02}$ versus 32.4 for PSA-$N_{0.02–0.2}$ versus 11.8 mo for PSA-$N_{>0.2}$ ($p < 0.001$; Fig. 1A). After multivariable adjustment for high-volume mHSPC and PSA at mHSPC, hazard ratios for ttCRPC were 2.17 (95% confidence interval [CI] 0.52–9; $p = 0.3$) for PSA-N >0.02–0.2 ng/ml and 5.56 (95% CI 1.55–20; $p < 0.01$) for PSA-N >0.2 ng/ml in comparison to PSA-N ≤0.02 ng/ml (Supplementary Table 2).

Analysis of OS revealed significant differences between the PSA-N groups, with median OS of NR for PSA-$N_{\leq 0.02}$ versus NR for PSA-$N_{0.02–0.20}$ versus 26.3 mo for PSA-$N_{>0.2}$ (Fig. 1 B; $p < 0.01$). Multivariable adjusted Cox regression models did not show a difference in OS among the three groups (Supplementary Table 2).

Of 33 patients with metachronous mHSPC treated with apalutamide, the PSA-N was ≤0.02 ng/ml in 52%, >0.02–0.2 ng/ml in 33%, and >0.02 ng/ml in 15%. Median follow-up for patients alive was 28 mo (IQR 15–41). The rate of high-volume mHSPC was 19% overall, and was also lower in the ng/ml cohort (18% in the PSA-$N_{\leq 0.02}$ group, 10% in the PSA-$N_{0.02–0.20}$ group, and 50% in the PSA-$N_{>0.2}$ group ($p = 0.3$). Although the difference did not reach statistical significance, median PSA at mHSPC was lower in the PSA-$N_{\leq 0.02}$ group (2 vs 7 ng/ml for PSA-$N_{0.02–0.20}$ vs 23 ng/ml

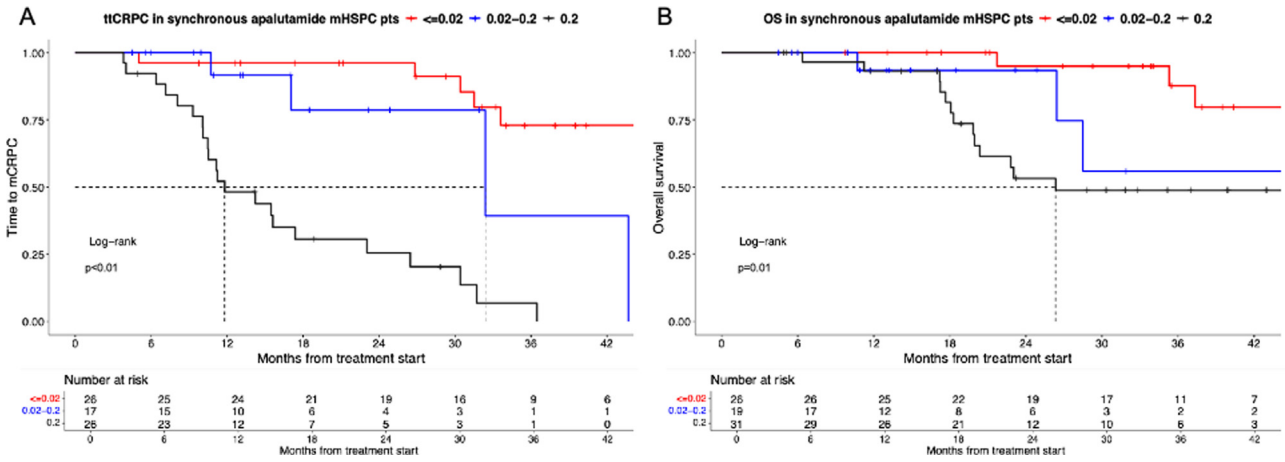


Fig. 1 – Kaplan-Meier curves of (A) time to metastatic castration-resistant prostate cancer (CRPC) and (B) overall survival by post-apalutamide PSA nadir category (≤0.02 vs 0.02–0.2 vs >0.2 ng/ml) in patients with synchronous metastatic hormone-sensitive prostate cancer. PSA = prostate-specific antigen.

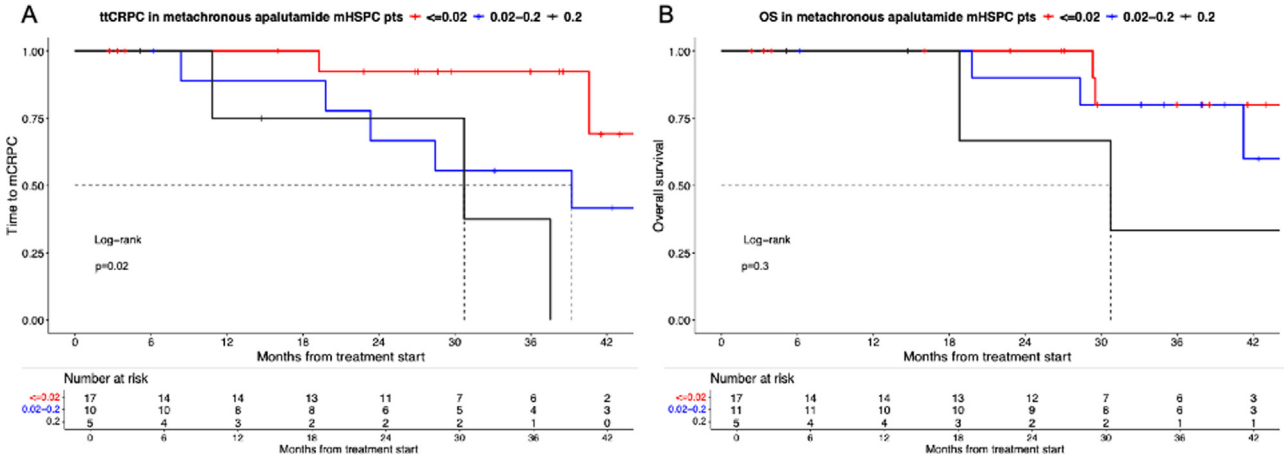


Fig. 2 – Kaplan-Meier curves of (A) time to metastatic castration-resistant prostate cancer (CRPC) and (B) overall survival by post-apalutamide PSA nadir category (≤0.02 vs >0.02–0.2 vs >0.2 ng/ml) in patients with metachronous metastatic hormone-sensitive prostate cancer. PSA = prostate-specific antigen.

for PSA-$N_{>0.02}$; $p = 0.2$). In total, 90.3% of the metachronous mHSPC cohort achieved a decline in PSA of at least ≥90%. No further significant differences in baseline characteristics were observed.

Analysis of ttCRPC revealed significant differences among the PSA-N groups, with median ttCRPC of NR for PSA-$N_{\leq 0.02}$ versus 39.2 mo for PSA-$N_{0.02–0.2}$ versus 30.7 mo for PSA-$N_{>0.2}$ ($p = 0.02$; Fig. 2A). After multivariable adjustment for PSA at mHSPC and high-volume mHSPC, the hazard ratios for ttCRPC were 4.12 (95% CI 0.08–21; $p = 0.07$) for PSA-N >0.02–0.2 ng/ml and 9.33 (95% CI 0.84–104; $p = 0.07$) for PSA-N >0.2 ng/ml in comparison to PSA-N ≤0.02 ng/ml (Supplementary Table 2).

Analysis of OS revealed a clinically meaningful difference that did not reach statistical significance between the groups (median OS: NR vs NR vs 30.7 mo; $p = 0.3$; Fig. 2B).

Finally, interaction tests revealed no interaction between the time of metastasis onset (synchronous vs metachronous) and PSA-N for ttCRPC and OS analyses (both $p > 0.05$). Furthermore, 6-mo landmark analyses revealed virtually similar results for all the comparisons.

Supplementary Table 1 summarizes baseline patient and tumor characteristics for synchronous versus metachronous mHSPC in the group with post-apalutamide PSA-N ≤0.02 ng/ml. Follow-up without an OS event was 31 mo (IQR 21-41). In the overall group of patients with post-apalutamide PSA-N ≤2 ng/ml, there was no difference in ttCRPC or OS between synchronous and metachronous mHSPC (both $p \geq 0.6$; Supplementary Fig. 1). Analyses after multivariable adjustment confirmed these findings (all $p > 0.3$; Supplementary Table 2).

We initially hypothesized that there would be differences between metachronous and synchronous mHSPC in terms of oncological outcomes and the proportions of patients in post-apalutamide PSA-N categories, especially as PSA values at mHSPC differ between these settings. We tested these hypotheses in a patient cohort from the FRAMCAP database and found that the proportion of patients with post-apalutamide PSA-N ≤0.02 ng/ml was greater in the metachronous mHSPC cohort (52% vs 26%). In the TITAN trial, in which 78% of patients had synchronous metastasis, the PSA-N ≤0.02 ng/ml rate in the overall cohort was 49%

[4,5]. Similar to the TITAN findings, our results demonstrate better cancer control in terms of ttCRPC and OS for post-apalutamide PSA-N $\leq$0.02 ng/ml in both synchronous and metachronous mHSPC. Moreover, in the overall group with post-apalutamide PSA-N $\leq$0.02 ng/ml, we did not find a difference in cancer control outcomes between synchronous and metachronous mHSPC, suggesting that PSA-N $\leq$0.02 ng/ml is an important and robust prognostic biomarker for apalutamide treatment in mHSPC regardless of the timing of metasasis onset. These findings are of particular importance for patient counseling and monitoring and could also help in selecting poor responders for closer follow-up or a change in regimen for further treatment lines. However, clinical follow-up should not rely on just the PSA nadir and should also include regular imaging for staging [10].

Our study is limited by its retrospective and single-center design and by the relatively small sample size for some subgroup analyses. The situation for individual patients may have resulted in adjusted follow-up schedules.

Conflicts of interest: Mike Wenzel reports speaker honoraria from or a consultant role for Accord, Johnson & Johnson, Pfizer, MSD, AstraZeneca, Ipsen, and Bayer. Benedikt Hoeh reports speaker honoraria from or a consultant role for Johnson & Johnson and Ipsen. Thomas Steuber reports speaker honoraria from or a consultant role for Amgen, Astellas, Astellas, AstraZeneca, Bayer, Johnson & Johnson, MSD, Novartis, Pfizer, Proteomedics, and Sanofi. Derya Tilki reports speaker honoraria from or a consultant role for Johnson & Johnson, Ipsen, Exact Sciences, Apogepha, AstraZeneca, Advanced Accelerator Applications, Roche, Takeda, and miR Science. Axel S. Merseburger reports speaker honoraria from or a consultant role for AstraZeneca, BMS, Eisai, Ipsen, MSD, Merck Serono, Bayer, Johnson & Johnson, Takeda, Novartis, Pfizer, Roche, Astellas, and EUSA Pharma. Felix K.H. Chun reports speaker honoraria from or a consultant role for Astellas, AstraZeneca, Bayer, Johnson & Johnson, Lumenis, Novartis, Molecular Health, Olympus, and Pfizer. Philipp Mandel reports speaker honoraria from or a consultant role for Amgen, Astellas, AstraZeneca, Bayer, Ipsen, Johnson & Johnson, MSD, Novartis, Orion, and Pfizer. Carolin Siech and Maximilian Kriegmair have nothing to disclose.

Data sharing statement: Data are available for bona fide researchers on request.

Ethics considerations: This study was approved by the local ethics review board and was conducted in accordance with the Declaration of Helsinki. Patient consent was not applicable for this retrospective analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2025.05.001.

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