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Prostate-specific Antigen Nadir and Cancer-Control Outcomes in Real-world Apalutamide-treated Metastatic Hormone-Sensitive Prostate Cancer Patients: A Single-Center Analysis

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Abstract

Background and objective: Currently available post hoc phase 3 trial–derived data suggest better cancer-control outcomes in apalutamide-treated metastatic hormone-sensitive prostate cancer (mHSPC) patients achieving an (ultra)low prostate-specific antigen (PSA) nadir. This study aims to validate ultralow PSA nadir cutoffs.

Methods: Relying on an institutional prostate cancer database, 107 eligible patients were yielded. The currently available PSA nadir cutoffs (SWOG trial: <0.2 ng/ml; ultralow TITAN trial: ≤0.02 vs 0.02–0.2 vs >0.2 ng/ml) and PSA responses (≥99%) were tested for time to castration-resistant prostate cancer (ttCRPC) and overall survival (OS) in mHSPC patients treated with apalutamide. Finally, comparisons were made against abiraterone mHSPC treatment.

Key findings and limitations: Overall, 107 mHSPC patients treated with apalutamide at a median age of 68 yr and baseline PSA of 29 ng/ml were included. The highest proportion of included patients (40.2%) achieved an ultralow PSA nadir of ≤0.02 ng/ml. Patients reaching the SWOG 9346–defined PSA nadir of <0.2 ng/ml and ultralow PSA nadir of ≤0.02 ng/ml harbored the longest time to metastatic castration-resistant prostate cancer (mCRPC) and OS (all $p < 0.05$). Moreover, 80% of mHSPC patients treated with apalutamide achieved a PSA response of ≥99%. These patients also harbored better time to mCRPC and OS outcomes, relative to patients with a <99% PSA response (both $p < 0.05$). In the second step of analyses, a comparison against abiraterone patients showed a significantly higher rate of achieving an ultralow PSA nadir of ≤0.02 ng/ml: 40.2% versus 8.8% for apalutamide versus abiraterone, resulting in a significantly longer ttCRPC for the apalutamide-treated (37 mo) than for the abiraterone-treated (22 mo) group ($p = 0.001$), even after multivariable adjustment and in sensitivity analyses for high-risk mHSPC patients only. The study is limited by its retrospective design.

Conclusions and clinical implications: In the real-world setting, most mHSPC patients treated with apalutamide achieve an ultralow PSA nadir, which is associated with better cancer-control outcomes. Moreover, a PSA response of ≥99% predicts better outcomes. In head-to-head comparisons, apalutamide achieves better PSA kinetics and ttCRPC outcomes than abiraterone.

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Patient summary: A prostate-specific antigen (PSA) nadir of <0.02 ng/ml and PSA responses ≥99% are associated with better cancer-control outcomes in metastatic hormone-sensitive prostate cancer patients treated with apalutamide.

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1. Introduction

For metastatic hormone-sensitive prostate cancer (mHSPC), the addition of an androgen receptor signaling inhibitor (ARSI) to androgen deprivation therapy (ADT) has become the standard of treatment care [1,2]. For mHSPC, the currently available ARSI treatment options include enzalutamide or apalutamide, either of which is approved irrespectively of the metastatic burden, and abiraterone, which is approved only for high-risk disease according to the LATITUDE criteria [3–9].

The current European Association of Urology (EAU) guidelines recommend and refer for overall survival (OS) estimates in mHSPC patients to PSA nadir stratifications suggested by the SWOG 9346 trial published in 2006, in which mHSPC patients were treated exclusively with ADT [1,10]. Here, the suggested PSA nadir cutoffs were <0.2 versus 0.2–4.0 versus >4.0 ng/ml. However, the currently available post hoc analyses have shown that with intensified combination therapies of ARSIs in addition to ADT, deeper PSA nadirs can be achieved. For example, data of the prospective phase 3 TITAN trial—investigating the effect of apalutamide for mHSPC patients—showed that the majority of apalutamide-treated mHSPC patients (68%) achieved a PSA nadir of <0.2 ng/ml [11]. In consequence, an even deeper PSA nadir for patient stratification and cancer-control outcome estimates was suggested in post hoc analyses, called the ultralow PSA nadir: <0.02 versus 0.02–0.2 versus >0.2 ng/ml [12].

The application of this ultralow PSA nadir cutoffs in the real-world mHSPC patient setting have recently been validated by our working group [13]. However, this previous study focused on all first-line treatments in mHSPC patients treated with intensified combination therapy within the recent years. In consequence, no currently available data tested the effect of the trial-suggested ultralow PSA nadir cutoffs in a homogenous cohort of mHSPC patients treated with apalutamide in the real-world setting regarding cancer-control outcomes. Moreover, only small sized ARSI head-to-head comparisons for PSA kinetics are currently available [14].

We addressed this void and relied on our single-institution mHSPC database to investigate the effect of PSA kinetics in mHSPC patients treated with apalutamide on cancer-control outcomes, namely, on time to metastatic castration-resistant prostate cancer (mCRPC) and OS. We hypothesized that significant differences in time to mCRPC and OS may be observed in the real-world setting regarding ultralow PSA nadir stratification. Moreover, we also hypothesized that important differences exist in the achievements of PSA nadirs according to the different types of ARSI molecular subtypes, such as apalutamide and abiraterone.

2. Patients and methods

2.1. Study population

With the approval of the local ethics committee (approval number: SUG-5-2018) and in compliance with the Declaration of Helsinki, all mHSPC patients treated with apalutamide plus ADT at the Department of Urology, University Hospital Frankfurt, Germany, were identified retrospectively (n = 131). The inclusion criteria required patients to have mHSPC status and the availability of a PSA nadir and its corresponding date if progressed to mCRPC. Patients with unknown follow-up status were excluded. As a result of these criteria, 107 mHSPC patients treated with apalutamide qualified for study inclusion.

2.2. PSA kinetics: PSA nadir and PSA response

A PSA nadir was defined as the lowest PSA value recorded during the apalutamide treatment administered to each mHSPC patient, irrespective of its time point after treatment initiation. Two different sets of PSA nadir cutoffs were applied: The SWOG 9346 trial derived the following PSA nadir cutoffs [9]: <0.2 versus 0.2–4.0 versus >4.0 ng/ml; the post hoc TITAN trial derived the following ultralow PSA nadir cutoffs: <0.02 versus 0.02–0.2 versus >0.2 ng/ml [12].

Additionally, PSA response analyses (<99% vs ≥99%), defined as the percentage decrease in PSA levels relative to the initial PSA measurement taken before the commencement of apalutamide treatment for mHSPC, were applied. Finally, head-to-head comparisons were performed for mHSPC patients treated with apalutamide versus abiraterone plus ADT regarding ultralow PSA nadir cutoffs (<0.02 vs 0.02–0.2 vs >0.2 ng/ml). Additional analyses focused on comparisons for time to mCRPC outcomes in patients treated with apalutamide versus abiraterone, as well as in sensitivity analyses for high-risk (according to the LATITUDE criteria) mHSPC patients only.

2.3. Statistical analysis

Descriptive statistics encompassed frequencies and proportions for the categorical variables used. Medians and interquartile ranges (IQRs) were reported for all continuously coded variables. The chi-square test was employed to assess the statistical significance of differences in proportions. Additionally, the t test and Kruskal-Wallis test were used to evaluate the statistical significance of differences in distributions.

For all analyses, Kaplan-Meier curve–derived estimates, as well as univariable and multivariable Cox regression models were applied. For time to mCRPC in multivariable

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Cox regression models, adjustment was made for absolute PSA value at mHSPC diagnosis, age at mHSPC diagnosis, metastatic burden (low vs high volume according to the CHAARTED criteria [15,16]), and Gleason score. For OS analyses in multivariable Cox regression models, additional adjustment was made for the number of therapy lines received for metastatic prostate cancer. All tests were two sided, with a level of significance set at $p < 0.05$. R software environment for statistical computing and graphics (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

3. Results

3.1. Study population and baseline characteristics

Overall, 107 mHSPC patients treated with apalutamide were included for the current analyses. The median age at mHSPC stage was 68 yr (IQR: 62–75 yr), with a median baseline PSA level of 29 ng/ml (IQR: 8–93 ng/ml; Table 1). In the overall cohort, the median PSA nadir was 0.07 ng/ml (IQR: 0.01–0.39 ng/ml). Most patients (30%) achieved their PSA nadirs within 3–6 mo after treatment initiation with apalutamide. The median follow-up period was 23 mo (IQR: 13–37 mo).

3.2. SWOG 9346 PSA nadir cutoffs

After stratification according to historical SWOG 9346–derived PSA nadir cutoffs, 65.4% achieved a PSA nadir of <0.2 ng/ml versus 28.0% achieving 0.2–4.0 ng/ml versus 6.5% achieving >4.0 ng/ml.

In time to mCRPC analyses (Fig. 1A), significant differences in the comparison between the three PSA nadir groups were observed ($p < 0.001$), with the median time to mCRPC of 47 versus 16 versus 16 mo for a PSA nadir of <0.2 versus 0.2–4.0 versus >4.0 ng/ml. Corresponding univariable hazard ratios (HRs) were 6.3 and 4.0 for, respectively, PSA nadirs 0.2–4.0 and >4.0 ng/ml (both $p<0.01$), relative to the PSA nadir of <0.2 ng/ml. After multivariable adjustment, PSA 0.2–4.0 ng/ml remained an independent predictor of shorter time to mCRPC (HR: 5.3, $p < 0.001$).

In time to OS analyses (Fig. 1B), significant differences were also observed in the comparison between the three PSA nadir groups ($p < 0.001$), with the median OS of not reached (NR) versus 31 mo versus 20 mo for a PSA nadir of <0.2 versus 0.2–4.0 versus >4.0 ng/ml, with corresponding HRs of 4.9 and 4.1 for PSA nadirs 0.2–4.0 and >4.0 ng/ml (both $p \leq 0.037$). In multivariable Cox regression models, no significant OS differences were observed.

3.3. Ultralow PSA nadir cutoffs

After stratification according to the more recent TITAN-derived ultralow PSA nadir cutoffs, 40.2% achieved a PSA nadir of ≤0.02 ng/ml versus 27.1% achieving 0.02–0.2 ng/ml versus 32.7% achieving >0.2 ng/ml. In comparisons between these three groups (Table 1), patients with a PSA nadir of >0.2 ng/ml harbored a significantly higher PSA value at mHSPC diagnosis (84 ng/ml), relative to the other

Table 1 – Descriptive characteristics of 107 metastatic hormone-sensitive prostate cancer (mHSPC) patients treated with apalutamide, stratified according to ultralow PSA nadir cutoffs

Characteristic	*N*	Overall (*N* = 107)[a]	PSA nadir ≤0.02 ng/ml (*N* = 43; 40%)[a]	PSA nadir 0.02–0.2 ng/ml (*N* = 29; 27%) [a]	PSA nadir >0.2 ng/ml (*N* = 35; 33%)[a]	*p* value[b]
Age at metastatic PCa (yr)	106	68 (62, 75)	68 (62, 73)	67 (63, 73)	70 (62, 79)	0.7
PSA at mHSPC (ng/ml)	99	29 (8, 93)	9 (4, 44)	25 (12, 84)	84 (26, 430)	<0.001
PSA nadir at mHSPC (ng/ml)	107	0.07 (0.01, 0.39)	0.001 (0.001, 0.01)	0.10 (0.06, 0.13)	0.90 (0.42, 2.58)	<0.001
PSA decline ≥99%	99	79 (80)	40 (98)	22 (85)	17 (53)	<0.001
PSA at mCRPC (ng/ml)	25	17 (1, 77)	1 (0, 5)	15 (2, 20)	21 (12, 89)	0.11
Systemic therapy lines for PCa	107	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	0.035
ECOG status ≥2	88	3 (3.4)	0 (0)	1 (4.0)	2 (7.1)	0.10
Gleason score 8–10	103	76 (74)	33 (77)	18 (72)	25 (71)	0.8
Local therapy with RP/RT	107	47 (44)	24 (56)	13 (45)	10 (29)	0.054
pT 3–4	48	40 (83)	22 (88)	10 (100)	8 (62)	0.041
pN1	45	20 (44)	11 (44)	4 (40)	5 (50)	>0.9
MDT	104	21 (20)	10 (24)	7 (25)	4 (11)	0.3
Visceral metastasis mHSPC	105	9 (8.6)	3 (7.1)	1 (3.4)	5 (15)	0.3
High-volume mHSPC	99	40 (40)	8 (20)	8 (30)	24 (75)	<0.001
High-risk mHSPC	100	50 (50)	18 (43)	8 (31)	24 (75)	0.002
De Novo mHSPC	106	74 (70)	26 (60)	19 (66)	29 (85)	0.052
Time to PSA Nadir (mo)	66					0.2
<3		13 (20)	3 (11)	6 (40)	4 (17)	
3–6		20 (30)	7 (25)	3 (20)	10 (43)	
6–12		16 (24)	7 (25)	4 (27)	5 (22)	
>12		17 (26)	11 (39)	2 (13)	4 (17)	
Treatment of mCRPC	107					0.01
ADT mono		1 (0.9)	0 (0)	0 (0)	1 (2.9)	
ARSI		12 (11)	2 (4.7)	4 (14)	6 (17)	
Chemotherapy		13 (12)	4 (9.3)	1 (3.4)	8 (23)	
Lu-PSMA		2 (1.9)	0 (0)	0 (0)	2 (5.7)	
None/other/NA		79 (74)	37 (86)	24 (83)	18 (51)	

ADT = androgen deprivation therapy; ARSI = androgen receptor signaling inhibitor; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; Lu-PSMA = lutetium prostate-specific membrane antigen radioligand therapy; mCRPC = metastatic castration-resistant prostate cancer; MDT = metastasis-directed therapy; NA = not available; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

[a] Data are presented as median (IQR) or *n* (%).

[b] Kruskal-Wallis rank sum test, Fisher's exact test, and Pearson's chi-square test.

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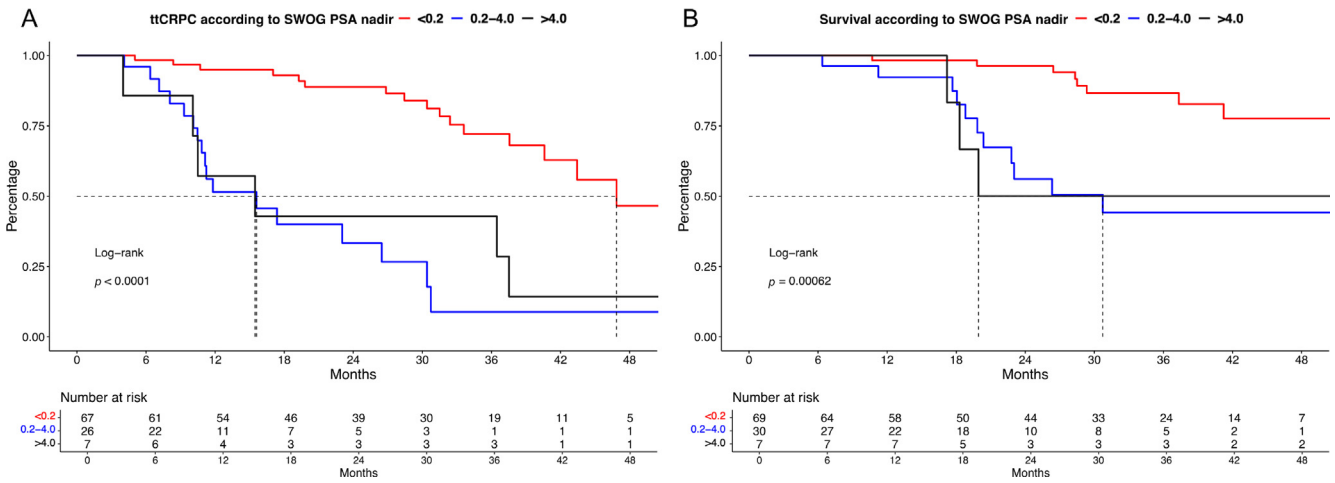


Fig. 1 – Kaplan-Meier curves depicting (A) time to metastatic castration-resistant prostate cancer (ttCRPC) and (B) overall survival, according to SWOG 9346 PSA nadir cutoffs (<0.2 vs 0.2–4.0 vs >4.0 ng/ml), in metastatic hormone-sensitive prostate cancer patients treated with apalutamide. PSA = prostate-specific antigen.

groups (9 and 25 ng/ml, $p < 0.001$). Conversely, mHSPC patients achieving a PSA nadir of ≤0.02 ng/ml harbored the lowest rates of high-volume mHSPC (20% vs 30% vs 75%, $p < 0.01$), as well as the lowest rates of de novo mHSPC (60% vs 66% vs 85%, $p = 0.052$).

In time to mCRPC analyses (Fig. 2A), significant differences were observed between the three PSA nadir groups ($p < 0.001$), with the median time to mCRPC of NR versus 38 mo versus 16 mo for a PSA nadir of ≤0.02 versus 0.02–0.2 versus >0.2 ng/ml. Corresponding univariable HRs were 2.6 and 10.2 for PSA nadirs 0.02–0.2 and >0.2 ng/ml (both $p \leq 0.047$), relative to the PSA nadir of ≤0.02 ng/ml. After multivariable adjustment, PSA 0.02–0.2 ng/ml did not achieve significance (HR: 2.5, $p = 0.087$), while PSA >0.2 ng/ml remained an independent predictor of shorter time to mCRPC (HR: 9.1, $p < 0.001$).

In time to OS analyses (Fig. 2B), significant differences in the comparison between the three PSA nadir groups were also observed ($p < 0.001$), with the median OS of not NR versus NR versus 26 mo for a PSA nadir of ≤0.02 versus 0.02–0.2 versus >0.2 ng/ml, with corresponding HRs of 7.1 and 14.8 for PSA nadirs 0.02–0.2 and >0.2 ng/ml (both $p \leq 0.01$). After multivariable adjustment, PSA >0.2 ng/ml was also associated with a higher risk of death (HR: 6.5, $p = 0.026$).

3.4. *PSA response: ≥99% versus <99%*

After stratification regarding relative PSA responses with apalutamide mHSPC treatment, 79.8% achieved a PSA response of ≥99%. In time to mCRPC analyses (Fig. 3A), the median time to mCRPC was 47 versus 11 mo for a PSA response of ≥99% versus <99% (HR: $p < 0.001$), with a protective HR of 0.22 for PSA response ≥99%. After additional multivariable adjustment, a PSA response of ≥99% was independently associated with a protective effect (HR: 0.15, $p < 0.001$).

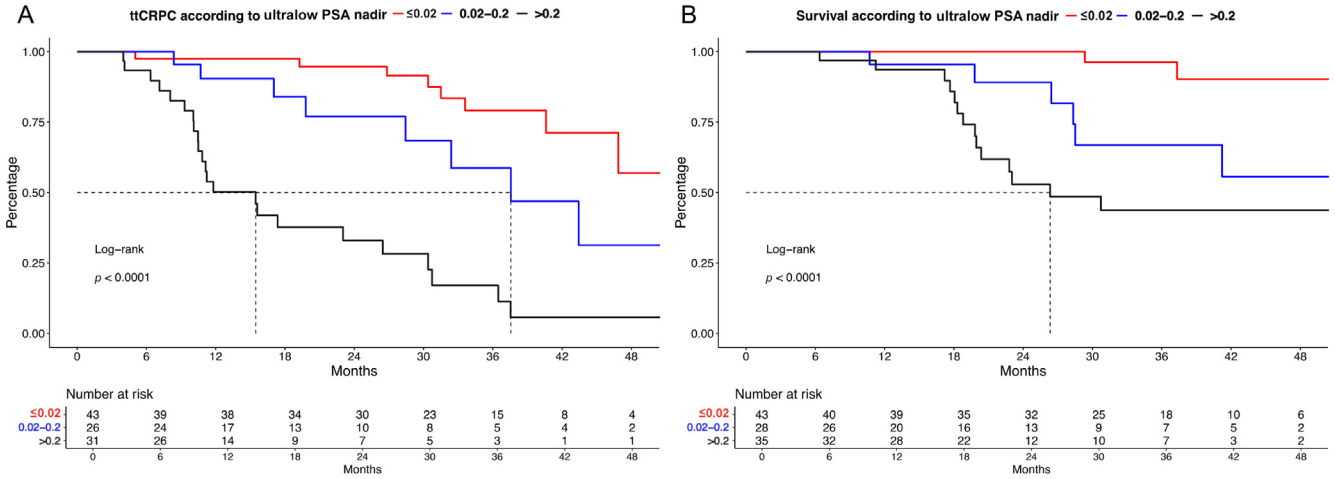


Fig. 2 – Kaplan-Meier curves depicting (A) time to metastatic castration-resistant prostate cancer (ttCRPC) and (B) overall survival, according to ultralow PSA nadir cutoffs (≤0.02 vs 0.02–0.2 vs >0.2 ng/ml), in metastatic hormone-sensitive prostate cancer patients treated with apalutamide. PSA = prostate-specific antigen.

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In OS analyses, significant differences were observed (Fig. 3B) in the median OS of NR versus 23 mo for a PSA response of ≥99% versus <99% (HR: 0.18, $p < 0.001$). In multivariable Cox regression models, a PSA response of ≥99% remained a protective effect (HR: 0.08, $p < 0.001$).

3.5. *ARSI comparisons: abiraterone versus apalutamide*

In the second part of the analyses, comparisons were made regarding reaching an ultralow PSA nadir cutoff in mHSPC patients treated with abiraterone versus apalutamide (Fig. 4A). Here, significantly more mHSPC patients achieved a PSA nadir of ≤0.02 ng/ml with apalutamide than with abiraterone (40.2% vs 8.8%, $p < 0.001$). These differences in PSA nadir proportions translated into significant time to mCRPC differences for abiraterone (22 mo) versus apalutamide (37 mo, $p = 0.001$). Univariable (HR: 0.51) and multivariable (HR: 0.31) Cox regression models showed a significant positive effect for apalutamide versus abiraterone regarding time to mCRPC (both $p \leq 0.001$). In additional sensitivity analyses of high-risk mHSPC patients only, patients were balanced with no differences in primary local treatment rates ($p \geq 0.05$), and virtually similar results were observed (Supplementary Fig. 1).

4. Discussion

We initially hypothesized that statistically significant and clinically meaningful differences in time to mCRPC and OS may be observed in the real-world setting regarding PSA nadir stratifications in mHSPC patients treated with apalutamide. Additionally, we also hypothesized that important differences exist in the achievements of PSA nadirs, as well as cancer-control outcomes according to the different types of ARSI subtypes. We tested these hypotheses within our metastatic prostate cancer database and made several important observations.

First, when stratification was made according to the more historical PSA nadir stratifications derived from the SWOG 9346 trial, the majority of mHSPC patients treated with apalutamide (65%) achieved a PSA nadir of <0.2 ng/ml. Conversely, only 6.5% of mHSPC patients treated with apalutamide had a PSA nadir of >4.0 ng/ml. In the SWOG 9346 trial, in which mHSPC patients received only ADT monotherapy, only 43% of patients achieved a PSA nadir of <0.2 ng/ml, while a large proportion (31%) had a PSA nadir of >4.0 ng/ml [10]. Moreover, despite the similarity to the SWOG 9346 trial published in 2006, within our study, the best cancer-control outcomes were observed in mHSPC patients treated with apalutamide with a PSA nadir of <0.2 ng/ml. Median OS times exceeded those of the historical study. For example, median OS in patients with a PSA nadir of >4.0 ng/ml was 20 mo in our study, while it was 14 mo in the SWOG 9346 trial [10]. One explanation may be that, besides the use of a combination therapy in mHSPC, especially within our study with apalutamide, the more frequent use of life-prolonging agents in later lines of mCRPC-progressed patients, with newer available systemic treatments [17–20]. Moreover, the SWOG 9348–derived distinction into subgroups of PSA nadirs of 0.2–4.0 and >4.0 ng/ml did not stratify patients very well within our study when cancer-control outcomes were compared. These observations indicate that the SWOG 9346 PSA nadir cutoffs do not properly stratify mHSPC patients treated with intensified combination therapies anymore, although these are still EAU guideline recommended [1]. Therefore, it might be better to combine these two subgroups and further define the "low" PSA subgroups as "ultralow" PSA subgroups. These assumptions are also supported by newly available data from post hoc analyses of the prospective ARASENS phase 3 trial, in which also the vast majority (67%) of patients achieved a PSA nadir of <0.2 ng/ml for triplet therapy with ADT plus docetaxel and darolutamide [21].

Second, when stratification was made according to the newly introduced ultralow PSA nadir cutoffs within our study, we observed that still 40% of apalutamide mHSPC patients achieved a PSA nadir of ≤0.02 ng/ml. These rates are slightly lower but comparable with the post hoc analyses from the TITAN trial, where 49% of mHSPC patients treated with apalutamide achieved a PSA nadir of ≤0.02 ng/ml

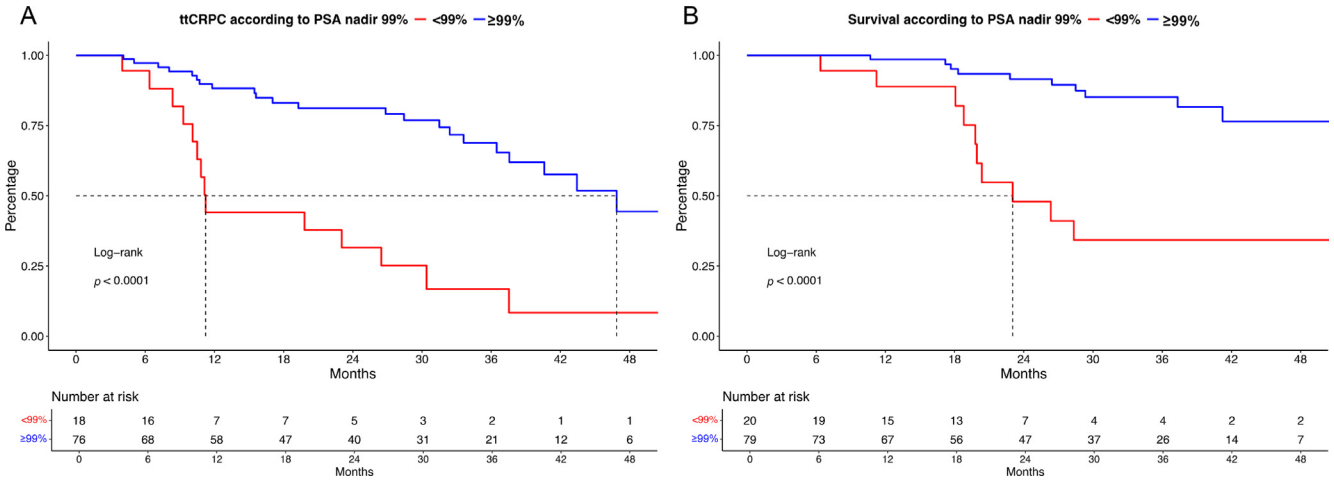


Fig. 3 – Kaplan-Meier curves depicting (A) time to metastatic castration-resistant prostate cancer (ttCRPC) and (B) overall survival relative to PSA decline (<99% vs ≥99%) in metastatic hormone-sensitive prostate cancer patients treated with apalutamide. PSA = prostate-specific antigen.

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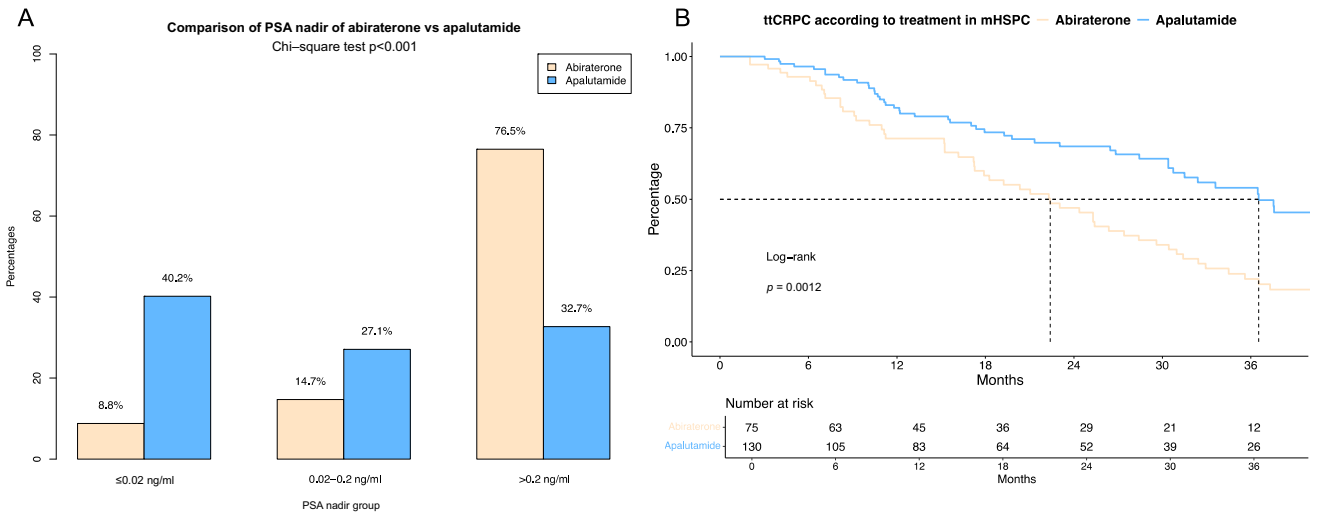


Fig. 4 – (A) Bar plot comparing the achievement of ultralow PSA nadir in comparison of metastatic hormone-sensitive prostate cancer (mHSPC) patients treated with abiraterone versus apalutamide, and (B) Kaplan-Meier curves depicting time to metastatic castration-resistant prostate cancer (ttCRPC) in mHSPC patients treated with abiraterone versus apalutamide. PSA = prostate-specific antigen.

[12]. However, patients within our study harbored clinically meaningful differences in initial characteristics, which may explain these proportional differences, such as the median baseline PSA of 29 versus 6 ng/ml in the TITAN trial [12]. In comparison with patients not achieving an ultralow PSA nadir in our study, mHSPC patients treated with apalutamide with a PSA nadir of ≤0.02 ng/ml harbored more favorable baseline and tumor characteristics, such as lower PSA at mHSPC diagnosis and lowest rates of high-volume, high-risk, and de novo mHSPC.

When cancer-control outcomes were analyzed, better distinction between the three groups suggests ultralow PSA nadir cutoffs. More specifically, in patients achieving a PSA nadir of ≤0.02 ng/ml under apalutamide treatment, the best time to mCRPC and OS rates were observed. These observations are also in an agreement with the post hoc TITAN ultralow PSA nadir data [12]. However, within our real-world setting of mHSPC patients treated with apalutamide, the median times to mCRPC and OS were lower than those reported in the post hoc analyses (median of NR after 48 mo in the TITAN trial). These observations may also be explained party by worse baseline characteristics within our study.

Third, when relative PSA responses (≥99% vs <99%) were compared, significantly better time to mCRPC and OS outcomes were also observed for mHSPC patients treated with apalutamide, with a PSA response of ≥99%. The application of a PSA response ≥99% cutoff may be interpreted as relatively high, since most post hoc analyses of phase 3 trials or real-world studies report on PSA ≥90% or even PSA ≥50% response rates [22–25]. However, as described above, with wide adoption of intensified combination therapies for mHSPC, a significant proportion of patients achieve very low PSA levels under treatment, and in, for example, a patient with an initial PSA value of 100 ng/ml, a PSA ≥90% response still remains a PSA nadir of 10 ng/ml, which is—as outlined—associated with poor cancer-control outcomes. Therefore, we believe that a PSA response of ≥99% selects mHSPC patients with intensified combination therapy in a more sufficient way than patients with a lower percentual decline of PSA levels. Comparing these arguments with currently available medical literature, two recently published real-world cohorts of mHSPC patients with triplet therapy achieved a median PSA response between 90% and 99% [26,27].

Finally, when comparisons were made between mHSPC patients treated with apalutamide and abiraterone, we observed that the proportions of patients achieving a PSA nadir of ≤0.02 was significantly higher for all included patients (40% vs 8.8%), as well as (in sensitivity analyses) for LATITUDE high-risk mHSPC patients under apalutamide (36% vs 3.7%). In consequence, these differences in PSA nadir achievements also translated into better time to mCRPC outcomes for mHSPC patients treated with apalutamide. Compared with previously reported post hoc analyses from the LATITUDE phase 3 trial in which only high-risk mHSPC patients were included, PSA nadir proportions are substantially lower within our real-world cohort. For example, in the LATITUDE trial, 40% achieved a PSA nadir of <0.01 ng/ml [25]. However, comparing time to mCRPC outcomes, results similar to those of the present study can be found in the current literature. For example, in a report of Lu et al [14], the median time to mCRPC was 24 mo for abiraterone (vs 22 mo in our report) and lower than for apalutamide (median time of NR). Similar observations were also made by an American population-matched analysis, in which 68% of apalutamide-treated versus 49% of abiraterone-treated mHSPC patients achieved a PSA response of ≥90% [28]. Unfortunately, these observations for apalutamide cannot be extrapolated to all molecular lutamide subtypes in this study, since other lutamide subgroups were too small for further analyses. However, data from phase 3 trials incorporated within network meta-analyses show mostly comparable results for apalutamide versus enzalutamide [29].

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Additional limitations of the current study should be acknowledged in its interpretation, such as the retrospective, single-center design. Moreover, some subgroups may be underpowered for subsequent analyses or multivariable adjustments. Some patients may be excluded from analyses due to unknown PSA nadir values or dates of progression, and may have possibly introduced an unaccountable bias. Additionally, no landmark PSA nadir analyses could be performed due to nonstandardized PSA measurement dates. Finally, differences in staging modalities such as prostate-specific membrane antigen positron emission tomography/-computed tomography might have detected patients at earlier metastatic stage and might have led to better cancer-control outcomes (lead-time bias).

5. Conclusions

Taken together, this real-world analysis of mHSPC patients treated with apalutamide suggests that historical PSA nadir cutoffs may not sufficiently distinguish between contemporary mHSPC patients. Moreover, the study shows that the newly introduced ultralow PSA nadir cutoffs are applicable in clinical practice and in the prediction of cancer-control outcomes. Finally, better short-term PSA responses and cancer-control outcomes can be achieved in all and high-risk mHSPC patients treated with apalutamide than in those treated with abiraterone, and therefore, among other reasons, apalutamide might be preferred to abiraterone in first-line mHSPC treatment.

Author contributions: Mike Wenzel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wenzel, Cano Garcia, Humke, Mandel.
Acquisition of data: Wenzel, Cano Garcia.
Analysis and interpretation of data: Wenzel, Cano Garcia, Humke, Hoeh, Mandel.
Drafting of the manuscript: Wenzel, Mandel.
Critical revision of the manuscript for important intellectual content: Steuber, Tilki, Merseburger, Kluth, Chun.
Statistical analysis: Wenzel, Hoeh.
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Data sharing: Data are available for bona fide researchers who request it from the authors.

Ethics statement: The current study was in accordance with the Declaration of Helsinki. Local review of the ethics board was approved.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.08.007.

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