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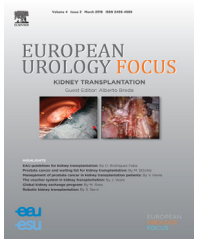

Prostate Cancer

Treatment of Metastasized Prostate Cancer Beyond Progression After Upfront Docetaxel—A Real-world Data Assessment

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Abstract

Background: Besides second-generation hormone therapy (sHT), upfront docetaxel along with androgen deprivation therapy is the current standard of care for metastasized hormone-sensitive prostate cancer (mHSPC). Evidence on second-line therapy upon progression on chemohormonal treatment outside clinical trials is scarce.
Objective: To comparatively assess the efficacy of subsequent therapy after upfront docetaxel in mHSPC in a real-world setting.
Design, setting, and participants: This is a retrospective multicenter analysis. Males with mHSPC on androgen-deprivation therapy progressed to castration-resistant prostate cancer (CRPC) after upfront docetaxel.
Outcome measurements and statistical analysis: Overall survival (OS), progression-free survival 2 (PFS2), and time to progression 2 (TTP2) were assessed. Chi-square test and Mann-Whitney *U* test were used for univariate comparison between the sHT and non-sHT (other therapies) cohorts. Median time to event was tested by Kaplan-Meier method and log-rank test. Univariate and multivariate analysis regression was performed with the Cox proportional-hazard model.
Results and limitations: Sixty-five patients were included in the final analysis. Median TTP2 was 20 mo, median PFS2 was 29 mo, and median OS was not reached; sHT was an independent predictor of favorable PFS2 as compared with non-sHT. Time to CRPC was also confirmed to be the strongest predictor for novel endpoints PFS2 and TTP2. Time to CRPC >18 mo conferred advantage to sHT over non-sHT in relation to PFS2 and OS. Second-line therapies were well tolerated. The analysis is prone to inherent flaws and biases due to its retrospective nature.
Conclusions: In real-world patients progressing after upfront docetaxel, sHT is independently associated with favorable PFS2 favoring drug class switch. Longer time to CRPC predicts strongly for superior PFS2 and TTP2. Further prospective research is

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warranted in order to guide treatment sequencing and improve outcomes and quality of life of males with metastasized prostate cancer.

Patient summary: We analyzed the efficacy of second-line therapy after docetaxel in hormone-dependent metastatic prostate cancer. Novel hormone therapy appears to be a preferable option for deferring progression optimally. Larger patient databases are eagerly awaited.

1. Introduction

After years of therapeutic status quo with androgen deprivation therapy (ADT) being the mainstay in systemic treatment of metastasized hormone-sensitive prostate cancer (mHSPC), CHAARTED was the first randomized controlled trial (RCT) to demonstrate significant prolongation of overall survival (OS) with docetaxel utilized upfront when commencing ADT [1]. This finding, further consolidated by the results of the STAMPEDE (arm C) RCT, enlivened the value of docetaxel in the therapeutic paradigm of metastatic prostate cancer (mPC), which eventually became less important due to registration of well-tolerated and orally administered second-generation hormone therapy (sHT) first in the context of metastasized castration-resistant prostate cancer (mCRPC) [2–6]. While long-term results of CHAARTED reported OS benefit of cytotoxic treatment particularly for de novo and high-volume mHSPC, follow-up data of STAMPEDE suggested no evidence that survival advantage differs by metastatic burden [7,8].

Recently, sHT was introduced also in the mHSPC setting, challenging the role of docetaxel once again. Thus, LATITUDE showed OS advantage for abiraterone acetate in patients with high-risk disease and led to the regulatory licensing in this indication [9]. Anticancer activity of abiraterone acetate in mHSPC was further corroborated by the findings of STAMPEDE (arm G) in all patients irrespective of the risk or volume stratification [10]. However, these results did not influence the approval status of the drug. Furthermore, TITAN yielded survival benefit for apalutamide, and ENZAMET (OS) and ARCHES (radiographic progression-free survival [PFS]) for enzalutamide in all males with mHSPC [11,12]. Thus, the standard of care in the first-line management of mHSPC is currently combined treatment of ADT and either docetaxel or sHT.

Importantly, evidence on the second-line therapy in mHSPC is scarce. Two reports including North American and Australian patients as well as an analysis of subsequent therapies of the French GETUG-AFU 15 RCT population were reported thus far [13–15]. Therefore, the objective of this multicenter European study was to comparatively analyze anticancer activity of second-line treatment options after progression on chemohormonal protocol in mHSPC in a real-world setting.

2. Patients and methods

2.1. Data collection

In this retrospective multicenter analysis including data of six institutions (Mainz, Munich, Milan, Utrecht, Toulouse, and Innsbruck) from five countries, clinical characteristics of 65 mPC patients were collected into the database in accordance to the local ethical standards and the declaration of Helsinki. The inclusion criteria were receiving first-line treatment with docetaxel (at least four and no more than six cycles) for mHSPC with at least one completed line of subsequent treatment. Two cohorts were formed based on the drug used in second-line treatment (sHT vs non-sHT). Docetaxel treatment was initiated between November 2014 and May 2019, and the standard dose was 75 mg/m^2 body surface. Adverse events were classified according to the Common Terminology of Adverse Events of the National Cancer Center version 5 [16]. Clinical outcomes were investigated by the analysis of OS (time from the start of ADT until death), time to progression 2 (TTP2; time from the start of ADT to clinical, biochemical, or radiographic progression during second line), and PFS2 (time from the start of ADT to clinical, biochemical, or radiographic progression or death from any cause). Time to castration-resistant prostate cancer (CRPC) was defined as the time from the start of docetaxel therapy to the start of second-line treatment. For time to CRPC subcohort analysis, the population was divided into two groups (time to CRPC $\leq$18 and $>$18 mo).

2.2. Statistical analysis

Chi-square and Mann-Whitney *U* test were used for univariate comparison between the sHT and the non-sHT cohort. Median time to event was tested by the Kaplan-Meier method and log-rank test. Further univariate and multivariate survival analysis regression was performed with the Cox proportional-hazard model, while time to CRPC was regarded as a time-dependent covariate. Significance level was set to $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

3. Results

Clinical characteristics of the 65 patients who underwent first-line chemotherapy with docetaxel for mHSPC followed by at least one subsequent treatment line are presented in Table 1. The majority of the patients (77.6%) had a good performance status (Eastern Cooperative Oncology Group [ECOG] 1) at the start of the first-line treatment. All patients had an initial histopathological diagnosis of adenocarcinoma of the prostate; 70% had an International Society of Urological Pathology (ISUP) grading $\geq$4 (Gleason score $\geq$8) and 74% a high-disease volume according to the CHAARTED criteria. Median time to CRPC was 19.07 mo. Most patients (90%) underwent six cycles of docetaxel chemotherapy. Forty-eight patients received sHT in the second line (31 abiraterone acetate and 17 enzalutamide), 12 patients underwent chemotherapy in the second line (six docetaxel and six cabazitaxel), four patients were treated with radium-223, and one patient was treated with lutetium-177 prostate-specific membrane antigen (LuPSMA). Of the patients, 91.2% presented a biochemical response to first-line chemotherapy with docetaxel as well as 75.5% to second-line

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Table 1 – Clinical baseline characteristics and group comparison (non-sHT vs sHT second-line therapy) of prostate cancer patients undergoing at least one subsequent treatment for CRPC after first-line docetaxel chemotherapy.

Variable	All patients (*N* = 65)		Non-sHT (*n* = 17)		sHT (*n* = 48)		*p* value
	%	*n*	%	*n*	%	*n*	
Median age (yr), IQR	66	61.00–71.75	64	60–68.5	66.00	62–73.0	0.21
ECOG at metastasis diagnosis							
0	76.6	49	76.5	13	75.0	36	0.74
1	23.4	15	17.6	3	25.0	12	
Median PSA at diagnosis (ng/mL), IQR	95.5	22.75–286.00	57	17–239	140.50	36.75–343.25	0.11
ISUP grade							0.78
1	2.0	1.0	6.7	1			
2	4.0	2.0	6.7	1	2.9	1	
3	14.0	7.0	6.7	1	17.1	6	
4	26.0	13.0	20.0	3	28.6	10	
5	54.0	27.0	60.0	9	51.4	18	
Median time to CRPC (mo), IQR	19.07	12.00–25.00	16.88	8.00–23.00	19.87	13.00–27.00	0.317
Primary tumor treatment							
Radical prostatectomy	4.7	3	11.8	2	2.1	1	0.14
Radiotherapy	3.0	2			4.2	2	
No primary treatment	92.3	60	88.2	15	93.7	45	
Disease volume (CHAARTED)							
High	74.1	40	23.5	12	58.3	28	1.00
Low	25.9	14	70.6	4	20.8	10	
Site of metastases							
Nodal	53.8	35	64.7	11	50.0	24	0.54
Osseous	81.5	53	88.2	15	79.2	38	0.50
Visceral	15.4	10	29.4	5	10.4	5	0.25
Number of docetaxel cycles							0.52
4	3.7	2	11.8	2	0	0	
5	5.6	3	0.0	0	6.25	3	
6	90.7	49	82.4	14	72.92	35	
Median PSA start second line (ng/mL), IQR	39.5	14.50–82.00	44	21.50–137.00	31	44.00–104.00	0.372
Second-line treatment							
Docetaxel	8.8	6	35.3	6			
Cabazitaxel	8.8	6	35.3	6			
Abiraterone	45.6	31			64.6	31	
Enzalutamide	25.0	17			35.4	17	
Radium223	5.9	4	23.5	4			
LuPSMA	1.5	1	5.9	1			
Subsequent treatments							
Docetaxel	8.1	3			12.5	3	
Cabazitaxel	37.8	14	33.3	4	41.7	10	
Abiraterone	27.0	10	50.0	6	16.7	4	
Enzalutamide	8.1	3	8.3	1	8.3	2	
Radium223	2.7	1			4.2	1	
LuPSMA	5.4	2			8.3	2	
Samarium	8.1	3			8.3	2	
Etoposide/carboplatin	2.7	1	8.3	1	0.0		

CRPC = castration resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; ISUP = International Society of Urological Pathology; LuPSMA = lutetium-177 prostate-specific membrane antigen; PSA = prostate-specific antigen; sHT = second-generation hormone therapy.

treatment. A decline in prostate-specific antigen (PSA) level of ≥50% from baseline could be observed for 84.2% of the patients after first-line treatment with docetaxel and for 53.1% after second-line treatment (Fig. 1). Four patients had a PSA progression of at least 25% during/after docetaxel therapy, indicating nonresponsiveness. Second-line treatments for these patients consisted of abiraterone (*n* = 2), enzalutamide (*n* = 1), and LuPSMA (*n* = 1). One of these patients died after 24 mo without tumor progression, and two patients had progression after 11 and 28 mo. Comparing the non-sHT and sHT cohorts, no significant difference in clinical characteristics could be noticed (Table 1). The non-sHT and sHT cohorts were also equally balanced, after creation of the subcohorts for time to CRPC ≤18 and >18 mo (data not shown).

Clinical outcomes of all patients and the sHT and non-sHT cohorts are presented in Table 2. For all patients, the median time to follow-up was 27 mo, median TTP2 was 20 mo, median PFS2 was 29 mo, and median OS was not reached. Frequencies of adverse events were equally balanced between the sHT and non-sHT cohorts. A better biochemical response to second-line treatment could be noticed in the sHT cohort (PSA change from baseline to nadir –46.04% vs 12.59%, $p = 0.04$). OS was significantly longer for sHT than for non-sHT treatment (median not reached vs 43 mo, $p = 0.019$; hazard ratio [HR] = 3.734, 95% confidence interval [CI] 1.135–12.280,

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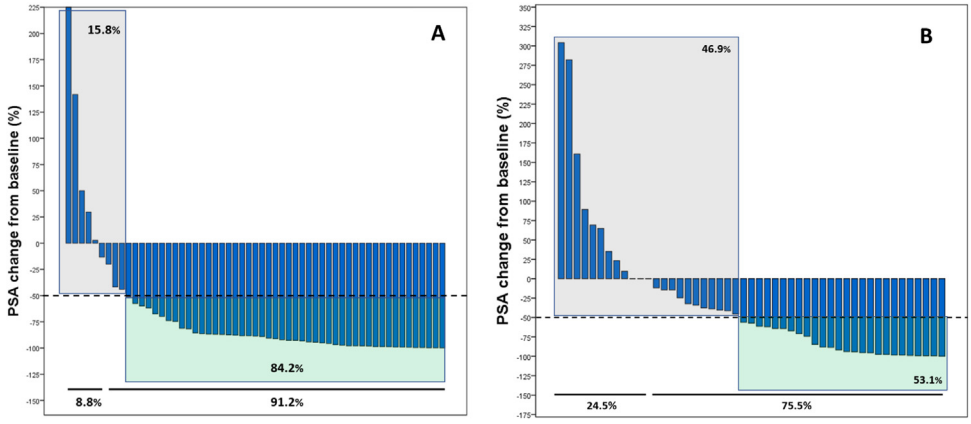

Fig. 1 – PSA change (%) from baseline to (A) end of first-line treatment with docetaxel and (B) nadir in second-line therapy, for all patients. PSA = prostate-specific antigen.

Table 2 – Clinical outcome characteristics and group comparison (non-sHT vs sHT second-line therapy) of prostate cancer patients undergoing at least one subsequent treatment after first-line docetaxel chemotherapy.

Variable	All patients			Non-sHT			sHT			
	Mean	Median	IQR	Mean	Median	IQR	Mean	Median	IQR	*p* value
Time to follow-up	29.16	27	21.75–38.500	25.17	25	15.5–35.75	30.48	28.00	23–40	0.28
OS	47.33	Not reached		37.73	43	21.00–58.00	47.33	Not reached		**0.019**
TTP2	23.74	20	16.00–20.00	23.66	19	11.00–30.00	23.77	20.00	18.00–28.00	0.914
PFS2	31.04	29	19.00–44.00	25.20	27	12.00–39.00	33.30	32.00	20.00–48.00	0.056
PSA change from baseline to end of first line (%)	−54.94	−88.6	−97.8 to −68.65	−62.42	−87.7	−93.2 to −57.5	−52.26	−89.80	−97.85 to −72.825	0.40
PSA change from baseline to nadir second line (%)	−30.49	−57.2	−94.05 to −5.85	12.59	0	−68.95 to 62.15	−46.04	−62.70	−97.025 to −72.825	**0.04**
PSA50 response first line										
Yes (%, *n*)	84.2	48		13	86.7		35	83.3		1.00
No (%, *n*)	15.8	9		2	13.3		7	16.7		
PSA50 response second line										
Yes (%, *n*)	53.1	26		5	38.5		21	58.3		0.332
No (%, *n*)	46.9	23		8	61.5		15	41.7		
CTCAE in second line										
Grade I–II (%, *n*)	55.7	39		58.8	10		60.4	29		0.089
Grade III–IV (%, *n*)	11.4	8		29.4	5		6.3	3		

CTCAE = Common Terminology Criteria for Adverse Events; IQR = interquartile range; OS = overall survival; PFS2 = progression-free survival 2; PSA = prostate-specific antigen; PSA50 response = PSA decrease of ≥50% from baseline; sHT = second-generation hormone therapy; TTP2 = time to progression 2.

p = 0.03). TTP2 and PFS did not differ significantly between both cohorts. Kaplan-Meier curves are presented in Figure 2. Analyzing the time to CRPC subgroups, the sHT group had significantly longer OS (median not reached vs 42 mo; p = 0.009; HR = 12.24, 95% CI 1.100–136.438, p = 0.038) and PFS2 (median 44 vs 30 mo, p = 0.024; HR = 3.16, 95% CI 1.092–9.146, p = 0.044) than the non-sHT group when time to CRPC was >18 mo (Fig. 3). Regarding TTP2 as well as PFS2 and OS for patients with time to CRPC ≤18 mo, no difference for both treatment options could be observed.

In the univariate Cox regression analyses, the status of visceral metastasis was associated with inferior PFS2 (HR = 4.234, 95% CI 1.277–14.036, p = 0.018), TTP2 (HR = 3.650, 95% CI 1.044–12.758, p = 0.043) and OS (HR = 9.650, 95% CI 1.002–92.074, p = 0.050). Moreover, PSA change from baseline to nadir in the second line was associated with OS (HR = 1.005, 95% CI 1.001–1.009, p = 0.021). Results are presented in Supplementary Table 1.

In the multivariate Cox regression model, more rapid progression to CRPC was associated with inferior PFS2 (HR = 18.729, 95% CI 6.010–58.362, $p < 0.001$), TTP2 (HR = 14.204, 95% CI 4.541–44.436, $p < 0.001$), and OS (HR = 16.688, 95% CI 1.818–153.212, p = 0.013). Moreover, non-sHT was inferior to sHT as the second-line treatment in regard to PFS2 (HR = 3.201, 95% CI 1.205–8.502, p = 0.020). The results are shown in Table 3.

4. Discussion

Upfront combination therapy consisting of ADT and docetaxel or sHT is the new standard of care in the first-line systemic management of mHSPC [17]. Given the lack of direct comparisons between the agents, potentiated by survival advantage conferred by radiotherapy of the primary tumor in patients with a low-burden disease as well as efficacy of stereotactic ablative radiotherapy of metastatic

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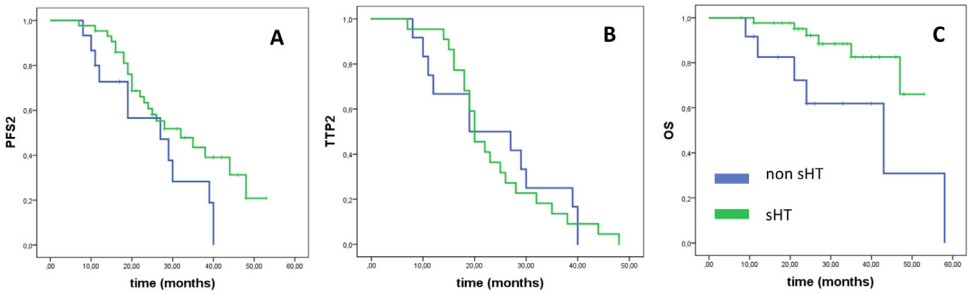

Fig. 2 – (A) Progression-free survival 2 (PFS2), (B) time to progression in second-line therapy (TTP2), and (C) overall survival (OS) for patients receiving at least one treatment for CRPC. CRPC = castration-resistant prostate cancer; sHT = second-generation hormone therapy.

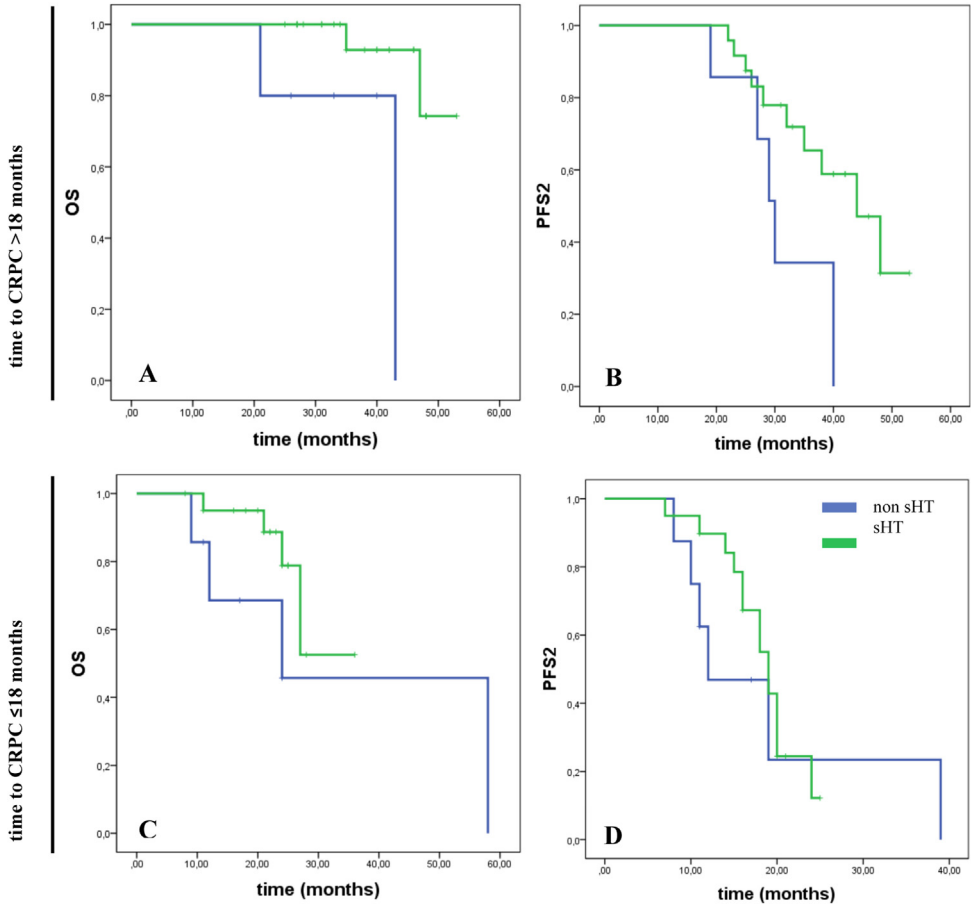

Fig. 3 – (A) Overall survival and (B) progression-free survival 2 for patients undergoing at least one treatment for CRPC with time to CRPC >18 mo. (C) Overall survival and (D) progression-free survival 2 for patients undergoing at least one treatment for CRPC with time to CRPC ≤18 mo. CRPC = castration-resistant prostate cancer; OS = overall survival; PFS2 = progression-free survival 2; sHT = second-generation hormone therapy.

sites in oligometastatic mHSPC, customized care is particularly challenging in this setting [17–19]. Since clinical benefit of the available drugs is comparable, safety profiles, country-dependent regional availability, and costs differ considerably [20]. Thus, further efforts on refinement of clinical subgroup classifications and incorporation of molecular features along with patient characteristics and preferences are warranted in order to provide precision medicine [21].

In this context, tailor-made second-line management of mPC is sophisticated, since an increasing number of men progressing after the upfront use of cytotoxic treatment or the combination of ADT and sHT in mHSPC are currently being treated with subsequent therapies, hence generating evidence right now. Among the limited data on successive treatment options after docetaxel, Lavaud et al [15] were the first to analyze its efficacy when used upon progression after initial chemohormonal therapy versus when applied

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Table 3 – Multivariate Cox regression analyses of clinical outcomes (PFS2, TTP2, and OS) and patient characteristics.

Risk factors for occurrence of event(s)	Endpoints								
	PFS2			TTP2			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Second-line treatment									
Non sHT	3.201	1.205–8.502	**0.020**	2.123	0.850–5.303	0.107	2.868	0.789–10.424	0.109
sHT	1.0 (Ref.)			1.0 (Ref.)			1.0 (Ref.)		
Rapidity of progression to CRPC	18.729	6.010–58.362	**<0.001**	14.204	4.541–44.436	**<0.001**	16.688	1.818–153.212	**0.013**
Age	1.020	0.971–1.071	0.429	1.041	0.986–1.096	0.147	1.007	0.919–1.103	0.888
PSA at diagnosis	0.999	0.999–1.000	0.153	1.000	0.999–1.001	0.693	1.000	0.999–1.001	0.856
PSA change from baseline to nadir in second line	0.998	0.995–1.002	0.279	0.998	0.994–1.001	0.220			

CI = confidence interval; CRPC = castration resistant prostate cancer; HR = hazard ratio; OS = overall survival; PFS2 = progression-free survival 2; PSA = prostate-specific antigen; Ref. = reference; sHT = second-generation hormone therapy; TTP2 = time to progression 2.
Bold: statistically significant p-values.

in second-line indication after initial ADT using the data of 245 males from the GETUG-AFU 15 RCT. Docetaxel used for the first time led to a trend for a higher percentage of men with PSA and PSA50 (PSA decrease of at least 50%) responses as compared with the rechallenge utilization (80% vs 55.2% and 45% vs 14%, respectively; $p = 0.07$). Notably, among men who received chemohormonal treatment initially, sHT upon progression was associated with virtually higher rates of PSA and PSA50 responses (84.2% vs 55.2% and 53% vs 14%, respectively). Taken together, this analysis showed that using a different agent than docetaxel upon progression after initial chemohormonal protocol might be associated with at least an improved biochemical response. Since in mCRPC docetaxel rechallenge was suggested beneficial for selected patients with stable disease of at least 6 mo after primary exposure, it is currently unknown which predictors of response for this strategy can be used in mHSPC, given much greater efficacy of concomitant ADT and thus longer absence of progression [22].

Another important insight was yielded by Francini and collaborators [14], who assessed efficacy of abiraterone acetate or enzalutamide after ADT with ($n = 52$) or without ($n = 50$) upfront docetaxel. Herein, OS did not differ between both the cohorts irrespective of being estimated from ADT commencement or the state of castration resistance. Based on these observations, switch of the drug class in the second-line indication appears to be a sensible option.

In our study, 60 out of 65 (92.3%) patients had de novo mHSPC, with high-volume disease in 74.1% without imbalance in baseline characteristics between sHT and non-sHT cohorts. The study population is herein comparable with that of the STAMPEDE (arm C) RCT (95% de novo, 77% high-volume disease) supporting the use of chemohormonal treatment as the first-line therapy in our study population.

In our analysis, the use of sHT was independently associated with an attenuated risk of progression while on second-line treatment or of death from any cause as compared with non-sHT mostly consisting of taxanes. Presumably due to the low sample size and number of deaths, this association with OS, being significant in univariate comparison ($p = 0.03$), showed a trend ($p = 0.11$) without reaching a statistical significance in the multivariate testing. Nonetheless, this finding supports the idea that patients might benefit from the switch of the drug class, provided that resistance to docetaxel has emerged in several prostate cancer (PC) cells during initial exposure. An independent association of improved PFS2 with the use of sHT in the second-line indication is essential, since to our best knowledge this observation has not been reported for this setting yet. Moreover, in men with time to CRPC of $\geq$18 mo, sHT outperformed non-sHT in terms of extended OS as well as PFS2. This can be interpreted in the way that mPC patients with a longer time to CRPC, thus presumably more depending on androgen receptor signaling, still benefit considerably from hormone-based therapy. In concert with this observation, Loriot et al [23] showed that previous duration of ADT $\geq$16 mo was the only significant predictive factor for efficacy of subsequent endocrine manipulations including abiraterone acetate in patients with CRPC. Though subgroup size in our investigation is small, hence attenuating generalization of potential conclusions, we believe that this finding is hypothesis generating for upcoming research.

Since the European Medicines Agency recommended its use as a clinical endpoint to evaluate the efficacy of maintenance therapy in hematology/oncology trials, PFS2 is gaining increasing clinical attention [24]. Particularly in slowly progressing malignancies such as PC, OS may be difficult to assess due to the need for lengthy follow-up, whereas PFS related only to the second-line therapy misses efficacy of the first-line protocol, often precluding reliable estimation of its association with OS [25]. Reviewing 15 trials of solid tumors including PC, Mainwaring and coworkers [25] described a positive correlation between PFS2 and OS, and voted for using PFS2 as a surrogate for OS before OS data are mature or when OS cannot be assessed.

Our findings are in concert with another retrospective analysis of subsequent therapies after progression on chemohormonal treatment reported by Barata et al [13], in which 48 patients received sHT and 12 others non-sHT. They used PFS on first mCRPC therapy and OS as coprimary endpoints, demonstrating that sHT was associated with improvement of both. An important shortcoming of that study is a lack of multivariate tests for the independence of survival associations. Notwithstanding this flaw, shorter

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time to CRPC was univariately associated with survival deterioration in that work. This goes in line with our observation of independent association of shorter time to CRPC with inferior PFS2, TTP2, as well as OS, thus being the strongest survival predictor in our series. Notably, similar observations have been done for mCRPC without upfront docetaxel as standard care. Thus, Suer and collaborators [26] recently reported on time to CRPC being an independent prognostic factor for OS among 162 mCRPC men receiving docetaxel. Earlier, Bournakis et al [27] demonstrated time to CRPC being an independent predictor of OS and PFS of mCRPC patients undergoing chemotherapy. According to our findings, it is a strong predictor of novel endpoints of PFS2 and TTP2 as well.

Sample size of our study cohort precluded further stratification and assessment of patients potentially bearing malignant features of aggressive variants of prostate cancer (AVPC) with a poor prognosis. Efforts on clinical and molecular definition of this particularly detrimental group of mPC are ongoing, being applied predominantly in the mCRPC setting [28]. Of note, inferior prognosis has recently been reported also for mHSPC patients classified as those having AVPC [29]. Further prospective research including molecular-based signatures and biomarkers in this subgroup is crucial in order to identify patients with a poor prognosis of mPC or AVPC, conveying insufficient response to the chemohormonal protocol, who might benefit more from the second-line treatment with combined platinum/etoposide- or /taxane-based therapy than from sHT [28].

Our analysis has several limitations. First, it is a retrospective assessment with all inherent flaws and possible biases. Second, the study is based on a limited sample size, necessitating grouping of different nonhormone second-line treatments into the non-sHT cohort. Third, due to the multicenter nature of the study, choice of the respective therapy was based on the policy of respective centers as well as individual physician's preference.

Notwithstanding these drawbacks, we believe to have contributed to the current concept of second-line therapy upon progression of real-world mHSPC patients after upfront docetaxel. We postulate that sHT appears to be a preferable treatment choice and independent predictor of favorable PFS2. Time to CRPC was confirmed to be the strongest predictor also for the novel endpoints PFS2 and TTP2. Hereby, time to CRPC >18 mo conferred an advantage to sHT over non-sHT in relation to PFS2 and OS. Second-line therapies were well tolerated without any difference between sHT and non-sHT. Our results support further prospective research as well as joint efforts on following patients in multicenter databases to gather larger and more robust data in order to optimize outcomes in patients with mPC.

5. Conclusions

In real-world patients progressing after upfront docetaxel, sHT is independently associated with favorable PFS2 favoring drug class switch. Longer time to CRPC predicts strongly for superior PFS2 and TTP2. Further prospective research is warranted in order to improve outcomes of males with mPC.

Author contributions: Igor Tsaur 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: Tsaur, Dotzauer, Gandaglia.
Acquisition of data: Tsaur, Dotzauer, Gandaglia, Tilki, Borgmann, Foti, Heidegger, Hunting, Kretschmer, Ploussard, van den Bergh, Bektic.
Analysis and interpretation of data: Tsaur, Dotzauer, Tilki, Gandaglia.
Drafting of the manuscript: Tsaur, Dotzauer, van den Bergh.
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Appendix A. Supplementary data

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