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Platinum Opinion

Updated Guidelines for Metastatic Hormone-sensitive Prostate Cancer: Abiraterone Acetate Combined with Castration Is Another Standard☆

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Metastatic prostate cancer (PCa) remains a deadly disease despite improved treatment options for patients progressing on standard hormone treatment [1]. The median overall survival (OS) of men presenting with metastatic hormone-sensitive PCa (mHSPC) starting standard androgen deprivation therapy (ADT) was approximately 45 mo in three large randomized controlled trials (RCTs) [2–4]. It was less for those with higher-volume disease where a median survival of only 35.1 [2] and 32.2 mo [3], respectively, was observed.

Recently, three large RCTs [3–5] compared the addition of six [3,4] or nine [5] cycles of docetaxel to ADT in patients with mHSPC. The primary end point in all three studies was OS. Patient characteristics within these trials differed with respect to clinical stage, risk factors, and overall extent of disease. In all three trials, toxicity was mainly hematological, with approximately 12–15% grade 3–4 neutropenia and 6–12% grade 3–4 febrile neutropenia.

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Early addition of docetaxel to ADT in mHSPC showed a significant OS benefit in two of the three trials (Table 1), and was substantiated in several meta-analyses that were based on published trial data but not on individual patient data [6–8]. New recommendations for the use of docetaxel in addition to ADT in mHSPC were implemented in most guidelines published by the urological and oncological societies [9–11] as the new standard for newly diagnosed metastatic patients fit enough to receive this drug and accept the associated side effects.

The new standard of care (SOC) for mHSPC implemented in 2016 [9] is now challenged by two large RCTs evaluating the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily; AA + P) to ADT in men with mHSPC [12,13]. The primary objective of both trials was improvement in OS. In LATITUDE, radiographic progression-free survival as defined by the Prostate Cancer Working Group 2

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☆ Patient summary: Metastatic prostate cancer remains a lethal disease, irrespective of improved treatment options for patients. Two large randomised clinical trials recently reported on a combination of androgen deprivation therapy (ADT) with added abiraterone acetate (1000 mg/d) plus prednisone (AA +) for metastatic hormone-sensitive (mHSPC) PCa. Both trials show a significant longer overall survival for patients that receive the combination of ADT and AA +, as compared to ADT alone.

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Table 1 – Comparison of results of combining docetaxel with ADT (table from guidelines)

Study	Population	*N*	Med FU (mo)	Median OS (mo)		HR	*p* value
				ADT + D	ADT		
Gravis et al [2]	M1	385	50	58.9	54.2	1.01 (0.75–1.36)	0.955
Sweeney et al [3]	M1 HV: 65%	790	28.9	57.6	44	0.61 (0.47–0.8)	<0.001
James et al [4]	M1 (61%)/N+(15%)/relapse	1184/593 (D)		81	71	0.78 (0.66–0.93)	0.006
		593 (D + ZA)		76	NR	0.82 (0.69–0.97)	0.022
	M1 only	725 + 362 (D)		60	45	0.76 (0.62–0.92)	0.005

ADT = androgen deprivation therapy; D = docetaxel; FU = follow-up; HR = hazard ratio; HV = high volume; *N* = number of patients; NR = not reported; OS = overall survival; ZA = zoledronic acid.
HV is defined by the location of metastases, any visceral deposit, or the location and number of bone metastases, at least one outside the axial skeleton in men with more than three bone lesions.

Table 2 – Main characteristics of the included patients

	STAMPEDE [13]		LATITUDE [12]	
	ADT	ADT + AA + pred	ADT + placebo	ADT + AA + pred
N	957	960	597	602
Age (median)	67	68	68	67
PSA (median), ng/ml	56	51	NA	NA
Gleason ≥8, %	75	74	98	97
Newly diagnosed N+, %	20	19	0	0
Newly diagnosed M+, %	50	48	100	100
Newly diagnosed M0N0, %	26	27	0	0
Key inclusion criteria	Patients intended for long-term ADT • Newly diagnosed M1 or N+ situations • High-risk locally advanced (at least two of cT3 cT4, Gleason ≥8, PSA ≥40 ng/ml) • Relapsing locally treated disease with a PSA of >4 ng/ml and a PSA-DT of <6 mo, or PSA of >20 ng/ml, or nodal or metastatic relapse		Newly diagnosed M1 disease and two out of these risk factors: Gleason ≥8, ≥3 bone lesions, measurable visceral metastasis	
Primary objective	Overall survival		Overall survival Radiographic progression-free survival	

AA + P = abiraterone acetate + prednisone; ADT = androgen deprivation therapy; *N* = number of patients; NA = not applicable, data not provided; pred = prednisone; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time.

Table 3 – Main results of both trials

	STAMPEDE [13]	LATITUDE [12]
N	1917	1199
Median follow-up (mo)	40	30.4
Deaths	446	406
3 yr overall survival	83% (ADT + AA + P), 76% (ADT)	66% (ADT + AA + P), 49% (ADT + placebo)
HR (95% CI)	0.63 (0.52–0.76)	0.62 (0.51–0.76)
M1 only		
N	1002	1199
Deaths	368	406
3 yr overall survival		66% (ADT + AA + P), 49% (ADT + placebo)
HR (95% CI)	0.61 (0.49–0.75)	0.62 (0.51–0.76)
Radiographic progression-free survival		0.49 (0.39–0.53)

AA + P = abiraterone acetate + prednisone; ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; *N* = number of patients.

[14] was the co-primary end point. The main population characteristics are summarized in Table 2. They are different in both trials with more advanced disease included in the LATITUDE trial (only newly diagnosed metastatic patients, all having high-risk features defined as at least two of the following three risk factors: a Gleason score of ≥8, at least three bone lesions, and the presence of measurable visceral metastases) [12]. A formal systematic review and meta-analysis has also been published [15].

The first pre-planned analysis has now been reported with a median follow-up of around 3 yr. Both trials are positive for the primary objective (ie, OS) with a practically identical overall survival outcome, a benefit of 38% at 3 yr (hazard ratio [HR]: 0.62 [0.53–0.71]; Table 3) [15], as well as

Table 4 – Main severe (grade ≥3) toxicities observed

	STAMPEDE [13]		LATITUDE [12]	
	ADT + AA + pred	ADT	ADT + AA + pred	ADT + placebo
N	1908		1199	
Overall, %	47	33	63	48
Cardiovascular, %	10	4	20	10
Hepatic (liver enzymes), %	7	1	11	2
Hypokalemia, %	1 [a]	<1	11	2
Respiratory, %	5	2	NR	NR
Toxicity leading to treatment stop, %	20		12	10
Death (*N*)	9 (1%) [a]	3 (<1%) [a]	28 (5%) [b]	24 (4%) [b]

AA + P = abiraterone acetate + prednisone; ADT = androgen deprivation therapy; pred = prednisone; N = number of patients.
[a] Cause of death: AA + P arm: two had pneumonia, two strokes, and one each dyspnea, lower respiratory tract infection, liver failure, pulmonary hemorrhage, and chest infection; ADT only: two myocardial infarction and one bronchopneumonia.
[b] Cause of death: AA + P arm: 10 cardiac disorders (one gastric ulcer perforation, one intestinal ischemia, and one intestinal obstruction); ADT + placebo: six cardiac disorders.

for radiographic progression-free survival (55%) (HR: 0.45 [0.40–0.51]) [15]. Most deaths were related to PCa, and there was no clear increased risk of death related to the combination of ADT and AA + P (Table 4). All the secondary objectives such as progression-free survival, time to radiographic progression, time to pain, or time to docetaxel were in favor of the combination. The benefit was consistent in most subgroups, and no unexpected toxicity was observed in either trial compared with that seen with AA + P in the castrate-resistant setting [16,17] despite the longer use of the agents in the hormone-sensitive state. No significant treatment-related death was observed using the combination of ADT + AA + P compared with the ADT monotherapy (HR: 1.37 [0.82–2.29]) [15]. However, twice as many patients on AA + P stopped their treatment for toxicity in the specific investigational arm of STAMPEDE (20%) compared with LATITUDE (12%). The key adverse events are summarized in Table 4.

Based on these results, adding AA + P to SOC, which in most patients was chemical androgen suppression therapy, in newly diagnosed metastatic PCa should be considered as an alternative to the addition of six cycles of docetaxel to castration. These findings highlight, once again, the importance of the intracellular androgen levels in the PCa cells for PCa growth. The new treatment strategy with the successful early addition of AA + P to ADT could be considered as returning to the so-called "complete androgen blockade" [18,19]. In this model, the rationale was to suppress the adrenal androgens as well as the remaining low serum testosterone. Even if this concept has previously led to minor and questionable benefits, it represents the rationale of both trials with the use of a potent suppressor of the adrenal androgen synthesis as well as the intracrine androgen production.

However, this new and additional recommendation leads to many questions, most of which are still unanswered.

1. Timing

Neither trial was designed to clarify the timing of AA + P (ie, early at the androgen-sensitive status or later as primary treatment at the castrate-resistant stage). In both trials, first-line treatment at the castrate-resistant status was at investigators' discretion (see Table 5). As with docetaxel, survival benefit with the addition of AA + P is clear for newly diagnosed metastatic patients. However, the most common presentation of patients with metastases is a relapse after some kind of local treatment. With docetaxel, these relapsing patients have been analyzed in CHAARTED and STAMPEDE [3,4] and it is still inconclusive based on the

Table 5 – Life-prolonging agents used at the castrate resistant stage

	STAMPEDE [13]		LATITUDE [12]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
Inclusion (*N*)	957	960	597	602
Progression [a] (*N*)	535	248	469	314
Number receiving a life-prolonging agent	310 (58%)	131 (53%)	246 (52%)	125 (39.8%)
Docetaxel (%)	37	46	40	34
Enzalutamide (%)	26	10	16	10
AA + P (%)	22	3	11	3
Cabazitaxel (%)	5	6	6	4
Radium 223 (%)	4	8	6	4

AA + P = abiraterone acetate + prednisone; ADT = androgen deprivation therapy; *N* = number of patients.
[a] Of note, a substantial number of patients on the investigational arms were still on treatment at data cut-off and thus not in need of additional treatment.

available subgroup analysis. The lack of significant survival benefit is the same for nonmetastatic situations [4,20]. The comparison of AA + P plus SOC versus SOC alone in STAMPEDE included M0 or M1 relapsing patients [13]. Again, no significant effect on survival for M0 in a pre-planned subgroup analysis was observed. This lack of benefit might be related to the relatively short follow-up period and very few events. Of note, the trial was positive for the intention-to-treat population (M1 plus M0). Nonetheless, and as of today, neither the combination of docetaxel plus ADT nor the combination of AA + P plus ADT should be considered as a SOC for M0 patients. The small subgroup of patients presenting with metastatic disease after local treatment was not addressed in a recently published meta-analysis [15]. For such patients, again, neither the combination of docetaxel plus ADT nor the combination of AA + P plus ADT should be considered as a SOC but rather as an option, and discussed as part of a joint and individualized decision-making process [15].

2. Disease burden

The extent and burden of disease when selecting appropriate patients for combined treatment remains a matter of debate in regards the use of docetaxel in mHSPC [21,22]. In the CHAARTED trial [3] only patients with high-volume disease benefited, according to an unplanned subgroup analysis. In that study, a high volume of disease was defined by either the location of metastases (any visceral deposit being considered as a high volume) or the location and number of bone metastases (at least one outside the axial skeleton in men with more than three bone lesions). This volume classification has not been uniformly used but is rather a hybrid of several definitions. It was not used in the STAMPEDE trial [4] where metastatic patients without any restriction for disease extent where included. None of the abiraterone trials [12,13] used a disease volume definition. LATITUDE [12] selected only metastatic patients, all having "high-risk disease," using a separate definition. There was no subgroup classification for the metastatic situations in the STAMPEDE trial [13]. The survival benefit associated with the early use of AA + P was observed in the entire STAMPEDE trial, as well as in the pre-planned subgroup of 1002 metastatic patients (941 newly diagnosed), with a consistent significant hazard ratio around 0.6 (see Table 3). This finding suggests that this combined modality should not be restricted to the high-risk group as defined in LATITUDE [12].

3. Decision between the two options

The current key question for many patients and their treating physicians is the choice between six cycles of docetaxel and the long-term use of AA + P in newly diagnosed mHSPC. Once approved for the mHSPC setting, and apart from cost considerations and general patient preference, specific side effects will be a critical factor in decision making. Both modalities have distinct side effects, with the risk of febrile neutropenia from docetaxel being potentially the most severe and life threatening. It ranged between 6% and 12% in the pivotal trials [3–5]. Outside clinical trials for PC, neutropenic fever from docetaxel 75 mg/m^2 has been reported to be even more frequent [23]. The primary use of granulocyte colony-stimulating factor in patients at a high risk for neutropenic fever [24,25] makes docetaxel definitely safer, but of course, cannot reduce the complete range of potential side effects.

The risks associated with AA + P seem to be different but might also be life threatening, such as hypokalemia from the mineralocorticoid effect. They are more easily managed, especially by urologists, provided a strict follow-up routine is maintained. However, the very long–term use of AA + P might also be associated with some specific side effects, even if manageable, as suggested in LATITUDE [12]. They require a strict follow-up policy.

The different modes of action of the two drugs suggest that some patients would be better candidates for docetaxel than for AA + P. This assumption, however, is purely speculative.

4. Treatment at progression

The last tricky question is about the treatment policy at disease progression. After docetaxel is given for mHSPC, it seems as if docetaxel retreatment at the castrate-resistant state might not be very effective. This assumption is based on exploratory data and small patient numbers [26]. After upfront AA + P for mHSPC, docetaxel was the most commonly used agent at progression in both trials, although only LATITUDE was blinded. Only a minority of patients received second-line enzalutamide. This is probably due to the known cross resistance between abiraterone and enzalutamide [9].

Recently, a survey among clinicians [27] revealed the extent of complexity surrounding the clinical implementation of the new data and early use of docetaxel as the SOC. This significant change of practice influences patient

Table 6 – New guidelines to consider now for metastatic hormone-sensitive prostate cancer

	Recommendation
Offer surgical or medical castration (luteinizing-hormone-releasing hormone agonist or antagonist) as androgen deprivation therapy	Strong
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy	Strong
Offer castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen	Strong
Offer castration, with or without an antiandrogen, to patients unfit for a combination with docetaxel or abiraterone acetate + prednisone, or who are unwilling to consider it	Strong

pathways, and calls for an early and close collaboration between multidisciplinary teams. This practice insight underlines the need not only for guideline recommendations based on the level of evidence, but also for guidance regarding practice where counseling of individual patients goes beyond levels of evidence and sophisticated interpretation of statistics and meta-analyses. The same issues are true when deciding between AA + P and docetaxel for mHSPC, although AA is the drug that has the advantage of being easier to prescribe and handle.

In 2017, major progress has been made regarding the management of newly diagnosed mHSPC. At least 1 yr of OS benefit can be gained when adding either docetaxel or AA + P to ADT. This has led to changes in the clinical practice guidelines (Table 6).

However, the application of guidelines in different patient groups, for example, in those developing metastases years after local therapy, currently remains controversial based on the limited number of such patients included in the respective trials and should ideally be clarified through dedicated prospective trials. Additional treatment intensification in the mHSPC setting is under investigation in multiple international trials. The next leap forward is expected to come from the results of ongoing RCTs, which explore the addition of local treatment in newly diagnosed mHSPC, as well as the role of metastasis-targeted treatment [28].

Guideline recommendations should help set the minimum SOC based on the best available evidence and for the benefit of the majority of patients. For men presenting with mHSPC and starting ADT, AA + P must be regarded as another standard therapy abreast docetaxel. When choosing between ADT combined with docetaxel or AA + P, given the lack of a direct comparison, agent-specific side effects, patient preference, and costs will dominate the decision-making process.

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