available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Opinion

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

Nicolas Mottet[a,*], *Maria De Santis*[b,c], *Erik Briers*[d], *Liam Bourke*[e], *Silke Gillessen*[f,g], *Jeremy P. Grummet*[h], *Thomas B. Lam*[i,j], *Henk G. van der Poel*[k], *Olivier Rouvière*[l,m], *Roderick C.N. van den Bergh*[k], *Philip Cornford*[n]

[a] *Department of Urology, University Hospital, St. Etienne, France;* [b] *Clinical Trials Unit, University of Warwick, UK;* [c] *Department of Urology, Medical University of Vienna, Austria;* [d] *Patient Advocate, Hasselt, Belgium;* [e] *Faculty of Health and Wellbeing, Sheffield Hallam University, Sheffield, UK;* [f] *Department of Oncology/Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland;* [g] *University of Bern, Switzerland;* [h] *Department of Surgery, Central Clinical School, Monash University, Melbourne, Australia;* [i] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [j] *Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK;* [k] *Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands;* [l] *Hospices Civils de Lyon, Radiology Department, Edouard Herriot Hospital, Lyon, France;* [m] *Université de Lyon; Université Lyon 1, Faculté de Médecine Lyon Est, France;* [n] *Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK*

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.

EU ACME
www.eu-acme.org/europeanurology

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

Please visit www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

☆ 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.

* Corresponding author. Department of Urology, University Hospital, St. Etienne, France. Tel. +33 477828331; Fax: +33 477517179.

https://doi.org/10.1016/j.eururo.2017.09.029

CrossMark

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