Reduced Dose of Abiraterone Acetate with Concomitant Low-dose Prednisone in the Treatment of ≥85 Year-old Patients with Advanced Castrate-resistant Prostate Cancer

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Abstract. *Aim: The aim of the study was to evaluate the activity and safety of reduced-dose abiraterone acetate (AA) in ≥85 year-old patients with advanced castrate-resistant prostate cancer (CRPC). Patients and Methods: Patients received 750 mg oral AA as three 250-mg tablets once daily, with concomitant oral prednisone, 5 mg daily. Results: Twenty-six patients were enrolled; median age was 88 years (range=85-93). Prostate-specific antigen (PSA) response was observed in 18 (69.2%) subjects, median time to PSA progression was 6.4 months (95% confidence interval (CI)=2.8-8.8) and median overall survival was 14.3 months (95% CI=7.2-18.3). The treatment was well-tolerated and adverse events, related to mineralocorticoid excess, were of grade 1-2 in all patients. Conclusion: Reduced dose of AA combined with a very low dose of prednisone is effective and well-tolerated in very elderly patients with advanced CRPC.*

Prostate cancer (PC) is the second leading cause of cancer-related death in men in most Western countries and can be considered as a disease of the elderly since, in most series, the median age at diagnosis is over 75 years (1-2). Although hormonal manipulation remains the mainstay of treatment in advanced or metastatic disease, all patients inevitably recur and are candidates to receive chemotherapy or other treatment options. Although a number of new agents are now available for the management of patients with advanced castration-resistant prostate cancer (CRPC), current guidelines do not offer specific recommendations for elderly subjects. This sub-group of patients often presents with concomitant comorbidities and may have a low tolerability to anti-tumoral treatments (1, 3).

Among the new drugs, abiraterone acetate (AA) at dose of 1,000 mg daily was recently approved by the FDA for the treatment of advanced CRPC. AA is a first-in-class selective irreversible inhibitor of cytochrome *P-450c17* (CYP17), a critical enzyme in extragonadal and testicular androgen synthesis. One of the main sources of androgens is the adrenal production of dehydroepiandrosterone and androstenedione, which serve as precursors to testosterone and can feed the prostate cancer tissue (4, 5).

A large randomized trial by de Bono *et al*. involved 1,195 metastatic CRPC patients who had been previously treated with docetaxel (D) to receive AA, 1,000 mg daily, and oral low-dose prednisone or placebo: overall survival (OS) was 14.8 months in the AA group compared to 10.9 months in the placebo group (hazard ratio (HR)=0.65, $p<0.001$) (6). All other end-points, including PSA response and time-to-PSA progression, favored the AA group. Although AA was well-tolerated, toxicities, including fluid retention, hypokalemia, hypertension, liver function test abnormalities and cardiac events, were more frequent in the AA group. Despite this trial included about 28% of patients older than 75 years, the median age of the AA group was 69 years and specific data for the very elderly subjects were not reported. Very elderly patients are frail and usually have several concomitant comorbidities, thus particular caution is required before administering full doses of a new drug. Moreover the co-administration of low-dose prednisone (5 mg twice daily) is used during AA treatment because of adverse events related to elevated mineralcorticoid serum levels as a consequence of the CYP17 blockade. The potential glucocorticoid–related adverse events, including hyperglicemia, mood and cognitive alterations, gastritis and myopathy, should be considered, especially in very elderly patients. Since in this

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frail population extreme caution is needed for a safe administration of full dose of a new drug, we designed this study in order to evaluate the activity and tolerability of reduced dose of AA with concomitant very low dose of prednisone in ≥85 year-old patients.

Patients and Methods

Eligibility criteria. The study involved ≥85 years aged patients with histologically confirmed, measurable or evaluable advanced and/or metastatic CRPC. Patients started AA provided that they met at least one of the following criteria: a positive bone scan and a ≥25% increase in PSA (PSA higher than 2 ng/ml) in comparison with a baseline on two successive measurements separated by at least two weeks for patients without measurable disease; new metastatic lesions revealed by a bone scan and a ≥25% increase in a bi-dimensionally measurable tumor mass with or without disease progression on the basis of the PSA value and ongoing androgen deprivation, with a serum testosterone level of 50 ng per decilitre or less (≤2.0 nmol per litre).

All patients were to have a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2, adequate hematological (leukocytes >3,000/mm^3; hemoglobin >10 g/dl, platelets >100,000/mm^3), renal (serum creatinine <2.0 mg/dl) and hepatic function (serum bilirubin <2.0 mg/dl).

Patients were excluded if they had abnormal aminotransferase levels (levels of aspartate aminotransferase or alanine aminotransferase ≥2.5-times the upper level of the normal range; patients with known liver metastases and levels of aspartate aminotransferase or alanine aminotransferase ≥5-times the upper level of the normal range were ineligible to participate), coexisting severe non-malignant diseases, active or symptomatic viral hepatitis or chronic liver diseases, uncontrolled hypertension, a history of pituitary or adrenal dysfunction, severe heart diseases or previous therapy with ketoconazole.

Biphosphonates were allowed in all patients presenting bone metastases.

Treatment plan. Because of the lack of robust data in very elderly subjects (>85 years), patients started with an initial AA dose of 500 mg daily and, after one month, a dose of 750 mg daily was applied as three 250 mg tablets orally once daily at least 1 h before or 2 h after a meal, with prednisone in a dose of 5 mg orally once daily. Each cycle of treatment was 28 days long. Treatment could be continued until disease progression was documented on the basis of the serum PSA, radiographic imaging and clinical findings. Safety and dosage compliance were evaluated on day 15 of every cycle for the first 3 months and, thereafter, on day 1 of each subsequent cycle at the time of treatment discontinuation, if applicable, and at the end of study visit.

Response assessment. Tumor response in patients with measurable lesions was evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (7). Serum PSA was measured every four weeks: a PSA response rate was defined as the proportion of patients with ≥50% decrease in PSA concentration from the pretreatment baseline PSA value, which was confirmed after ≥4 weeks by an additional PSA evaluation; whereas PSA progression was defined as an increase from nadir of at least 25% and ≥2 ng/ml (8).

Laboratory tests, red blood cell, white blood cell and platelet counts, as well as a comprehensive screening, including electrolyte profile, were performed at baseline and every two weeks. Serum testosterone levels were measured only in patients who experienced an increase of PSA with a stable disease.

Radiological investigations included abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), bone scan and chest X-ray. All measurable diseases were re-evaluated at 12-week intervals. In all cases, a baseline electrocardiogram (ECG) and echocardiogram were obtained and further cardiac work-up was performed if indicated. Bone disease progression was defined as the appearance of any new bone lesion or the progression of existing bone metastases.

Palliative response. Pain symptomatology was measured at baseline and, then, every 6 weeks by the McGill Melzack Pain Questionnaire and pain response was defined as a 2-point reduction in the 6-point present pain intensity scale (or the complete disappearance of pain if the initial score was 1+) (9). These results had to be maintained on two consecutive evaluations made at least 3 weeks apart and without any increase in analgesic consumption. Patients were asked to rate their average level of pain during the previous 24 h. We used a translated form of the McGill Melzack Questionnaire to which the "reconstruction-based method" was applied (10). Analgesic consumption evaluation was based on the average daily quantities taken by the patient during the previous week and on the assigned oral morphine equivalents before analysis (11).

Treatment-related adverse events. Toxicity was defined using the National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0. In case of grade IV toxicity, treatment was interrupted and a maximum of three weeks was allowed for recovery. In case of a second episode of grade III or IV toxicity in the same patient, the treatment was resumed after recovery and the subsequent administration of AA was reduced.

Statistical considerations. The primary end-point was PSA response. At the time of designing of this study, no robust data were available about emerging treatments on very elderly patients with CRPC. Assuming a response rate of approximately 10% for other therapies in advanced CRPC after the standard first-line D and a target level of interest of 30% with an α of 0.05 and a β of 0.80, a sample size of 25 patients was planned in accordance with Simon's minimax design. Secondary end-points were time to PSA progression, OS and pain response. PSA progression was defined as the time from the beginning of therapy to the first occurrence of objective or PSA progression, OS was measured from the start of AA treatment to death due to any cause of death or censoring.

The study was approved by the Ethics Committee of Siena University and all patients provided written informed consent.

Results

From April 2011 to June 2014, 26 patients aged ≥85 years with locally advanced and/or metastatic CRPC received AA and were evaluated for safety and efficacy. Patients' baseline characteristics are shown in Table I.

The median age was 88 years (range=85-93): eight patients were >90 years. Twenty-one (80.7%) patients had bone

Table I. *Patients' characteristics*.

Enrolled patients	26
Median age (range) in years	88 (85-93)
ECOG performance status	
0-1	17
2	9
Gleason Grade	
≤7	12
>8	14
Laboratory	
Median PSA ng/ml (range)	72.49 (6.65-243.7)
Median hemoglobin, g/dl	11.4
Elevated ALP	19
Elevated LDH	7
Sites of metastases	
Bone	21
Lymph nodes	13
Lung/liver	3
Pain	
Pain present	19
Requiring opiates	9
Previous treatment	
Hormonal therapy	26
Prostatectomy	1
Radiotherapy	7
Previous Docetaxel	
Yes	12
No	14

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.

Table II. *Patient's comorbidities*.

Comorbidities	Number of patients (%)
Cardiovascular	18 (69.2%)
Diabetes mellitus	7 (26.9%)
Dyslipidemia	7 (26.9%)
Respiratory	9 (34.6%)
Genitourinary	4 (15.3%)

Table III. *Number of patients experiencing the most frequent abiraterone acetate-related treatment events*.

Adverse events	Grade 1	Grade 2
Hypokalemia	2 (7.6%)	0
Peripheral edema	3 (11.5%)	1 (3.8%)
Hypertension	2 (7.6%)	2 (7.6%)
Cardiac disorders	2 (7.6%)	1 (3.8%)
Fatigue	3 (11.5%)	2 (7.6%)

metastases; median PSA level at baseline was 72.49 ng/ml (range=6.65-243.7 ng/ml). Twelve (46.1%) out of 26 enrolled patients have been previously exposed to weekly D chemotherapy at least 30 days before entry into the study. Our study population presented with frequent comorbidities, with the most frequent being low-moderate-grade cardiovascular diseases (69.2%) (Table II).

The median duration of treatment was 32 weeks. One patient received only one month of AA for treatment-unrelated reasons. One patient was lost to follow-up after four months from the start of treatment. All patients were included in the overall analysis (intent-to-treat).

Treatment was generally well-tolerated and there were no unexpected toxic effects. No patient died and no discontinuation occurred for an adverse event due to AA. Most adverse events were associated with elevated mineralocorticoid levels due to CYP17 blockade were grade 1 or 2. Peripheral edema was reported in 4 (15.3%), hypokalemia in 2 (7.6%) patients and hypertension in 4 (15.3%). Cardiac disorders were reported in 3 (11.5%) patients. Other grade 1-2 adverse events included constipation, back pain and bone pain (Table III).

Twenty-three out of 25 patients who were treated for more than 2 months could safely escalate the AA dose to the planned 750 mg daily after the first month of treatment: the other two patients (90 and 92 years) interrupted the treatment for 10 and 15 days due to transitory liver function test abnormalities and urinary infection, respectively, after the first months of treatment. Although toxicity did not reached grade 3 in these two subjects, considering the favorable PSA response in both cases, it was decided to maintain the AA dose of 500 mg daily. In other two patients, AA was interrupted for about one week because of atrial fibrillation and tachycardia episodes, which occurred after 7 and 9 months of treatment: in these cases AA restarted at 500 mg daily.

Efficacy data. A decrease in PSA levels >50% was observed in 18 patients (69.2%) and these responses were all confirmed at least 4 weeks later with a second PSA level evaluation (Table IV). The proportion of PSA response was high both in D-pre-treated (8/12, 66.6%) than in non-D pre-treated patients (10/14, 71.4%). The median time to PSA progression was 6.4 (95% CI=2.8 to 8.8) months and the median OS was 14.3 (95% CI=7.2 to 18.3) months. Median time to PSA progression was 5.5 (95% CI=2.2 to 7.9) months and 7.9 (95% CI=4.8 to 9.1) months in D-pre-treated and non-D pre-treated patients, respectively. Median OS was 12.8 (95% CI=6.4 to 15.7) months and 16.4 (95% CI=8.9 to 17.4) months in D-pre-treated and non-D pre-treated patients, respectively.

After 24 weeks from the start of AA, PSA progression was found in 12 (46.1%) patients but a reduction in bone pain with decrease in analgesic use and improvement in

Table IV. *Summary of outcomes*.

Enrolled patients	26
Median duration of treatment, weeks	32
Palliative response	15 (78.9%)
Median duration of palliative response, months	4.6 (95% CI=1.5 to 7.6)
PSA decline ≥50%	18 (69.2%)
Median time to PSA progression, months	
Median OS, months	6.4 (95% CI=2.8 to 8.8) 14.3 (95% CI=7.2 to 18.3)

PSA, Prostate-specific antigen; OS, overall survival, CI, confidence interval.

performance status were observed in 8 of them. Imaging techniques did not reveal progressive disease in these 8 men. Despite the initial end-point of the study, on the basis of the achieved clinical benefit, our oncology group and the scientific ethical committee decided to continue AA in these 8 patients until worsening of pain and/or performance status.

At the time of this writing, 7 patients were still receiving ongoing AA therapy with clinically stable disease; among these, two men (89 and 92 years, respectively) continue to have a confirmed PSA response after 18.5 and 23.3 months after starting AA, respectively.

Among the subjects who were symptomatic at baseline, pain was reduced in 15 patients (78.9%) with a significant decrease in analgesic use. The median duration of palliative response has been 4.6 months.

Discussion

A general reluctance among physicians to treat elderly cancer patients, especially >80-85 years, with anticancer drugs is understandable because, above all, toxicity might be expected greater than in younger counterparts. On the other hand, it was reported that the majority of elderly patients wished to be treated as younger patients, willing to accept the potential risks of anti-tumoral treatment (12). However, attention should be paid on the use of new agents at full doses in this elderly population that usually suffer of a number of concomitant diseases.

The current study is the first to report data on activity and tolerability of the new agent AA at a lower dose than that usually applied (500-750 mg *vs*. 1,000 mg) in a consistent group of very elderly (>85 years) patients with locally advanced or metastatic CRPC. A point of interest was that, despite the very advanced age and the potential frailty of the study population, treatment was very active and well-tolerated, compliance with AA treatment was high and toxicity was very mild. Although our sample included about 69% of men with concomitant cardiovascular diseases, cardiac-related adverse events were observed in only few subjects, were of 1-2 grade and did not require treatment discontinuation. These data are in line with the recently reported safety of AA in CRCP patients who presented with concomitant cardiovascular risk factors (13). The lower prednisone dose compared to standard-dose we applied concomitantly to AA (5 mg *vs*. 10 mg, daily) seemed to be able to adequately control the adverse events usually related to mineralocorticoid excess resulting from blockade of CYP17. Nevertheless, a slightly lower AA dose was proposed in our study, as well. Although the standard 10 mg of prednisone usually associated to AA is a low dose, which can be safely assumed by the majority of patients, we believe a lower dose (5 mg in the current study), if associated to low-dose AA, could limit the potential glucocorticoid–related adverse events. Furthermore, it may be underlined that the frequent monitoring of the patients and laboratory parameters may have contributed to avoid major toxicities in the study.

Another point of interest was the 69.2% PSA response rate, 6.4 months median time to PSA progression and 14.3 months median OS that seem to confirm the AA efficacy in very elderly patients also with a lower daily dose, both in D-pre-treated than in non-D pre-treated patients. Recently, in a *post hoc* analysis of COU-AA301 trail, Mulders *et al*. examined the efficacy and safety of AA plus prednisone versus placebo plus prednisone in subgroups of elderly (aged ≥75 years) (n=331) and younger patients (<75 years) (n=863) (14). The authors showed that AA improved OS and was well-tolerated in both elderly and younger patients with metastatic CRPC (mCRPC) following D. Although our patients included men older than those enrolled in the study by Mulders *et al*. (median=88 *vs*. 78 years), our results compared well with those reported in that trial in terms of tolerability, with a superior PSA response rate. However, in the aforementioned study all the patients had been D-pre-treated. Our results are also in line with data of a recent retrospective analysis on the efficacy and toxicity of AA and D in mCRCP octogenarians, which reported similar treatment outcomes in patients over and under the age of 80 years (15). In the field of hormonal manipulation,

enzalutamide is another recent drug that, as well as AA, targets the androgen receptor (AR) signaling pathway, which has shown to improve OS in patients with mCRCP after D failure (16). A *post hoc* analysis of AFFIRM trail examined the efficacy and safety of enzalutamide versus placebo in subgroups of elderly and younger patients. The authors showed that, despite the higher rate of some adverse events, the tolerability of enzalutamide appeared to be generally similar in elderly and young patients (17).

In the current study, the activity of reduced AA dose was supported by improvements in pain symptomatology; pain was reduced in 15 out of 19 symptomatic subjects at baseline with a significant decrease in analgesic use. Additionally, although after 24 weeks from the start of AA, a PSA progression was found in 12 patients, a reduction in bone pain with decrease in analgesic use and improvement in performance status were observed in 8 of them. These 8 patients did not exhibit progressive disease at radiological evaluation and continued AA until worsening of pain and/or performance status. These data may suggest that only few very elderly patients who exhibit PSA progression might continue to benefit of AA therapy. Nevertheless, we acknowledge that the small sample size of the current study is a limitation for data interpretation and, therefore, caution may be taken before drawing firm conclusions.

Despite the lack of specific trials, a similar activity of anti-tumoral therapy in elderly patients compared to younger counterparts has been also reported by the use of chemotherapy agents. A retrospective analysis on D, largely used in mCRPC, described a promising 70% PSA response in >75 year-old patients who received first-line D-based chemotherapy plus prednisone (18). However, besides activity, particular caution must be taken when treating very elderly patients with chemotherapy because of the potential development of toxicity. In a retrospective study by Halabi *et al*., the risk for death for patients aged 80-89 years receiving D was higher than for patients 70-79 years (HR=1:3 p=0.015) (19). The TROPIC trial, which led to the FDA approval of cabazitaxel as second-line treatment for mCRPC, showed that patients aged ≥65 years and ≥75 years receiving cabazitaxel have a greater incidence of neutropenia and diarrhea than younger patients (20).

In summary, the results of the current study suggest that reduced dose of AA with concomitant very low dose prednisone is effective and well-tolerated in >85 years aged patients with advanced CRPC.

Conflicts of Interest

No author has actual or potential conflicts of interest, including any financial, personal or other relationships with other people or organizations within three years of the beginning the submitted work that could influence, or be perceived to influence, their work.

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References

1 Shelke AR and Mohile SG: Treating prostate cancer in elderly men: how does aging affect the outcome? Curr Treat Options Onco *l12*: 263-275, 2011.

2 Scosyrev E, Messing EM, Mohile S, Golijanin D and Wu G: Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. Cancer *118*: 3062-3070, 2012.

3 Sajid S, Mohile, SG, Szmulewitz R, Posadas E and Dale W: Individualized decision-making for older men with prostate cancer: balancing cancer control with treatment consequences across the clinical spectrum. Semin Oncol *38*: 309-325, 2011.

4 Bedoya DJ and Mitsiades N: Abiraterone acetate, a first-in-class CYP17 inhibitor, establishes a new treatment paradigm in castration-resistant prostate cancer. Expert Rev Anticancer Ther *12*: 1-3, 2012.

5 Locke JA, Guns ES, Lubik AA, Adomat HH, Hendy SC, Wood CA, Ettinger SL, Gleave ME and Nelson CC: Androgen levels increase by intratumoral *de novo* steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res *68*: 6407-6415, 2008.

6 de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu LChi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI and COU-AA-301 Investigators: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med *364*: 1995-2005, 2011.

7 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein LVerweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

8 Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M and Prostate Cancer Clinical Trials Working Group: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol *26*: 1148-1159, 2008.

9 Melzack R: The McGill Pain Questionnaire: major properties and scoring methods. Pain *1*: 277-299,1975.

10 De Benedittis G, Massei R, Nobili R and Pieri A: The Italian Pain Questionnaire. Pain *33*: 53-62, 1988.

11 McCormack A, Hunter-Smith D, Piotrowski ZH, Grant M, Kubik S and Kessel K: Analgesic use in home hospice cancer patients. J Fam Pract *34*: 160-164,1992.

12 Extermann M, Albrand G, Chen H, Zanetta S, Schonwetter R, Zulian GB, Cantor A and Droz JP: Are older French patients as willing as older American patients to undertake chemotherapy? J Clin Oncol *21*: 3214-3219, 2003.

13 Procopio G, Grassi P, Testa I, Verzoni E, Torri V, Salvioni R,Valdagni R and de Braud F: Safety of Abiraterone Acetate in Castration-resistant Prostate Cancer Patients With concomitant Cardiovascular Risk Factors. Am J Clin Oncol Sep 21 (Epub ahead of print), 2013.

14 Mulders PF, Molina A, Marberger M, Saad F, Higano CS, Chi KN, Li J, Kheoh T, Haqq CM and Fizaki K: Efficacy and Safety of Abiraterone Acetate in an Elderly Patient Subgroup (Aged 75 and Older) with Metastatic Castration-resistant Prostate Cancer After Docetaxel-based Chemotherapy. Eur Urol *65*: 875-883, 2014.

15 Leibowitz-Amit R, Templeton AJ, Alibhai SM, Knox JJ, Sridhar SS, Tannock IF and Joshua AM: Efficacy and toxicity of abiraterone and docetaxel in octogenarians with metastatic castration-resistant prostate cancer. J Geriatr Oncol *6*: 23-28, 2015.

16 ScherHI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS andAFFIRM Investigators: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med *367*: 1187-97, 2012.

17 Sternberg CN, De Bono J, Chi K, Fizazi K, Mulders PCerbone L, Hirmand M, Forer D and Scher HI: Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial Ann Oncol *25*: 429-434, 2014.

18 Italiano A, Ortholan C, Oudard S, Pouessel D, Gravis G, Beuzeboc P, Bompas E, Fléchon A, Joly F, Ferrero JM and Fizaki K: Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration resistant prostate cancer. Eur Urol *55*: 1368-1376, 2009.

19 Halabi S, Vogelzang NJ, Ou SS, Kelly WK and Small EJ: Clinical outcomes by age in men with hormone refractory prostate cancer: a pooled analysis of 8 Cancer and Leukemia Group B (CALGB) studies. J Urol *176*: 81-86, 2006.

20 de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO and TROPIC Investigators: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet *376*: 1147-1154, 2010.

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