Clinical outcomes in octogenarians treated with docetaxel as first-line chemotherapy for castration-resistant prostate cancer

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Aim: To assess clinical outcomes in octogenarians treated with docetaxel (DOC) for metastatic castration-resistant prostate cancer. Patients & methods: The multicenter retrospective study was based on a review of the pre- and post-DOC clinical history, DOC treatment and outcomes. Results: We reviewed the records of 123 patients (median age: 82 years) who received DOC every 3 weeks or weekly, without significant grade 3–4 toxicities. Median progression-free survival was 7 months; median overall survival from the start of DOC was 20 months, but post-progression treatments significantly prolonged overall survival. Conclusion: The findings of this study suggest that toxicity is acceptable, survival is independent of patient’s age and survival can be significantly prolonged by the use of new agents.

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Prostate cancer is the most frequently diagnosed cancer affecting men in the USA [1] and Europe [2], and the second most frequent cause of cancer-related death. It can be considered a disease of the elderly men: the median age at the time of diagnosis is 66 years, and its incidence is highest in men aged 70–74 years [3]. Its incidence is expected to increase significantly in the future because of the longer life expectancy of patients, and it is therefore necessary to develop a better understanding of treatment options for the elderly, most of whom are in an advanced stage of disease [4]. Docetaxel is the reference front-line therapy for metastatic castration-resistant prostate cancer (mCRPC) patients [5,6] but the risk of severe side effects sometimes limits the use of chemotherapy in older patients, who may therefore be undertreated. However, most of the few published data concerning the elderly are based on subgroup analyses of Phase III studies [7–9] rather than specifically designed clinical trials. Furthermore, recently published guidelines [10] suggest that decisions concerning the treatment of elderly prostate cancer patients should be guided by geriatric assessment (including co-morbidities, level of dependence, nutritional status and neuropsychological problems) rather than age.

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Keywords
• castration-resistant prostate cancer • docetaxel • elderly • geriatric assessment
The aim of this retrospective study was to describe clinical outcomes in octogenarians treated with first-line docetaxel-based chemotherapy.

**Patients & methods**

**Data collection**

In order to be included in the study, the patients needed to have a diagnosis of histologically proven mCRPC and to be aged ≥80 years at the time they received their first-line docetaxel-based chemotherapy in clinical practice. For the purposes of this study, after Ethics Committee approval, we recorded the patients’ pre-docetaxel history of prostate cancer (Gleason score at diagnosis, the presence of metastatic disease at diagnosis, local treatments, the type and duration of hormonal therapy before mCRPC, the time between diagnosis and the development of mCRPC), their baseline parameters at the start of chemotherapy (prostate-specific antigen [PSA] level, pretreatment PSA doubling time, calculated at the Memorial Sloan–Kettering Cancer Center website, hemoglobin, alkaline phosphatase and lactate dehydrogenase levels, performance status, the presence of pain), their docetaxel treatment history and outcomes, and their post-docetaxel history.

When available in their clinical records, we also recorded their Cumulative Illness Score Rating-Geriatrics (CIRS-G), Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scores. The CIRS-G, the best means of assessing the risk of nonprostate cancer death, rates organ dysfunction on the basis of severity and the potential degree of controlling it by means of treatment (grade 0 = no problem; grade 4 = severe condition requiring immediate intervention) [10]. The ADL assesses a patient’s ability to bath/shower, dress, eat, feed him/herself and manage continence and bodily functions: any impairment in one of these activities (with the exception of continence) is considered abnormal in elderly prostate cancer patients [10]. The IADL assesses activities requiring cognition and judgement, such as managing money and medications, and using transport and the telephone; the presence of one impairment is classified as abnormal [10].

A record was made of each patient’s biochemical and instrumental response, the date of progression, the date of the last follow-up examination and vital status, and the safety data were analyzed using the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.0.

**Statistical analysis**

Continuous variables are expressed as median values and discrete variables as relative frequencies.

An assessment was made of the biochemical response rate (defined as the percentage of patients showing at least a 50% reduction in PSA levels in comparison with the levels recorded at the start of treatment) and the objective response rate (defined as the percentage of complete and partial responses on the basis of the RECIST criteria). The Kaplan–Meier method was used to calculate progression-free survival (PFS) from the start of docetaxel until progression or the time of the last follow-up visit, whichever occurred first, and overall survival (OS) from the start of docetaxel until death or the time of the last follow-up visit, whichever occurred first. Cox regression analysis was used to calculate the differences in PFS and OS between groups stratified on the basis of their Gleason scores at the time of diagnosis, the time between the diagnosis of prostate cancer and mCRPC, the duration of hormonal therapy before starting docetaxel, PSA doubling time, baseline ECOG performance, baseline PSA hemoglobin, alkaline phosphatase and lactate dehydrogenase levels, the baseline presence of pain, the presence of visceral metastases, the timing of chemotherapy (weekly or every 3 weeks), and CIRS, ADL and IADL scores.

An additional analysis was made in order to assess the impact of post-docetaxel progression treatments on OS by distinguishing the patients who did not receive any further therapy, those who received one or more old-generation drugs (a docetaxel rechallenge and/or other chemotherapy such as mitoxantrone, vinorelbine, among others) and those who received at least one of the new agents (abiraterone acetate, cabazitaxel and/or enzalutamide).

Continuous variables were categorized on the basis of their median values and the categorical variables were compared using the chi-squared test. The data were statistically analyzed using SPSS 12 software (SPSS, Inc., IL, USA).

**Results**

**Patients’ characteristics**

We collected data relating to 123 patients (median age 82 years; range: 80–90) treated...
in 29 Italian institutions (Table 1). Most of the patients had a good ECOG performance status: 0 in 33 (26.8%) and one in 72 (58.5%).

Several lines of hormonal therapy were administered before docetaxel, with 23 patients (18.7%) receiving more than four. The median duration of hormonal therapy was 46 months (range: 3–233), and the median interval between diagnosis and starting docetaxel chemotherapy was 63.5 months (range: 7–257). Only 39 patients (31.7%) received the standard 3-weekly docetaxel dose; the others received a reduced 3-weekly dose or were treated using a weekly schedule, mainly to reduce the risk of toxicity. Data allowing to define CIRS, ADL and IADL scales were available for most of the patients (81%). The main characteristics of the patients are showed in the Table 1.

● Safety & tolerability

Docetaxel treatment was well tolerated. There were only a few grade 3–4 hematological toxicities (neutropenia 10.6%, febrile neutropenia 1.6%, thrombocytopenia 1.6% and anemia 1.6%) and only a few patients reported nonhematological grade 3–4 toxicities: fatigue (9.7%), diarrhea (4.1%), nausea (1.6%) and renal impairment (1.6%). There were no significant differences between the various schedules except for neutropenia (more frequent in the patients who underwent weekly schedules) and weight loss, which was more frequent in the patients on 3-weekly schedules (Table 2). Toxicity was the main reason for stopping treatment in 19 patients (15.4%).

The other reasons for discontinuation were protocol completion (43, 34.9%), disease progression (36, 29.2%), consent withdrawal (7, 5.7%) and death in the absence of progression (3, 2.4%).

● Efficacy

More than 50% reduction in PSA levels was observed in 55% of the patients, and an objective response in 15% of the 60 patients who underwent radiological re-evaluation at the end of treatment.

Median PFS and OS were 7 and 20 months, respectively (Figures 1 & 2), and the 1-year PFS and OS rates were 18.5 and 71.8%, respectively.

Cox regression analysis showed that there were no statistically significant differences in PFS in relation to any of the considered variables, whereas OS was significantly influenced by baseline ECOG performance status (p = 0.013), the baseline presence of pain (p = 0.002) and CIRS scores (p = 0.001). The type of schedule administered (3-weekly or weekly) did not influence survival outcomes (Table 3).

OS was also significantly influenced by further treatment: median OS was 14 months in the patients who did not receive further treatment, 20 months in those who received an old chemotherapy and 33 months in those who received at least one new agent (p < 0.0001) (Figure 3).

In order to verify the effect of further treatment after first-line docetaxel, we also compared survival from the time of first progression after docetaxel treatment in the three groups using

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics from clinical history.</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Patients (n)</td>
</tr>
<tr>
<td>Median age (range)</td>
</tr>
<tr>
<td>Gleason score:</td>
</tr>
<tr>
<td>– ≤7</td>
</tr>
<tr>
<td>– 8–10</td>
</tr>
<tr>
<td>– Unknown</td>
</tr>
<tr>
<td>Metastases at diagnosis:</td>
</tr>
<tr>
<td>– Yes</td>
</tr>
<tr>
<td>– No</td>
</tr>
<tr>
<td>– Unknown</td>
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<tr>
<td>Median CIRS score (range)</td>
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<tr>
<td>Median ADL score (range)</td>
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<td>Median IADL score (range)</td>
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<td>Pain at baseline</td>
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<tr>
<td>Median baseline PSA (range)</td>
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<tr>
<td>Median PSA doubling time</td>
</tr>
<tr>
<td>Docetaxel dose and schedule‡:</td>
</tr>
<tr>
<td>– Standard dose every 3 weeks</td>
</tr>
<tr>
<td>– Alternative weekly schedules</td>
</tr>
<tr>
<td>Post-docetaxel treatments:</td>
</tr>
<tr>
<td>– No further treatment</td>
</tr>
<tr>
<td>– No new agents§:</td>
</tr>
<tr>
<td>• Old agent chemotherapy</td>
</tr>
<tr>
<td>• Docetaxel rechallenge</td>
</tr>
<tr>
<td>– New agents§</td>
</tr>
<tr>
<td>• Abiraterone acetate</td>
</tr>
<tr>
<td>• Cabazitaxel</td>
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<td>• Enzalutamide</td>
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</table>

1Nonevaluable in 23 cases.
2Alternative schedules: 50–60 mg/m² every 3 weeks; continuous weekly 30–35 mg/m²; weekly 35 mg/m² for 1 of every 2 weeks; weekly 35 mg/m² for 2 of every 3 weeks; weekly 30–35 mg/m² for 3 of every 4 weeks; weekly 30–35 mg/m² for 4 or every 5 weeks; weekly 30–35 mg/m² for 5 or every 6 weeks; weekly 30–35 mg/m² for 6 of every 8 weeks; weekly 30–35 mg/m² for 8 of every 10 weeks.
3Two patients received more than one type of treatment sequentially.
4Eight patients received more than one type of treatment sequentially.

3-month landmark analysis, avoiding the clear bias due to patients who died soon after progression. Once again, median OS was significantly longer in the patients who received as further therapy a new agent (26 months) than in those who received an old drug (14 months) or no further treatment (9 months; \( p = 0.010 \)) (Figure 4).

**Discussion**

To the best of our knowledge, the present is the largest study of octogenarian mCRPC patients treated with docetaxel showing that docetaxel-based first-line chemotherapy is well tolerated and leads to the survival outcomes similar to those obtained in younger patients.

After the publication of pivotal trials in 2004 showing that it offered a significant survival advantage compared with mitoxantrone, docetaxel became the reference drug for the first-line treatment of patients with mCRPC [5,6]. However, this raised the problem of treatment compliance in elderly patients, particularly in those >80 years old, who are very likely to have

<table>
<thead>
<tr>
<th>Toxiches</th>
<th>3-week schedules, n (%)</th>
<th>Weekly schedules, n (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (28.3)</td>
<td>13 (24.5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (24.5)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (13.2)</td>
<td>5 (9.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (7.5)</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8 (15.1)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (9.4)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Edema</td>
<td>6 (11.3)</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>Sensitive neuropathy</td>
<td>3 (5.7)</td>
<td>6 (11.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (7.5)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (9.4)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Nail changes</td>
<td>7 (13.2)</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Weight loss†</td>
<td>5 (9.4)</td>
<td>2 (3.8)</td>
</tr>
</tbody>
</table>

\( p = 0.01 \)

**Figure 1. Progression-free survival.**
a considerable burden of co-morbidities [11]. Due to the fear of excessive toxicity, physicians are cautious in proposing chemotherapy and often adopt weekly schedules, based on the results of TAX327 study, which found a more favorable toxicity profile of weekly docetaxel in comparison with the 3-weekly schedule [6]. Furthermore, a recently published subanalysis of the same study confirmed this finding in elderly patients aged ≥75 years, who represented 20% of the study population [9].

A pooled analysis of two Phase II clinical trials of weekly docetaxel in CRPC patients did not show significant differences in efficacy or toxicity in elderly compared with younger patients [12]. Similar results were reported by Sinibaldi [13] and Italiano [14].

This is even more relevant now as it has been shown that new-generation hormonal agents such as abiraterone acetate and enzalutamide, whose toxicity is quite different from that of chemotherapy, offer a survival advantage in front-line mCRPC treatment [15–17] and can be used in elderly patients.

However, the first question that needs to be addressed is how we define ‘older’ mCRPC patients. As stated before, most of the studies describing outcomes in ‘elderly’ mCRPC patients have used a cutoff age of 75 years [7–9,14,18], but the median age of the patients enrolled in the pivotal studies ranged from 68 to 71 years [6,16,19–23]. We therefore believe that only patients aged >80 years should be considered ‘older mCRPC patients’ and that is why we only included octogenarians in our analysis.

The fear of toxicity is clearly reflected in our population as only 32.2% of the patients were treated using the standard 3-week docetaxel schedule: the others were all treated on the basis of a weekly schedule or a 3-weekly schedule with a reduced dose: it is noteworthy that no differences were observed in terms of both PFS and OS by schedule type. In any case, our findings indicate that the treatment was well tolerated, and the low rate of grade 3–4 hematological and nonhematological toxicities confirms the results observed in the patients aged ≥75 years treated in the TAX 327 study [9] and the findings of a French retrospective study of patients treated in a ‘real-world’ setting [14].

Leibowitz-Amit et al. found no age-related differences in docetaxel-treated octogenarians in terms of PSA response rates or OS, but the frequency of febrile neutropenia was significantly higher than that observed in younger men [24].

A more recent study similarly reviewed the use of docetaxel in 20 octogenarian patients (median age of 83 years; range: 80–93), most of them (19 patients) treated with 3-weekly docetaxel. Significant response rates were reported but at the cost of many toxicities (grade 3–4
Table 3. Overall and progression-free survival in months by selected factors.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OS (months)</th>
<th>p-value</th>
<th>PFS (months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRS-G score:</td>
<td></td>
<td></td>
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<tr>
<td>– ≤3</td>
<td>25</td>
<td>0.001</td>
<td>7</td>
<td>0.058</td>
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<tr>
<td>– &gt;3</td>
<td>16</td>
<td></td>
<td>8</td>
<td></td>
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<tr>
<td>ADL score:</td>
<td></td>
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<td></td>
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<tr>
<td>– 0</td>
<td>24</td>
<td>0.061</td>
<td>8</td>
<td>0.099</td>
</tr>
<tr>
<td>– ≥1</td>
<td>17</td>
<td></td>
<td>6</td>
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<tr>
<td>IADL score:</td>
<td></td>
<td></td>
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<tr>
<td>– 0</td>
<td>22</td>
<td>0.064</td>
<td>8</td>
<td>0.099</td>
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<tr>
<td>– ≥1</td>
<td>16</td>
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<td>PS:</td>
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<tr>
<td>– 0</td>
<td>27</td>
<td>0.013</td>
<td>8</td>
<td>0.160</td>
</tr>
<tr>
<td>– 1</td>
<td>20</td>
<td></td>
<td>7</td>
<td></td>
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<tr>
<td>– 2</td>
<td>10</td>
<td></td>
<td>7</td>
<td></td>
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<tr>
<td>Pain:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>– No</td>
<td>25</td>
<td>0.002</td>
<td>8</td>
<td>0.078</td>
</tr>
<tr>
<td>– Yes</td>
<td>16</td>
<td></td>
<td>7</td>
<td></td>
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<tr>
<td>Treatment timing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Every 3 weeks</td>
<td>20</td>
<td>0.956</td>
<td>7</td>
<td>0.563</td>
</tr>
<tr>
<td>– Weekly</td>
<td>20</td>
<td></td>
<td>8</td>
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</table>

The p-values were calculated using Cox regression analysis.


showed better OS even though this was of only borderline statistical significance. The selection of elderly mCRPC patients is highly important, and the recently published guidelines of the International Society of Geriatric Oncology underline the need for a comprehensive three-stage geriatric assessment (CGA) when choosing treatment [10]; in particular, this is crucial in identifying vulnerable and frail patients, who could receive standard treatment after medical intervention and adapted treatment, respectively. It is clear that the retrospective nature of this study means that the collected information concerning CIRS, ADL and IADL scores (which were not available for all of the patients and in most cases derived from the patient history rather than a formal validated assessment) needs to be considered cautiously, but the critical role of appropriate patient selection is reflected by the other factors found to influence OS negatively: in other words, a poor performance status, pain at baseline and the presence of more co-morbidities. On the contrary, a good performance status can allow patients to receive more lines of therapies and potentially to live longer.

Our study is also the first to provide data concerning the survival impact of the post-docetaxel use of new-generation drugs: median OS in the population as a whole was 20 months, but there were clear differences between those receiving different further treatments. The

Figure 3. Overall survival by further treatment administration.
patients who did not receive any of the new agents (cabazitaxel, abiraterone acetate and/or enzalutamide) had a median OS of 20 months, which is quite similar to that observed in the pivotal TAX 327 trial [6], whereas the 43 who received at least one of the new agents had a median OS of 33 months, which is comparable with the median cumulative survival of respectively 29 and 32.6 months observed in other patients receiving cabazitaxel or abiraterone acetate after first-line docetaxel [26,27]; on the contrary, the patients who did not receive any treatment after docetaxel progression had a median OS of only 14 months. These findings confirm the activity of the administration of the new agents after docetaxel and indicate that they can also significantly improve the survival of octogenarians. About the use of new hormonal agents in chemo-naïve setting, in our study no patient received abiraterone or enzalutamide because they were treated before the introduction of these drugs in clinical practice.

Recent clinical studies highlighted the question of the use of docetaxel plus androgen deprivation therapy in hormone sensitive prostate cancer patients [28,29]. The CHAARTED subgroup analysis supported the efficacy of docetaxel in patients aged ≥70 years also in hormone-sensitive prostate cancer [28].

Our study has several limitations leading to a cautious interpretation of the results. First of all, the sample size is modest, mainly considering the number of involved centers. Then, data were retrospectively collected from the clinical records of patients treated according to current clinical practice of different Italian institutions, which may have led to heterogeneity in terms of both the selection criteria, mainly driven by the subjective feelings of the treating physicians, and the type of treatment, particularly for weekly schedules, who were slightly different among hospitals. Moreover, the retrospective nature of the study affected the reliability of the data concerning geriatric assessment. Finally, our population was highly selected as most of the patients had a good performance status, were asymptomatic and did not show serious co-morbidities.

**Conclusion**

Despite some limitations, our results suggest that an appropriate selection plays a central role in the management of older patients with mCRPC. The decision to use a docetaxel-based treatment should not simply depend on the patients’ chronological age, but also on their health status and the results of a comprehensive geriatric assessment. This is very important considering that new treatment options in chemotherapy-naïve patients, as abiraterone and enzalutamide, improve OS in all patient subgroups, including the elderly. Prospective clinical trials specifically
designed for older patients should be developed in the future in order to optimize the treatment of the elderly population.

Future perspective
In next years, the incidence of prostate cancer will continue to rise due to an increasingly aging population and earlier diagnosis. Therefore, the problem of treating elderly mCRPC patients will be more perceived.

Although the availability of new generation hormonal agents provides a therapeutic option with manageable toxicity profile representing a valid alternative to docetaxel for asymptomatic patients, docetaxel will continue to be the treatment of choice for elderly patients with symptoms and visceral involvements. The possible role of cabazitaxel in first-line setting, according to the awaited results of FIRSTANA trial (NCT01308576), could change the first-line chemotherapy options, but will arise questions in the elderly population about the different safety profiles of the two taxanes and possible alternative schedules for cabazitaxel. Moreover the impressive survival improvements observed by combining docetaxel to androgen deprivation therapy in hormone-sensitive metastatic prostate cancer will open the issue of treating very elderly patients in this phase of the disease, mainly about the possibility of adopting alternative and more tolerable schedules, for example, with weekly timing.

Financial & competing interests disclosure
O Caffo received honoraria from Sanofi Aventis, Astellas and Janssen; U Basso received honoraria from Sanofi Aventis; U De Giorgi received honoraria from Janssen; G Procopio received honoraria from Bayer, Bristol, GSK, Novartis, Astellas, Janssen and Pfizer; V Zagonel received honoraria from Novartis, Bayer, Roche, Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY
Aim
● To assess clinical outcomes in octogenarians with metastatic castrate-resistant prostate cancer treated with docetaxel.

Patients & methods
● Multicenter study on octogenarians treated in 29 Italian institutions.
● Data about pre- and post-docetaxel clinical history, docetaxel treatment and outcomes were retrospectively collected; when available in clinical records, geriatric assessment was recorded.

Results
● A total of 123 patients (median age 82 years) were treated with docetaxel every 3 weeks or weekly, without significant grade 3–4 toxicities.
● Median progression-free survival was 7 months, while median overall survival was 20 months.
● Post-progression treatments significantly prolonged overall survival.

Conclusion
● The findings of this study suggest that toxicity is acceptable, survival is independent of patient’s age and survival can be significantly prolonged by the post-docetaxel use of new agents.
● Limitations are the retrospective nature of the study and the highly selected population.
● The use of chemotherapy should not simply depend on the patient chronological age but also on an appropriate geriatric assessment.
● Prospective studies need to be designed for very old patients.
Clinical outcomes in octogenarians treated with docetaxel for CRPC RESEARCH ARTICLE

References
Papers of special note have been highlighted as:
• of interest

• Updated International Society of Geriatric Oncology recommendations on treatment of prostate cancer in older than 70 years men. Elderly patients should be classed into healthy or fit, vulnerable and frail, so that their treatment is defined according to individual health status, not according to age.
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