Systemic Medical Treatment in Men with Metastatic Castration-Resistant Prostate Cancer: Recommendations for Daily Routine

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Introduction

Aside from skin cancers, prostate cancer is the most common cancer in men living in the USA and Europe [1–3]. About 1 in 9 men will develop prostate cancer during their lifetime, and in 2012, 1,094,916 new cases were diagnosed worldwide [4]. 10–20% of all patients will develop castration-resistant prostate cancer (CRPC) within 5 years of follow-up [5]. Approximately 84% of men with CRPC will present with metastatic disease at the time of diagnosis, and another 5% will develop metastatic disease within 2 years of being diagnosed with CRPC [6, 7]. According to recent analyses, median survival of patients with CRPC is 14 months [8]. However, in none of these analyses, new therapeutic options such as abiraterone acetate, enzalutamide (ENZ), cabazitaxel (CBZ), sipuleucel-T, and radium-223, which will prolong survival significantly, were taken into account [9–15].

Metastatic CRPC (mCRPC) is characterized by disease progression following surgical or medical castration. The European Association of Urology (EAU) defines mCRPC as castrate levels of serum testosterone, 3 consecutive increases in prostate-specific antigen (PSA) resulting in two 50% increases above the nadir, antiandrogen withdrawal for at least 4 weeks, PSA progression despite secondary hormonal manipulations, and/or progression of osseous or soft tissue lesions [16].

Docetaxel plus prednisone still represents the EAU guideline-recommended first-line cytotoxic therapy of choice (since 2004), and CBZ plus prednisone (CBZ/P) is the EAU guideline-recommended second-line cytotoxic therapy in mCRPC patients who progress during or after docetaxel [16]. Cytotoxic treatment of metastatic neuroendocrine or small cell prostate cancer is cisplatin-based [16].

It is the aim of the current article to i) summarize the data of established treatment options in mCRPC, ii) provide clinically useful algorithms for the daily routine, and iii) point out future developments in medical treatment.

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scribe parameters and cytotoxic regimens for the identification and treatment of small cell/neuroendocrine prostate cancer, and iv) point out future developments in medical treatment.

**First-Line Treatment**

**Corticosteroids**

Corticosteroids have been reported to exert symptomatic responses in patients with mCRPC [17]. In this prospective randomized trial, the therapeutic efficacy of flutamide versus prednisone was evaluated, and the authors did not find any statistically significant differences in terms of time to progression, overall survival (OS), and symptomatic response; however, gastrointestinal toxicity and quality of life were in favor of prednisone [17]. A recently published randomized phase II trial evaluated the therapeutic efficacy of dexamethasone 0.5 mg/day and prednisone 2×5 mg/day in a cohort of 82 men with mCRPC [18] with a PSA decrease ≥ 50% as the primary endpoint. The primary endpoint was met with a PSA response rate of 47 versus 24% (p < 0.05) in favor of dexamethasone. Also, the median time to PSA progression was significantly longer in the dexamethasone group (9.1 vs. 5.1 months; p < 0.05). However, there were no significant differences with regard to objective remissions (15 vs. 6%; p = 0.6) and subjective symptomatic response. Rate response was dependent on PSA and alkaline phosphatase serum concentrations with best responses in patients with normal alkaline phosphatase levels. Despite these well documented response rates, the indication to initiate corticosteroids is rather limited in the field of mCRPC with the availability of new life-prolonging agents. Furthermore, the potential drawbacks with regard to response to sequential endocrine therapy have to be considered [19]. In the COU-AA-301 study, baseline corticosteroids were associated with adverse prognostic features, inferior OS, and lower baseline androgen levels, but did not add substantial information to the final prognostic model.

**Abiraterone Acetate plus Prednisone**

In 2012, abiraterone acetate plus prednisone (AA/P) was approved for the treatment of mCRPC with no or minimal symptoms based on the results of the COUGAR-302 trial [9]. AA is an orally available inhibitor of 17α-hydroxylase and C17,20-lyase which inhibits the adrenal, testicular, and intratumoral synthesis of androgens from their precursor cholesterol. The COUGAR-302 trial randomized 1,088 men with asymptomatic/mildly symptomatic mCRPC to either receive AA/P at a dose of 1,000 mg/2×5 mg/day or placebo plus prednisone. Co-primary endpoints of the trials were OS and radiographic progression-free survival (PFS) which was defined as i) progression of soft tissue metastases on computed tomography/magnetic resonance imaging according to RECIST criteria, or ii) progression of osseous metastases on bone scans according to the Prostate Cancer Working Group Criteria. Secondary study endpoints were PSA response, PFS, time to chemotherapy, time to opioid use, and time to deterioration of performance status. Median OS was 35.3 and 27.2 months (p = 0.01) in the AA/P and the placebo group, respectively. Radiographic PFS was 16.5 versus 8.3 months (p < 0.001). All secondary study endpoints were also reached, and they were in favor of AA/P. Grade 3 and 4 treatment-associated side effects were observed in 48 and 42% of patients with AA/P and placebo, respectively. The most frequent treatment-associated side effects were fatigue, back pain, arthralgia, nausea, and gastrointestinal disorders [9].

Quite recently, it was demonstrated that pretreatment with corticosteroids might exert a negative impact on the treatment results of first-line AA/P [19]. Stratifying the patients of the COUGAR-302 trial according to previous treatment with corticosteroids, a survival difference was demonstrated for both the AA/P arm (17.3 vs. 13.4 months) and the placebo group (12.7 vs. 9.3 months). Whereas the OS difference reached statistical significance in men without baseline corticosteroids (17.3 vs. 12.7 months; p = 0.0044), there was no statistically significant difference in men who received baseline steroids (13.4 vs. 9.3 months; p = 0.502). Although multivariate analysis did not identify baseline corticosteroids as an independent risk factor associated with poorer survival, serum testosterone concentration (< 4.99 ng/dl vs. > 4.99 ng/dl) was a significant prognostic marker (hazard ratio (HR) 1.51, 95% confidence interval (CI) 1.28–1.79; p < 0.0001). It is noteworthy that patients with baseline steroids exhibited lower testosterone serum levels indicating that the combination of steroids with androgen deprivation therapy (ADT) potentially exerts some synergistic effect on androgen synthesis.

**Enzalutamide**

Among the clinical trials concerning first-line therapy in mCRPC, the TERRAIN trial evaluated the oncological efficacy of ENZ versus bicalutamide in men with mCRPC failing first-line hormonal therapy with luteinizing hormone-releasing hormone analogues/antagonists [20]. The trial demonstrated a statistically significant benefit in terms of PFS (15.7 vs. 5.9 months; HR 0.44, p < 0.0001), time to PSA progression (19.4 vs. 5.8 months; HR 0.28, p < 0.0001), and PS response rate (82 vs. 21%). Furthermore, it has been shown that early treatment with ENZ instead of bicalutamide significantly improves quality of life in men with mCRPC: median time to FACT-P (Functional Assessment of Cancer Therapy-Prostate questionnaire) total score deterioration was 13.83 versus 5.84 months (p = 0.0067, HR = 0.63, 95% CI 0.46–0.88).

PREVAIL was a prospective randomized phase III clinical trial in men with mCRPC who failed first- and second-line ADT. 845 men with asymptomatic or mildly symptomatic docetaxel-naive mCRPC were recruited to receive ENZ or placebo. The co-primary endpoints of the trial were OS and radiographic PFS [10]. After a median follow-up of 22 months, the primary endpoints were reached with a median OS of 32.4 versus 30.2 months (p < 0.0001).
Radiographic PFS was improved from 3.8 to 13.4 months (p < 0.0001). A PSA reduction > 50% and > 90% was observed in 78 versus 47% of patients; median time to PSA progression was 11.2 versus 2.8 months (p < 0.0001). Treatment-associated side effects were minimal, with fatigue and back pain representing the most frequent complaints. Seizures were observed in < 1% of patients.

**Docetaxel/Prednisone**

Following the publication of 2 large prospective randomized phase III clinical trials, TAX327 and SWOG 99–16, systemic cytotoxic therapy with docetaxel represents the standard therapeutic approach for men with mCRPC [21, 22]. The TAX 327 study compared the oncological efficacy of docetaxel 75 mg/m² administered every 3 weeks, docetaxel 30 mg/m² administered weekly for 5 of 6 weeks, or mitoxantrone 12 mg/m² every 3 weeks, each with prednisone 10 mg daily. 1,006 patients with progressive CRPC were recruited, and after a mean follow-up of 21 months and 557 patients having died, a significant survival benefit of 20–25% (18.9 vs. 16.4 months; p = 0.009) was demonstrated for patients receiving docetaxel in the 3-weekly arm, but there were no significant differences between the weekly arm and mitoxantrone. Furthermore, a significant improvement with regard to pain control (35 vs. 22%; p = 0.01) and quality of life (p = 0.005) was observed for the docetaxel arm whereas no significant differences were demonstrated concerning objective remission rates of target lesions (12 vs. 7%). Patients in the 3-weekly docetaxel arm experienced alopecia (65%), fatigue (53%), neutropenia (32%), and neuropathy (30%) as the most common side effects.

In the SWOG 99–16 trial [22], 674 patients with mCRPC were randomly assigned to receive mitoxantrone at 12 mg/m² every 3 weeks or docetaxel and estramustine 60 mg/m² every 3 weeks. In an intention-to-treat analysis, median survival was 17.5 and 15.6 months (p = 0.02) in the docetaxel and the mitoxantrone group, respectively. Also, the median time to progression was significantly longer in the docetaxel group with 6.3 months compared with 3.2 months in the mitoxantrone group (p < 0.001). A PSA decline of ≥ 50% was achieved in 50 and 27% of patients in the docetaxel and the mitoxantrone group, respectively. Pain relief was similar among both groups, though side effects occurred significantly more often in the docetaxel group due to the toxicities of estramustine. An updated survival analysis of the TAX 327 study was performed evaluating the outcome of 867 patients having died since initiation of treatment [23]. The median survival time in the 3-week arm was 19.2 months as compared to 17.8 and 16.3 months in the weekly arm and the mitoxantrone arm, respectively. Compared to the initial data analysis, survival improved slightly to 2.9 months and the HR improved minimally. There was still no significant difference in survival between the weekly arm and the mitoxantrone arm.

In addition, the authors defined subgroups as a function of treatment arms. Similar survival trends were demonstrated for patients aged > or < 68 years, for patients with a greater or lesser burden of disease using a PSA cut-off of 115 ng/ml, and for patients with minimal symptoms. Patients with visceral metastases survived 6 months less than those without visceral disease. Also, patients with substantial pain at initiation of treatment had a significantly shorter survival time than those without or with minimal pain. Similar data were identified for men with a significant decrease in Karnofsky performance status (KPS, < 80%), who died about 8 months earlier than those with KPS ≥ 80%.

Quite recently, a better risk group definition was presented based on the data of the TAX327 study [24]. Presence of visceral metastases, significant pain, anemia with a serum hemoglobin level < 13 g/dl, bone scan progression, and prior exposure to estramustine were identified as predictive factors associated with response to docetaxel treatment. Depending on the number of risk factors, patients were grouped into 3 risk groups with different lengths of median survival which was 25.7 months in the low-risk group (0 or 1 risk factor) and 18.7 and 12.8 months in the intermediate- (2 risk factors) and high-risk groups (3 or 4 risk factors), respectively.

Retrospective analysis of the TAX327 trial suggested that patients with an initial biopsy Gleason score of 7–10 experienced a better treatment response as compared to men with a Gleason score of 6 [25]. The median OS benefit of docetaxel versus mitoxantrone was 18.9 versus 14.5 months (p = 0.009), and it was 21.6 versus 20.7 months (p = 0.674) in the poorly differentiated and the well differentiated groups, respectively. However, due to the lack of prospective data comparing the impact of initial Gleason score on treatment outcome in docetaxel versus abiraterone, Gleason score should not be the main trigger to select for chemotherapy or non-cytotoxic therapy.

In order to reduce treatment-associated side effects while maintaining oncological efficacy, a prospective randomized phase III clinical trial was initiated [26] which randomized 177 and 184 patients with mCRPC to a 2-weekly docetaxel group (50 mg/m² at days 1 and 15 of a 4-week regimen) and a 3-weekly docetaxel group (75 mg/m² at day 1 of a 3-week regimen). The 2-weekly administration was associated with significantly longer time to treatment failure than was the 3-weekly administration (5.6 months; 95% CI 5.0–6.2 vs. 4.9 months, 4.5–5.4; HR 1.3, 95% CI 1.1–1.6, p = 0.014). Grade 3–4 adverse events occurred more frequently in the 3-weekly than in the 2-weekly administration group, and included neutropenia (93 (53%) vs. 61 (36%)), leucopenia (51 (29%) vs. 22 (13%)), and febrile neutropenia (25 (14%) vs. 6 (4%)). Neutropenic infections were reported more frequently in patients who received docetaxel every 3 weeks (43 (24%) vs. 11 (6%); p = 0.002). Based on these data, the 2-weekly regimen might represent an alternative approach in patients who might not tolerate the 3-weekly treatment schedule.

None of the combinations with docetaxel have improved the oncological outcome as compared to docetaxel alone [27–29] (table 1). Quite recently, the results of the READY trial (docetaxel vs. docetaxel plus dasatinib), the VENICE trial (docetaxel versus docetaxel plus afiblercept), and the CALGB 90401 (docetaxel, prednisone plus bevacizumab (DP + B) versus docetaxel, pred-
nisone) were disappointing [27–29]. The median survival after docetaxel and docetaxel/dasatinib was 21.2 versus 21.5 months, respectively, and the median survival after docetaxel versus docetaxel plus alibfercept was 21.1 versus 22.1 months, respectively. Also, the CALGB 90401 study did not result in an oncological benefit for the combination group, with a median OS of 22.6 months compared with 21.5 months (HR 0.91; 95% CI 0.78–1.05; stratified log-rank p = 0.181). Median PFS was superior in the DP + B arm (9.9 vs. 7.5 months; stratified log-rank p < 0.001) as was the proportion of patients with objective response (49.4 vs. 35.5%; p = 0.0013). Grade 3 or greater treatment-related toxicity was more common with DP + B (75.4 vs. 56.2%; p ≤ 0.001), as was the number of treatment-related deaths (4.0 vs. 1.2%; p = 0.005). Since the combination therapy of docetaxel and bevacizumab did not improve OS but increased toxicity, this approach cannot be favored for daily routine.

**Chemotherapy in Variants of Castration-Resistant Prostate Cancer**

Aggressive, non-adenocarcinoma variants of prostate cancer are increasingly recognized in the clinic [30–33]. Most probably, these aggressive variants develop due to transformation of androgen-sensitive into androgen receptor (AR)-independent prostate cancer as part of the adaptive resistance to AR-targeted therapies. Neuroendocrine and small cell carcinoma of the prostate are anaplastic variants which are diagnosed in about 10–20% of patients with CRPC [30–33]. It is evident that these subtypes of CRPC need different therapeutic approaches since AR-targeted therapies are biologically ineffective and docetaxel exerts only modest activity.

There are several clinical features that might raise the suspicion of the presence of neuroendocrine/small cell CRPC [33]: i) visceral metastases only; ii) osteolytic bone metastases; iii) bulky (> 5 cm) lymphadenopathy or bulky (> 5 cm) high-grade (Gleason score 8–10) tumor mass in the small pelvis, iv) low PSA and high-volume metastases, v) elevated lactate dehydrogenase (LDH) (≥ 2× upper limit of normal (ULN), malignant hypercalcemia, elevated carcinoembryonic antigen (CEA) (≥ 2 x ULN), vi) short interval (< 6 months) to androgen-independent progression following ADT, and vii) histologic evidence of small cell prostate cancer.

Cytotoxic combination therapy with cisplatin/carboplatin and etoposide or docetaxel and carboplatin has been shown to be effective in small cell prostate cancer [33]. In a recent prospective clinical trial, 121 patients with features of small cell prostate cancer were enrolled and received first-line chemotherapy with carboplatin (area under the curve (AUC) 5) and docetaxel (75 mg/m²) on day 1 every 3 weeks for at least 4 cycles. Second-line chemotherapy consisted of etoposide (120 mg/m²) and cisplatin (25 mg/m²) for 3 consecutive days every 3 weeks. The median follow-up was 39.1 months (range 1.07–62.47 months), and 92.9% (105/114) of the patients experienced progressive disease with a median time to progression of 5.1 months (range 4.2–6.0 months). 70.5% of those 105 patients underwent a median of 4 cycles of second-line etoposide, and 97.3% experienced progression after a median time of 3.0 months (range 1.6–3.5 months). Median OS was 16 months (range 13.6–19 months). The authors assumed that patients benefited from chemotherapy if they demonstrated stable or regressing disease for at least 2 cycles. 50% of the 74 patients who received both treatment regimens were considered to have benefited from treatment with a median OS of 19.33 months (range 10.4–23.2 months). Bulky disease and the presence of highly elevated LDH or CEA serum levels were correlated with OS. Especially highly elevated serum concentrations of LDH and/or CEA were associated with poor OS (11.5 vs. 18.2 months; p = 0.007) [33].

### Table 1. Indication for front-line chemotherapy in metastatic castration-resistant prostate cancer (mCRPC)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rationale</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic disease</td>
<td>abiraterone acetate + prednisone (AA/P), enzalutamide (ENZ), sipuleucel-T only approved for asymptomatic/mildly symptomatic mCRPC</td>
<td>I</td>
</tr>
<tr>
<td>Prostate-specific antigen (PSA) doubling time &lt; 6 months</td>
<td>biologically aggressive disease; poorer response rates following non-cytotoxic therapy</td>
<td>III</td>
</tr>
<tr>
<td>Gleason score 8–10</td>
<td>docetaxel + prednisone (Doc/P) with significant oncological benefit as compared to lower Gleason score; NB: no prospective randomized trials on Doc/P versus AA/P or ENZ</td>
<td>I</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>metastases with higher Gleason score; higher probability of small cell/neuroendocrine elements</td>
<td>III</td>
</tr>
<tr>
<td>Rapid increase in lactate dehydrogenase, alkaline phosphatase, C-reactive protein</td>
<td>biologically aggressive disease; poorer response rates following non-cytotoxic therapy</td>
<td>IIa</td>
</tr>
<tr>
<td>Progression following AA/P or ENZ</td>
<td>ENZ after AA/P with poor response</td>
<td>III</td>
</tr>
<tr>
<td>No response to androgen deprivation therapy (ADT)</td>
<td>PSA decrease to &gt; 4 ng/ml after 6 months of ADT is associated with a median overall survival time of 17 months</td>
<td>III</td>
</tr>
<tr>
<td>Low PSA, high metastatic burden</td>
<td>surrogate for small cell/neuroendocrine prostate cancer → biopsies from metastases; initiate platinum-based chemotherapy</td>
<td>III</td>
</tr>
</tbody>
</table>
Summary First-Line Chemotherapy

Based on level I evidence data, docetaxel plus prednisone remains the cytotoxic treatment regimen of choice in mCRPC patients who are candidates for chemotherapy (tables 1 and 2). The 2-weekly regimen should be preferred in mCRPC patients who are at risk of not tolerating the 3-week regimen. Initiation of first-line chemotherapy needs to take symptoms, previous treatments, extent of disease, anatomic sites of metastasis, comorbidities, PSA kinetics, and patient preference into consideration. Currently, there is no strong scientific evidence on variables which might inform about the optimal timing of chemotherapy except for the presence of highly symptomatic disease or high metastatic burden. In patients with neuroendocrine or small cell components, cisplatin/carboplatin-based chemotherapy should be initiated at the time of diagnosis.

Prognostic Risk Factors to Predict Response to First-Line Chemotherapy with Docetaxel

Biomarkers

Ideally, predictive molecular biomarkers should be able to match the biological aggressiveness of the disease with its response to systemic therapy. However, none of the evaluated biomarkers has been validated so far in larger prospective or retrospective studies. Circulating tumor cell (CTC) counts at initiation of chemotherapy have been shown to be of prognostic relevance in men who undergo systemic chemotherapy with docetaxel [34]. CTC are strong prognostic markers and need to be validated as a surrogate marker in prospective trials. Goldkorn et al. [35] evaluated the number of CTC at baseline and 2 days before cycle 2 of docetaxel administration in the SWOG 99–16 trial. CTC < versus > 5 per 7.5 ml at day 0 was significantly associated with median OS of 26 versus 13 months (HR = 2.74). In addition, rising CTC counts after cycle 1 were associated with a poorer survival (HR = 2.55). However, these data have to be interpreted with caution, and an early increase in CTC should not prompt an early change in therapy based on the negative experiences in metastatic breast cancer [30]. In another approach, Goldkorn et al. [36] evaluated the prognostic value of CTC counts for OS in the SWOG-S0421 study which compared the therapeutic efficacy of docetaxel with or without abiraterone. On Cox regression analysis, the CTC count on day 0 (< 5 CTC/7.5 ml) turned out to be the most significant prognosticator of survival (HR = 2.74, 95% CI 1.72–4.37, p < 0.001) when compared to other clinical or serological markers.

In another approach, KLK3, PCA3, and TMPRSS2-ERG mRNA was measured in CTC prior to and during systemic treatment with docetaxel in a small cohort of 20 mCRPC patients and 3 control groups [37]. At baseline, mRNA for KLK3 was detected in 17 (89%), PCA3 in 10 (53%), and TMPRSS2-ERG in 7 (37%) of 19 evaluable patients whereas the blood samples from all 32 healthy volunteers were reproducibly negative for all markers. In response to docetaxel treatment, KLK3 levels decreased in 80% (95% CI 60–100%), PCA3 in 89% (95% CI 68–100%), and TMPRSS2-ERG in 86% (95% CI 60–100%) of patients. The role of these biomarkers as surrogate marker for response needs to be explored in larger trials. Circulating cell-free DNA (cfDNA) might represent another biomarker associated with response to systemic chemotherapy [38]. Of 59 men, 48 (81.4%) had a measurable PSA decrease from baseline. Median follow-up was 15.0 months (range 2.4–58.4 months). The median cfDNA concentration in all men in this study was 27.71 ng/ml (mean 32.64 ng/ml). A threshold of 55.03 ng/ml was significantly associated with a poor PSA response of less than 30% (p = 0.005). In univariate and multivariate analysis, circulating cfDNA was an independent predictor of OS (HR 0.36, 95% CI 0.13–0.97, p = 0.044 and HR 0.34, 95% CI 0.12–0.91, p = 0.032, respectively). Limitations of the study were its retrospective character, and first- and second-line therapies. The trial showed that cfDNA concentration before therapy may be a useful predictive and prognostic biomarker for PSA response and survival.

Clinical Predictive Markers

For the moment, one has to rely on unspecific clinical parameters such as extent of disease, asymptomatic versus symptomatic disease, anatomic sites of metastasis, ECOG performance status, PSA doubling time, Gleason score, and response to first-line therapy. Furthermore, serum concentrations of PSA, C-reactive protein (CRP), LDH, hemoglobin, alkaline phosphatase have been...
shown to correlate with response to therapy and survival [32–34]. Elevated LDH levels are thought to be reflective of the underlying tumor burden or an aggressive phenotype. Disease-related anemia can also indicate a more aggressive form of disease. Anemia can be easily monitored but may be a consequence of long-term ADT, renal disease, chemotherapy toxicity, chronic disease, iron deficiency from blood loss, bone marrow infiltration, or comorbidity. The degree of anemia correlates with prognosis and was found to be the strongest prognostic factor for docetaxel-related PSA decline, tumor response rate, and OS in mCRP [39, 40]. Lastly, CRP is a marker of systemic inflammation that may also be prognostic of survival in patients previously treated with docetaxel [41]. Various studies have proven that the neutrophil-to-lymphocyte ratio (NLR) might represent a useful biomarker associated with response to chemotherapy and abiraterone acetate [42, 43]. An NLR < 5 was associated with a higher probability of PSA response during AA/P treatment (HR 4.3, 95% CI 1.4–13.3, p = 0.01) as compared to an NLR ≥ 5. In a variety of retrospective studies, an NLR < 3.0 was associated with better response and longer median OS in men undergoing systemic chemotherapy with docetaxel. Nuhn et al. [42] demonstrated that a lower NLR (≤ 3.0) was associated with lower risk of all-cause mortality (p = 0.002). In Kaplan-Meier analysis, median OS was higher (18.3 vs. 14.4 months) in patients that did not have an elevated NLR compared to those with an elevated NLR (log-rank p < 0.001). In the study of Templeton et al. [43], NLR and other known prognostic variables were evaluated among a cohort of chemotherapy-naive patients treated with 3-weekly docetaxel. Liver metastases, hemoglobin < 12 g/dl, alkaline phosphatase > 2.0× ULN, lactate dehydrogenase > 1.2× ULN, and NLR > 3 were associated with significantly worse OS in multivariable analysis. 4 risk categories were subsequently established with 0, 1, 2, and 3–5 points. 2-year OS rates for these categories were 43, 37, 12, and 3%, respectively. The AUC for the training cohort was 0.78 (95% CI 0.72–0.84) compared with 0.66 (95% CI 0.58–0.74) for the 215 patients in the validation cohort.

Based on these studies, NLR may be a potentially useful clinical marker of systemic inflammatory response in predicting OS in men with mCRPC who receive docetaxel, and it may be helpful when stratifying patients for clinical trials. These findings derived from a retrospective analysis need to be validated in larger populations in prospective studies and in the context of different therapies.

Although the evidence is low, CRPC with features of aggressive disease such as < 16 months response to first-line ADT [44], Gleason score ≥ 8 [25], and presence of visceral metastases might better respond to first-line chemotherapy [45]. In addition, anatomic sites of metastasis harbor significant and clinically important prognostic information. Liver metastases are associated with the poorest median OS of only 10.0 months in the TAX327 trial whereas men with lymph node-only metastases experienced the best response with a median OS of 26.7 months [45]. Median OS was intermediate with 19.0 and 15.7 months in men with skeletal metastases and those with skeletal plus lymph node metastases, respectively. However, one has to consider that patients with visceral metastases were excluded from the COUGAR-302 trial and the IMPACT trial [9, 14] whereas men with visceral and minimally symptomatic disease were allowed in the PREVAIL trial and they did benefit from therapy with ENZ [15]. Objective response rates were 59 and 5% in the ENZ and the placebo group, respectively. Complete and partial responses were observed in 29 and 39%, respectively, of the patients in the ENZ group as compared to 1 and 4% in the placebo group. Currently, there are no data on comparative trials between chemotherapy and AR-targeting agents available so that the level of evidence is quite low for an individual treatment decision.

### Second-Line Treatment following Docetaxel

There are several treatment options available for patients with mCRPC who progress following first-line docetaxel chemotherapy: docetaxel rechallenge, AA/P, CBZ/P, ENZ, and radium-223 are active agents in this clinical scenario. Certainly, CBZ/P is the cytotoxic treatment of choice based on level I evidence data from the TROPIC trial [10]. However, docetaxel rechallenge might be considered in those who respond well to docetaxel chemotherapy [39–44] and are not good candidates for CBZ.

**Abiraterone Acetate plus Prednisone**

AA/P versus placebo was evaluated in the prospective randomized clinical phase III COUGAR-301 trial which recruited 1,195 patients [11]. The primary study endpoint was OS whereas radiological PFS, time to progression, and PSA response rate served as secondary study endpoints. After a median follow-up of 12.8 months, there was a significant survival benefit favoring AA/P (14.8 vs. 10.9 months; p < 0.001). All secondary endpoints were also met with AA/P.

Treatment with AA/P is also effective in the presence of liver and lung metastases with a median OS of 12.9 and 8.3 months, respectively, which is much lower than in patients without visceral metastases [39]. Following discontinuation of AA/P, an abiraterone withdrawal syndrome can be observed in about 32% of patients with a median time to progression of 5.7 months [40].

Concerning the toxicity profile, there were clinically meaningful differences compared to the COUGAR-302 trial. In addition, no statistically significant differences were observed between the treatment and the placebo arm. For daily routine, only the typical CYP17-induced side effects such as fluid retention, edema, hypokalemia, liver function disorders, and arrhythmias have to be considered.

**Enzalutamide**

ENZ has been prospectively evaluated in the AFFIRM trial which recruited 1,199 men with mCRPC following failure of docetaxel therapy [15]. OS was the primary study endpoint, and PSA
Docetaxel Rechallenge

This approach has never been tested in prospective randomized clinical trials, but there is level II–III evidence from retrospective series to identify patients who might be good candidates for re-exposure to docetaxel [46–51] (table 3). Patients who respond with a PSA decrease ≥ 30% maintained for at least 8 weeks after the end of docetaxel treatment demonstrate a positive PSA response in about 35–60% during re-exposure without increasing treatment-related toxicity. Patients with a sufficient progression-free interval (3–6 months), good ECOG performance status, and previous acceptable safety profile represent good candidates for this approach. An overall biochemical response rate (PSA reduction > 50%) of 66% and median OS of 32 months with a projected 2-year OS from first docetaxel administration of 77.5% indicate the feasibility and therapeutic efficacy of this treatment option. Multivariate analysis showed that time slope log PSA, time from the previous cycle, and response to the previous cycle were predictive of response to rechallenge [46].

Similar data have been described by Oudard et al. [47] in a retrospective study analyzing 223 and 47 mCRPC patients with good response to first-line docetaxel who were exposed to a docetaxel rechallenge or who received non-taxane-based chemotherapy. Although there was a statistically significant difference in terms of PSA response and symptom relief (40.4 vs. 10.6%; p = 0.001) for the docetaxel arm, OS was not prolonged (18.2 vs. 16.8 months; p = 0.0044) between the 2 groups.

Heck et al. [48] evaluated the outcome of 44 mCRPC patients who underwent docetaxel rechallenge after first-line docetaxel. According to their data, re-exposure to docetaxel might only be indicated if patients experienced a PSA decrease > 50% during first-line treatment which resulted in a significantly improved OS (22.1 vs. 7.2 months; p = 0.03) following second-line exposure.

Loriot et al. [49] demonstrated that the interval between the last docetaxel infusion and progression correlated well with median PFS following docetaxel rechallenge. Median PFS was 3.4 versus 6.3 months (p = 0.04) if the interval was < 3.0 months versus > 3.0 months, respectively.

Cabazitaxel plus Prednisone

CBZ is a second-generation tubulin-binding taxane which was selected for further clinical trials based on its antitumor activity in models resistant to docetaxel and paclitaxel and its high cytotoxicity. The TROPIC trial was a prospective randomized open-label phase III clinical trial which recruited 755 patients with mCRPC who progressed during or after docetaxel-based chemotherapy [10]. Patients were randomized in a 1:1 fashion to receive CBZ at 25 mg/m² and prednisone 5 mg twice daily at 21-day intervals for 10 cycles or mitoxantrone at 12 mg/m² and prednisone 5 mg twice daily at 21-day intervals for 10 cycles. The primary study endpoint was OS, secondary endpoints were PFS, PSA response rate, objective tumor response rate, pain response, and safety. The primary endpoint was achieved, and CBZ/P chemotherapy resulted in a significant improvement in OS compared to mitoxantrone and prednisone (15.1 vs. 13.4 months; p < 0.0001).

Table 3. Summary of data of retrospective trials concerning docetaxel rechallenge after exposure to first-line docetaxel

<table>
<thead>
<tr>
<th>Author [ref.]</th>
<th>n</th>
<th>Median overall survival, months</th>
<th>Prostate-specific antigen response, %</th>
<th>Time to treatment failure, months</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oudard et al. [47]</td>
<td>223 vs. 47*</td>
<td>18.2 vs. 16.8 (p = 0.35)</td>
<td>40.4 vs. 10.6 (p = 0.001)</td>
<td></td>
<td>II</td>
</tr>
<tr>
<td>Caffo et al. [46]</td>
<td>46</td>
<td>32</td>
<td>66</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Heck et al. [48]</td>
<td>41</td>
<td>21.8</td>
<td>28</td>
<td>5.9</td>
<td>III</td>
</tr>
<tr>
<td>DiLorenzo et al. [50]</td>
<td>45</td>
<td>13.0</td>
<td>24.5</td>
<td>5.0</td>
<td>III</td>
</tr>
<tr>
<td>Loriot et al. [49]</td>
<td>39</td>
<td>15.8</td>
<td>38</td>
<td>4.3</td>
<td>III</td>
</tr>
<tr>
<td>Pfister et al. [51]</td>
<td>25</td>
<td>n.s.</td>
<td>56</td>
<td>n.s.</td>
<td>III</td>
</tr>
</tbody>
</table>

*Comparative study in patients receiving docetaxel rechallenge or a non-taxane based chemotherapy. n.s. = not specified
median OS of 15.1 months compared with 12.7 months for patients receiving mitoxantrone plus prednisone (HR 0.70, 95% CI 0.59–0.83, \( p < 0.0001 \)). All secondary endpoints of the trials were reached, and they were in favor of CBZ.

With regard to safety, the CBZ/P group experienced significantly more grade 3/4 toxicities than the placebo group (53 vs. 45%). The most common side effects were hematological, and the most common grade 3/4 toxicity were neutropenia (82 vs. 58%), leukopenia (68 vs. 42%), and anemia (11 vs. 5%). Diarrhea was the most common non-hematological side effect and occurred in 6% and <1% in the CBZ/P and the mitoxantrone plus prednisone group, respectively. This very high frequency of significant treatment-related adverse events could not be reproduced by the German and the European groups when evaluating the safety data of the compassionate use programs (CUP) and the expanded access programs \[52, 53\]. The German CUP included 111 patients with mCRPC who met the inclusion criteria of the TROPIC trial, and the frequency of neutropenia, leukopenia, and anemia decreased to 7.2, 9.0, and 4.5%, respectively. Grade 3/4 gastrointestinal toxicity was observed in only 0.9% of the patients. It has to be mentioned that even in the presence of these risk factors, prophylactic application of G-CSF significantly reduced the risk of neutropenic complications by 30% (odds ratio (OR) 0.70, 95% CI 0.50–0.99, \( p = 0.04 \)). In another study by the French group, Oudard et al. \[47\] demonstrated that CBZ/P is equally effective in poorly differentiated prostate cancer with a Gleason score of 8–10 resulting in a survival benefit of 2.5 months over mitoxantrone/prednisone (15.2 vs. 12.7 months; \( p < 0.001 \)).

### Radium-223 in mCRPC

Radium-223 dichloride is the first \(\alpha\)-particle-emitting bone-targeting agent approved for use in mCRPC patients with symptomatic bone metastases. The randomized phase III double-blind

<table>
<thead>
<tr>
<th>Table 4. Predictive factors for grade ≥ 3 neutropenia, febrile neutropenia, or neutropenic sepsis</th>
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</thead>
<tbody>
<tr>
<td><strong>Predictive factor</strong></td>
</tr>
<tr>
<td>Age (70–75 vs. &lt; 70 years)(^a)</td>
</tr>
<tr>
<td>Age (≥75 vs. &lt; 70 years)(^a)</td>
</tr>
<tr>
<td>Cycle 1 vs. cycle &gt; 1(^b)</td>
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<tr>
<td>Prior docetaxel cycles (≥10 vs. &lt;10)(^a)</td>
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<tr>
<td>ECOG performance status (1 vs. 0)</td>
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<tr>
<td>ECOG performance status (2 vs. 0)</td>
</tr>
<tr>
<td>G-CSF prophylaxis at a given cycle(^b)</td>
</tr>
<tr>
<td>Time since initial diagnosis (≥59.6 vs. &lt;59.6 months)</td>
</tr>
<tr>
<td>Neutrophils at previous cycle (&lt;4.0 vs. ≥4.0 giga/l)(^a)</td>
</tr>
<tr>
<td>Visceral metastatic site(s) (at least 1)</td>
</tr>
</tbody>
</table>

\(^a\)Variables retained after initial univariate process (\( p \) value ≤0.25).

\(^b\)Univariate ORs were estimated via a simple logistic generalized estimating equation (GEE) regression. Multivariate ORs were estimated via a multivariate logistic regression using data from patients with available data for all parameters (\( n = 732 \)).

CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte-colony stimulating factor; OR = odds ratio.
placebo-controlled ALSYMPCA study investigated radium-223 in mCRPC patients with symptomatic bone metastases (no visceral disease) who were not eligible to receive, or who had declined, docetaxel [55]. Patients received radium-223 at a dose of 50 kBq/kg body weight and best standard of care (BSoC) or BSoC alone. After a follow-up of < 3 years, a significant OS benefit of 14.0 months versus 11.3 months was identified for radium-223 (HR 0.695, 95% CI 0.581–0.8732, p < 0.0001). The survival benefit was independent of prior use of docetaxel or zoledronic acid. In addition, a significant delay in the time to first symptomatic skeletal event (15.6 vs. 9.8 months; p < 0.001) was reported. The treatment-associated adverse events were similar between both groups, and no statistically significant difference in hematotoxic events (3–12%) was reported between the groups with an acceptable safety profile compared to those receiving placebo and BSoC [55, 56].

Quite recently, safety, OS, and effect of concomitant therapies in patients with mCRPC treated with radium-223 was evaluated in an international early access phase IIIb trial [57]. 696 patients received radium-223 at a dose of 50 kBq/kg body weight and best standard of care (BSoC) or BSoC alone. After a follow-up of < 3 years, a significant OS benefit of 14.0 months versus 11.3 months was identified for radium-223 (HR 0.695, 95% CI 0.581–0.8732, p < 0.0001). The survival benefit was independent of prior use of docetaxel or zoledronic acid. In addition, a significant delay in the time to first symptomatic skeletal event (15.6 vs. 9.8 months; p < 0.001) was reported. The treatment-associated adverse events were similar between both groups, and no statistically significant difference in hematotoxic events (3–12%) was reported between the groups with an acceptable safety profile compared to those receiving placebo and BSoC [55, 56].

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Qu...
who have been treated with docetaxel alone is more difficult. There are data from a small retrospective study indicating that the sequence of docetaxel–CBZ/P appears to be more effective than the sequence of docetaxel followed by AA/P or ENZ and followed by CBZ/P as the third-line approach. Furthermore, patients who progress during docetaxel chemotherapy after 3 cycles and in whom a flare-up phenomenon can be ruled out seem to respond much better to CBZ/P as compared to the non-cytotoxic approaches.

The potentially optimal sequence of CBZ/P and AA/P after docetaxel was retrospectively evaluated in 130 patients with mCRPC [65]. Significantly more patients (p < 0.001) were treated with docetaxel followed by CBZ/P and AA/P (67.7%) as compared with the sequence of docetaxel followed by AA/P and CBZ/P (32.3%). The sequence docetaxel and AA/P was prevalent among patients not eligible to receive more than 2 lines of treatment, while the sequence docetaxel–CBZ/P–AA/P was preferable for patients suitable for 3 lines of treatment. Thus, the unbalanced favoring of the sequence docetaxel–CBZ/P–AA/P could be partially related to clinical a priori selection. A retrospective analysis was conducted on an American electronic database (iKnowMed Electronic Health Records). A total of 113 patients were treated with sequential docetaxel, CBZ/P, and AA/P. 77 with the sequence docetaxel–CBZ/P–AA/P and 36 with docetaxel–AA/P–CBZ/P. OS was superior in the sequence docetaxel–CBZ/P–AA/P versus docetaxel–AA/P–CBZ/P (18.2 vs. 11.8 months; HR = 0.12) [66].

In addition, 2 small retrospective studies showed that CBZ/P is still active in men who underwent pretreatment with docetaxel and AA/P. A PSA decline > 50% and an objective response were achieved in 31.5 and 15.3% of the patients, respectively [67]. The median OS was 8.2, 16.1, and 32 months from initiation of CBZ/P, AA/P, and docetaxel therapy, respectively. In another study, Pezaro et al. [68] evaluated 59 mCRPC patients who were treated for progression following docetaxel. The authors retrospectively focused on a small cohort of 59 patients who had been treated with docetaxel, the EAU guideline-recommended first-line chemotherapy of choice once patients become castration-resistant. In 41 patients, docetaxel was followed by second-line therapy with AA/P and/or ENZ at the time of progression; the remainder received CBZ/P. The results of the retrospective single-center experience reported by Pezaro et al. [68] are interesting and important to urologists and medical oncologists involved in the management of mCRPC patients since it appears that CBZ/P after AA/P and/or ENZ seems to be as oncologically effective as the sequence docetaxel followed by CBZ/P. Median OS and PFS (15.8 and 4.6 months, respectively), PSA decline ≥ 50% in 39%, and radiological responses of soft tissues metastases in 14% are in the same range as seen in the TROPIC trial [11].

If CBZ/P is chosen as second-line chemotherapy, patients need to have a good performance status (ECOG 0–1), the treating physicians should be experienced in the application of taxane-based chemotherapy, and currently available recommendations for the prevention of significant treatment-related side effects should be followed. In elderly patients aged > 70 years, geriatric assessment should be applied to further facilitate optimal patient selection [69, 70].

**Mechanisms of Resistance and Sequencing**

**First-Line Treatment in mCRPC Patients**

It is common sense that patients with primary resistance to AA/P and ENZ (no PSA decline, no radiological soft tissue response, and no clinical benefit after 3 months of treatment) should be switched to chemotherapy and that the patients should not be exposed to second-line hormonal therapy with ENZ or AA/P [71]. Also, in patients with acquired resistance to AA/P or ENZ, the recently published recommendations of the St. Gallen Advanced Prostate Cancer Consensus Conference recommended second-line treatment with chemotherapy in the majority of patients [71].

Primary resistance is most commonly due to the presence of AR-V7 splice variants which lack the ligand-binding domain so that both AA/P and ENZ have no chance of blocking AR activity [72]. It has been shown in a small group of 31 patients that no response to 1 of the AR signal inhibitors was observed in the presence of AR-V7. Also, median PFS, clinical or radiographic PFS, and median OS were significantly lower in the AR-V7-positive group as compared to the AR-V7-negative group. However, these data need external validation in a larger cohort of patients since a recently published study reported a 10% response rate to AA/P or ENZ in AR-V7-positive patients [73].

There might be cross-resistances between different taxanes, between the taxanes and androgen axis-targeting drugs, as well as between the different androgen axis-targeting drugs. In vitro studies suggest that one mechanism of action for taxanes is inhibition of microtubule-dependent AR translocation to the nucleus, impairing AR signaling and reducing PSA expression [74]. It has become evident from a recent in vitro study that taxanes exert their cytotoxic effects in part through cytoplasmic AR sequestration and/or nuclear accumulation of the AR function repressor FOXO1. Preclinical studies have demonstrated an impaired cytotoxic activity of docetaxel and CBZ/P in AA/P-resistant prostate cancer cell lines, which was explained by the fact that all substances exerted an inhibitory effect on AR nuclear translocation.

AA/P impairs AR signaling by reducing CYP17-dependent androgen production as well as directly binding to AR and reducing AR signaling in a dose-dependent manner. This raises concerns regarding the potential for cross-resistance between microtubule inhibitors and hormonal therapies such as AA/P, based on the hypothesis that use of AR signaling inhibitors may impair the ability of taxanes to subsequently inhibit this pathway. In a retrospective analysis of 54 patients with AA/P-pretreated CRPC, 35 patients progressed on AA/P and subsequently received docetaxel at 75 mg/m² every 3 weeks with a median number of 6 cycles being administered [75]. 8 patients never responded to AA/P and were considered to be primary AA-refractory patients. All 8 patients were docetaxel-refractory and did not demonstrate any significant PSA response. PSA declines ≥ 50% were observed in 9/35 (26%) patients, a PSA decrease ≥ 30% was observed in 13/35 (37%) patients. Out
of 27 patients who experienced a PSA decline ≥ 50% with AA/P, 9 had a PSA decrease of 50% or greater with docetaxel. The median time to PSA progression was only 4.5 months, and median OS was 12.5 months. In the TAX327 trial, the PSA response was 45%, median OS was 18.9 months, and the objective remission rate was 12%. Clearly, there are significant differences between first-line and second-line docetaxel supporting the hypothesis that docetaxel resistance might be triggered by AR overexpression or AR mutation.

Primary or acquired resistance to AA/P might be due to mutations in the AR facilitating the affinity of the AR for a wider range of other steroid hormones. Some groups have shown that prednisone treatment might activate mutant promiscuous AR and initiate disease resistance [76]. The CYP17 enzyme is crucially implicated in this process, which is consistent with the effectiveness of CYP17 inhibitors, such as AA/P, in CRPC patients [77]. Importantly, increased intracellular expression of CYP17 in biopsied metastatic lesions in CRPC patients treated with AA/P was associated with longer time on treatment and may serve as a tool to predict sensitivity to this class of agents. This finding raises the possibility that sustained dihydrotestosterone synthesis might contribute to AA resistance. Resistance to AA/P might also derive from increased intratumoral concentration of dihydrotestosterone and might be overcome by dose escalation of AA/P to inhibit 3β-hydroxysteroid dehydrogenase [78, 79]. This approach has been demonstrated to be active in in vitro studies. It also has been suggested that AA/P resistance might be induced by glucocorticoid-induced activation of mutated AR and that steroid medication, which is mandatory to be added when AA is administered, might induce resistance. This resistance might be reversed by the addition of pure AR antagonists or by the administration of lyase inhibitors without the need of steroids such as orteronel or galacterone.

**Disclosure Statement**

The authors declare no potential conflict of interest.

**References**


