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Therapeutic Options for First-Line Metastatic Castration-Resistant Prostate Cancer: Suggestions for Clinical Practise in the CHAARTED and LATITUDE Era

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Introduction

Prostate cancer (PC) is a major health issue in Western countries, representing the most frequent tumour and the second leading cause of cancer-related deaths among males [1].

In the natural history of the majority of advanced PC patients, it is possible to identify two phases. In the first so-called castration-sensitive prostate cancer (CSPC) phase, the androgen receptor (AR) pathway plays a fundamental role in disease growth and progression. As a consequence, tumour cells are highly responsive to the reduction in serum testosterone levels and androgen-deprivation therapy (ADT), achieved by either surgical or medical castration, which represents the mainstay of therapy. Although ADT induces biochemical and clinical responses in more than 90% of patients, after a median of 24-36 months, all progress to the second phase of the disease, called castration-resistant prostate cancer (CRPC) [2].

CRPC, previously defined as hormone-refractory prostate cancer, is now understood to still be androgen dependent. Multiple mechanisms of resistance contribute to the progression to castration resistant disease, and the AR remains an important driver in this progression.

Recently, the therapeutic strategy for CRPC patients radically changed due to improved knowledge of PC biology and progression mechanisms. At present, we know that AR plays a critical role in CRPC and the interplay between bone resident and prostatic cancer cells is responsible for metastatic progression in bone [3,4].

Consequently, several new drugs able to increase overall survival (OS) have been introduced in daily clinical practice for the management of metastatic CRPC (mCRPC). Results of randomised phase III trials showed the activity of an immunotherapeutic agent (sipuleucel-T) [5], two next-generation hormonal treatments (abiraterone acetate [AA] [6,7] and enzalutamide [8,9]), an innovative taxane (cabazitaxel) [10], and an α particle-emitting agent (radium-223) [11].

Moreover, the last three years saw a revolutionary change in the treatment paradigm of metastatic CSPC (mCSPC). Recent findings demonstrated that in patients with de novo mCSPC, the addition of chemotherapy with docetaxel (DOC) to ADT significantly improves OS compared to ADT alone [12,13].

Additionally, two recent studies (LATITUDE and STAMPEDE) performed in the same disease phase established that adding AA to ADT significantly increases OS in mCSPC [14,15].

Due to the evolution of metastatic prostate cancer treatment scenarios, clinicians presently face important therapeutic challenges. The main challenge is the choice of the best treatment sequencing for each specific patient. In this context, we have only some limited retrospective data to guide decision-making in patients experiencing disease progression after DOC or AA treatment for mCSPC.

This review provides an overview of the therapeutic options available to both mCSPC and mCRPC patients and offers some clinical and biological insights to select the best treatment for patients with progressive disease progression after mCSPC treatment with DOC or AA.

Evidence for docetaxel and abiraterone use in mCSPC

a) Docetaxel

GETUG-AFU 15 trial

The GETUG-AFU 15 randomised phase III trial enrolled patients with newly diagnosed mCSPC who were randomised to receive ADT with or without DOC 75 mg/sqm IV every three weeks for a maximum of nine courses [16].

The results of the trial, which enrolled 385 patients between October 2004 and December 2008, were first published in 2013 after a median follow-up of 50 months. The experimental arm showed significantly longer biochemical progression-free survival (PFS) compared to the standard treatment arm (median 22.9 and 12.9 months, respectively; $p = 0.005$); similar findings were observed in terms

of the clinical PFS, which was significantly longer in the DOC arm (median 23.5 months) than in the ADT-alone arm (median 15.4 months; p = 0.015). This clear PFS advantage did not lead to a significant OS improvement: the median OS in the chemotherapy group and in the ADT-alone group was 58.9 months and 54.2 months, respectively (p = 0.955).

After the publication of the CHAARTED trial results (see below), an updated analysis of the GETUG-AFU 15 trial was published in 2016 [17]. This analysis, based on a longer follow-up than the first report (83.9 months), aimed to assess the impact of metastatic burden by applying the same criteria of the CHAARTED trial for the identification of patients with high vs low volume of disease (see below). Although in the overall population there was an absolute difference of 13.5 months in terms of median OS in favour of the chemotherapy group (62.1 vs 48.6 months), this did not reach statistical significance (HR: 0.88; p = 0.3). No statistically significant differences were observed between the two treatment groups according to the metastatic burden and the timing of the metastases diagnosis (after radical local treatments or at diagnosis).

CHAARTED trial

The CHAARTED randomised phase III trial enrolled patients with newly diagnosed mCSPC who were randomised to receive ADT with or without DOC 75 mg/sqm IV every three weeks for a maximum of six courses[12].

The results of the CHAARTED trial, which enrolled 790 patients between July 2006 and December 2012, were published in 2015 after a median follow-up of 28.9 months. The experimental arm was clearly superior to the standard arm in terms of both PFS (median 20.2 vs 11.7 months; HR 0.61; p < 0.001) and OS (median 57.6 vs 44.0 months; HR 0.61; p < 0.001). The differences were more significant and impressive for the group of patients with high disease volume (defined as having visceral metastases and/or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis) who

showed a gain in median OS of 17.0 months if they had received DOC and ADT instead of ADT alone (49.2 vs 32.2 months; HR 0.60; $p < 0.001$). In the group of patients with low-volume disease, no statistically significant differences in OS were observed, although the reduction of death risk was quite similar to that observed in the high-volume group, HR 0.60 (95% CI: 0.32-1.13), $p = 0.11$, suggesting that the low number of deaths made the results premature. An update of the survival results with a longer follow-up confirmed the large advantage for the experimental arm in the high-volume patients but failed to show reduction in the death risk in favour of DOC treatment for the patients with low-volume disease, HR 1.04 (95% CI: 0.70-1.55), $p = 0.86$ [18].

The non-significant result of the CHAARTED trial in the low-volume subgroup of patients may depend on the lower mortality compared to the high-volume disease patients, to immature survival end-point and on the small number of patients, with inadequate power to detect an OS benefit.

By combining the disease burden and the metastatic timing, the combined results from the CHAARTED and GETUG-AFU 15 trials clearly supported a survival advantage in metastatic "de novo" patients with high-volume disease with an OS gain in the DOC + ADT arm compared to the ADT-alone arm, 48.0 months vs 33.1 months; HR 0.63 (95% CI: 0.49-0.81); $p = 0.0004$ [19].

STAMPEDE trial

STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy), a multi-centre, open-label, multi-arm, multi-stage randomised trial, aimed to evaluate if the addition of new treatments to the standard of care (SOC, ADT ± radiotherapy) improves the OS in men with high-risk locally advanced prostate cancer or mCSPC. The main characteristic of this trial is its ability to test treatments that could potentially be efficacious in mCSPC by opening new treatment arms to be compared to the standard treatment arm over time[20]. The comparison of one or more new

treatment arms vs SOC may be considered a new randomised study and the sample size is defined according to a specific statistical design, with primary endpoint OS.

The results of the STAMPEDE trial were published in 2016. The four treatment arms included: standard of care only (SOC-only), SOC plus zoledronic acid (ZA), SOC plus DOC, and SOC plus ZA and DOC[13].

The experimental treatments consisted of ZA given at the standard 4 mg dose every three weeks for six cycles, then every four weeks until 2 years and/or DOC at the standard dose of 75 mg/m2 every three weeks for six cycles with prednisolone 10 mg daily. A total of 2962 men were randomly assigned to the four groups between October 2005 and March 2013. After a median follow-up of 43 months, the median OS was 71 months in the SOC-only arm, not reached in the SOC + ZA arm (HR 0.94, 95% CI: 0.79-1.11; p = 0.450), 81 months in the SOC + DOC arm (HR 0.78, 95% CI: 0.66-0.93; p = 0.006), and 76 months in the SOC + ZA + DOC arm (HR 0.82, 95% CI: 0.69-0.97; p = 0.022). From these results, it was clear that the addition of ZA did not improve OS, while the addition of DOC led to a clear OS advantage. By selecting the population with metastasis (1817 patients), the results were confirmed, with a median OS of 45 months in the SOC-only arm, 46 months in the SOC + ZA arm (HR 0.93, 95% CI: 0.77-1.11; p = 0.416), 60 months in the SOC + DOC arm (HR 0.76, 95% CI: 0.62-0.92; p = 0.005), and 55 months in the SOC + ZA + DOC arm (HR 0.79, 95% CI: 0.66-0.96; p = 0.015).

In terms of failure-free survival, the addition of ZA only to SOC did not lead to a risk reduction (HR 0.92, 95% CI: 0.81-1.04; p = 0.198), while the addition of DOC to SOC led to a statistically significant risk reduction either without ZA (HR 0.61, 95% CI: 0.53-0.70; p = 0.413 x 10-13) or with ZA (HR 0.62, 95% CI: 0.54-0.70; p = 0.134 x 10-12). In a metastatic setting, DOC significantly reduced the risk of failure (HR 0.61, 95% CI: 0.53-0.71; p = 0.283 x 10-10).

b) Abiraterone acetate

LATITUDE trial

The LATITUDE trial enrolled high-risk newly diagnosed mCSPC patients who were randomised to receive either ADT plus AA 1000 mg daily plus prednisone (5 mg daily) or ADT plus dual placebos[14]. The definition of high-risk disease required at least two of the three following factors: a Gleason score of 8 or more, at least three bone lesions, and the presence of measurable visceral metastases. The trial enrolled 1199 patients from February 2013 to December 2014.

The results of the LATITUDE trial were published after a planned interim analysis performed after a median follow-up of 30.4 months. The OS was significantly longer in the experimental arm than in the control arm (median not reached vs 34.7 months; HR 0.62; 95% CI: 0.51-0.76; $p < 0.001$), while the median radiographic PFS was 33.0 months in the AA arm and 14.8 months in the ADT-only arm (HR 0.47; 95% CI: 0.39-0.55; $p < 0.001$).

STAMPEDE trial

The results of the comparison between the arm with SOC plus AA and the arm with SOC alone within the STAMPEDE trial development [15] were published in 2017. In the experimental arm, the patients received SOC plus daily AA at a standard dose of 1000 mg with 5 mg prednisolone.

A total of 1917 patients were randomised between the two groups between November 2011 and January 2014. At a median follow-up of 40 months, there was a reduction of risk of death of 27% in favour of the experimental arm (HR 0.63; 95% CI: 0.52-0.76; $p < 0.001$) with a 3-year survival of 83% compared to 76% in the SOC-only group. Considering the 1002 patients with metastatic disease at entry, the HR for death was 0.61 (95% CI: 0.49-0.75). The HR for treatment failure was 0.29 (95% CI:

0.25-0.34; p < 0.001), with a confirmed efficacy of AA in the metastatic patients (HR 0.31; 95% CI: 0.26-0.37).

c) Meta-analyses

Docetaxel

In 2015, Vale et al. [21] published a meta-analyses based on published data regarding the potential advantage of adding DOC or bisphosphonates to the standard of care in patients with localised or metastatic CSPC. In a metastatic setting, they analysed the results of the GETUG-AFU 15 trial, CHAARTED trial, and STAMPEDE trial and concluded that the addition of DOC to ADT led to an absolute improvement in the 4-year survival of 9% (95% CI: 5-14), with a reduction in the death risk of 23%, with an HR of 0.77 (95% CI: 0.68-0.87; p < 0.0001), while in terms of failure-free survival, the reduction in the absolute 4-year failure rates was 16% (95% CI: 12-19), with an HR of 0.64 (95% CI: 0.58-0.70; p < 0.0001).

Meta-analysis by Tucci et al. (2016) evaluated only the addition of DOC in the group of mCSPC patients [22]. Their results were quite similar: the administration of DOC was associated with a statistically significant OS benefit (HR 0.73; 95% CI: 0.60-0.90; p = 0.002). In the patients with high-volume disease, the HR was 0.67 (95% CI: 0.51-0.88), while in the patients with low-volume disease, the HR was 0.80 (95% CI: 0.49-1.32). In terms of PFS, treatment with chemotherapy reduced the progression risk of the mCSPC patients by 27% (HR: 0.63; 95% CI: 0.57-0.70; p < 0.001).

Because both meta-analyses demonstrated a lack of statistically significant heterogeneity among the three trials with DOC, their findings clearly supported the use of DOC in mCSPC.

Abiraterone acetate

The STOPCAP report [23], based on a framework for adaptive meta-analysis, summarised the results of the LATITUDE and STAMPEDE trials but also planned to take into account the potential impact of the results of PEACE-1, another trial testing the addition of AA and DOC to ADT in mCSPC that is still ongoing. Based on the PEACE-1 recruitment information available at the time this report was published, the available trials represent 82% (2201/2677) of all patients randomised to AA plus ADT vs ADT.

The meta-analysis showed a 14% absolute improvement in 3-year OS, with a 38% reduction in the risk of death in favour of AA (HR 0.62, 95% CI: 0.53-0.71, p = 0.55 x 10-10). Similarly, the addition of AA to ADT produced a 28% absolute clinical/radiological PFS improvement at 3 years, with a 55% reduction in the progression risk (HR = 0.45, 95% CI: 0.40-0.51, p = 0.66 x 10-36).

In this meta-analysis, there was no evidence of statistical heterogeneity between the trials, and the results supported the use of AA in mCSPC patients.

d) Comparison between Abiraterone and Docetaxel

Although not planned to test a direct comparison between the two treatment strategies according to a formal hypothesis, the STAMPEDE multi-arm, multi-stage platform protocol provides the only direct, randomised comparative data of standard of care (SOC) + AA versus SOC + DOC in mCSPC patients.[24] This study showed no evidence of a difference in OS (HR 1.16; 95% CI: 0.82-1.65) or prostate cancer-specific survival (HR 1.02; 95%CI: 0.70-1.49), nor in other important outcomes such as symptomatic skeletal events (HR 0.83; 95% CI: 0.55-1.25) between the two treatments, suggesting that both currently remain viable new standard-of-care.

Post-progression treatments after docetaxel and abiraterone

The use of DOC and AA in mCSPC patients affects the subsequent treatments for mCRPC and, to date, there are little data on the efficacy and tolerance of post-progression therapies.

In the GETUG-AFU 15 trial, most of the patients treated upfront with ADT and DOC for mHSPC (245/345) received at least one post-progression treatment. A recent paper analysed the outcomes of patients who received one life-prolonging agent for mCRPC[25].

Among the 24 patients who received a DOC rechallenge as a first-line treatment for mCRPC, 4 out of the 20 evaluable (20%) had a PSA decline ≥ 50%: this biochemical response rate was lower than observed in the patients enrolled in the ADT control arm (38%), although the difference did not achieve statistical significance (p = 0.14). The patients treated with DOC rechallenge showed a median biochemical progression-free survival of 4.1 months (95% CI: 1.3-4.9). Considering the cumulative analysis of the patients who received DOC either in first- or second-line treatment, a PSA decline ≥ 50% was observed in 4/29 patients (14%) previously treated with ADT plus DOC (p = 0.07 vs DOC activity in the ADT control arm). It is noteworthy that the rate of patients who received a DOC rechallenge in the GETUG-AFU 15 trial was significantly lower compared to the CHAARTED trial, where 50% of the patients (191/385) received DOC after progression. Among the 10 patients who were treated with AA or enzalutamide at disease progression after DOC, only six were evaluable, with a rate of PSA decline ≥ 50% of 67%. However, this report had limited value in supporting the decision-making process in a first-line mCRPC setting. In fact, the authors did not distinguish between those patients treated at the time of castration-resistance occurrence and those who received DOC rechallenge in subsequent treatment lines. Moreover, the number of patients evaluated was very limited, with a relevant number of cases not evaluable for biochemical response. Nevertheless, the authors concluded that at the occurrence of mCRPC, DOC rechallenge had limited activity in a very small number of patients while the new hormone agents maintained their efficacy.

Recently, Francini et al. retrospectively evaluated a cohort of 102 patients treated with first-line AA or E for mCRPC, 52 of which had received DOC in mCSPC setting[26]. No statistically significant difference in any of the evaluated outcomes was observed in patients treated with ADT + DOC and those treated with ADT alone in mCSPC setting. Deaths in the ADT+DOC group were 12 versus 21 in the ADT alone, after a median follow-up of 24.4 and 29.8 months, respectively.

Another study retrospectively evaluated the outcomes of first-line treatments in 136 mCSPC patients who had progressed after DOC plus ADT. In patients treated with new-generation hormonal therapies, the median radiological PFS was 9.0 months compared to 3.0 months observed in those who did not receive new-generation hormonal treatments ($p = 0.024$) [27].

No data are yet available from the literature concerning the outcomes of life-prolonging agents after AA administered in a mCSPC setting.

Drivers for decision-making

a) Biological knowledge

The evolving treatment landscape of metastatic PC is due to an expanded comprehension of the biological drivers that cause disease progression and particularly induce the shift from hormone-sensitive to castration-resistant disease.

At present, two progression models have been considered to describe the biological processes sustaining the occurrence of castration-resistant disease: the adaptation model and the clonal model [28]. In the adaptation model, it is postulated that progression to CRPC is not due to a true androgen-independence but is induced by the adaptation of androgen receptor (AR)-dependent PC cells to a micro-environment characterised by low androgen levels.

Although androgen-deprivation treatment can cause a significant reduction in serum androgen levels, tumour cells could change the AR conformation, so that reduced androgen levels could stimulate it and produce androgens essential for their proliferation.

The processes implicated in these androgen-deprivation therapy-resistance events consist of ligand-dependent AR activation (AR overexpression or mutation, AR gene amplification, intratumoral androgen production) and ligand-independent AR activation (expression of AR splice variants, inactivation of retinoblastoma tumour suppressor protein (RB), upregulation of transcriptional AR co-activators) [28,29].

However, although AR is necessary for neoplastic progression, mechanisms not dependent from AR play a critical role in the treatment of CRPC patients. In this context, preclinical evidence showed that prostatic cancer cell lines (DU145 and PC3 cells) derived from hormone-sensitive metastatic tumours are able to induce the development of castration-resistant xenograft neoplasms in cases of AR signalling pathway absence [30]. Adaptation mechanisms independent from AR mainly include epithelial-mesenchymal transition and apoptosis inhibition [29,31 32]. In particular, B-cell CLLC/lymphoma 2 (BCL-2) is an anti-apoptotic protein able to interfere with the activation of caspases cascade, responsible for apoptosis, through the inhibition of the discharge of cytochrome C by the mitochondria of the cells [33].

In physiological situations, epithelial prostatic cells do not express BCL-2. Preclinical data demonstrated that androgen-deprivation treatment is able to provoke the shift from hormone-sensitive to CRPC also inhibiting cellular apoptosis through the increase of BCL-2 expression in PC cells [34].

AR-dependent and -independent mechanisms of progression can be the result of neoplastic cell adaptation to a low testosterone environment, but they also may be found in metastatic hormone-naïve patients not yet treated with androgen-deprivation therapy [28].

This biological evidence allows us to assume that adaption theory is not the only process behind the progression to castration-resistant prostate carcinoma.

The selection model states that prostate cancer is characterised by cellular clones with different grades of androgen dependence that are present before androgen-deprivation starts and that the development of the castration-resistance state is related to clonal selection and the further growth of pre-existing androgen-independent clones [28].

Preclinical evidence demonstrated that in physiological conditions, the prostate gland is mainly composed of three kinds of epithelial cells: luminal cells, basal intermediate cells, and basal cells [35]. These cells, present at various differentiation stages in prostatic cancer, have different AR expression and consequently different sensibilities to androgen-deprivation [36].

Epithelial luminal cells are characterised by the presence of AR enzymatic machinery and high levels of AR expression, but in basal cells, it is possible to find only small AR concentrations. A preclinical study showed that androgen-deprivation therapy kills most luminal cells; however, this treatment is almost completely ineffective against basal cells [37]. Hormonal therapy reduces luminal cells and favours the expansion of basal cells and basal intermediate cells [38].

This biological evidence shows that prostatic carcinoma is a heterogeneous disease since the hormone-sensitive phase, in which the shift to the castration-resistant phase is due to the coexistence of AR-positive and AR-negative cells and mechanisms of progression both dependent and independent from AR [28].

Because of this strong biological basis, the DOC activity in association with hormone therapy in advanced CSPC does not surprise. In fact, chemotherapy in combination with castration induces the inhibition of the growth of AR-independent cellular clones, provoking the death of cells before the occurrence of multiple resistance mechanisms [22].

In this context, the main activity of taxanes on cellular mitosis is characterised by their capability to provoke the phosphorylation of BCL-2. This process induces the inactivation of BCL-2 favouring the apoptosis of neoplastic cells [39].

In addition, taxanes have a peculiar mechanism of action that allows their synergistic activity with ADT. These drugs are able to interfere not only with AR-independent mechanisms of progression but also with the AR signalling pathway[40].

Taxanes inhibit AR nuclear translocation and gene expression through interference with microtubule polymerisation[41]. Furthermore, taxanes induce an improved expression of a transcriptional repressor of AR, the forkhead box 1 (FOX01), causing the blockage of neoplastic progression [42].

Finally, taxanes are able to interfere with one of the fundamental ligand-independent resistance mechanisms, the lack of function of RB. An estimated 25-50% of PC patients face an inactivation of RB that promotes the progression of neoplastic cells during ADT. Preclinical data showed that taxanes are more active in prostatic cancer cells with RB deficiency[43].

At present, we know that the heterogeneity of PC in terms of both cellular subclones and mechanisms of resistance increases during the shift from the castration-sensitive to the castration-resistant phase of disease, particularly in rapidly progressing disease, leading to an increase in resistance mechanisms bypassing the AR pathway [35].

We believe that these biological factors should guide the decision-making process, especially in mCRPC patients with more aggressive disease, such as those with poor ADT response and short PSA-doubling time at progression. In these patients, taxanes administration could be the best therapeutic option, due to the capability of these drugs to interfere with several steps of resistance mechanisms. In this context, in patients already treated with DOC for mCSPC and rapidly progressing, the treatment of

choice could be cabazitaxel. In fact, although there is no direct randomized evidence supporting this preference, these patients are most likely to be resistant to DOC and new-generation hormonal therapy.

Cabazitaxel has a peculiar mechanism of action with a unique strength. It is potentially able to overcome resistance mechanisms to both DOC and new-generation hormonal therapy. In fact, preclinical evidence showed that cabazitaxel is active in cellular lines resistant to DOC [44] and has superior antitumour activity compared to DOC in enzalutamide-resistant tumours[45].

On the other hand, increasing experimental evidence suggests a possible cross-resistance between AA and enzalutamide. Although prospective randomised trials are needed to prove the predictive value of AR-V7 expression, the occurrence of this AR splice variant seems to influence the activity of AA and enzalutamide, which is significantly reduced, but not that of taxanes [46-49]

b) Disease control by previous treatment line

The timing of progression occurrence is usually considered an indicator of resistance to a specific treatment and may influence the choice of subsequent therapy. Thus, all pivotal trials assessing new second-line drugs have carefully described their efficacy according to first-line PFS.

In the COU-AA-301 trial, the effect of AA was similar between the prognostic groups according to the time of the last dose of DOC to the first dose of AA (≤ 3 months vs > 3 months) : in the patients treated within 3 months from the last dose of DOC, the median OS was 15.0 (95% CI: 13.7-17.4) compared to 16.1 months median OS observed in the patients who started AA > 3 months after the last dose of DOC [50].

In the case of cabazitaxel, this agent maintained its efficacy regardless of the time since the last DOC exposure, showing a survival advantage even in patients with shorter (< 3 months) PFS from previous DOC treatment or in patients progressing on DOC first-line therapy [10].

Regarding the DOC rechallenge, PFS of first-line treatment has been considered a variable that can predict the potential ability of this strategy to prolong disease control. Loriot et al. showed a statistically significant correlation between the treatment-free interval since the last cycle of DOC-based chemotherapy and the efficacy of subsequent rechallenge with DOC, which appeared higher as longer was the interval since the last cycle of DOC [51]. Similar results were observed by Caffo et al. [52]. Their retrospective analysis showed that the time from the previous administration of DOC was predictive of the response to a rechallenge, together with the time slope-log PSA and the response to the previous cycle. Most studies evaluating the DOC rechallenge strategy after first-line DOC reported good disease control in patients with first-line PFS longer than 6 months[52,53].

c) PSA doubling time

A short PSA doubling time is a well-known prognostic factor, associated with more aggressive disease and consequently with poor outcomes in all phases of progressive prostatic cancer.

A retrospective study enrolling 379 patients with biochemical recurrence after radical prostatectomy showed that PSA-DT (< 3.0 vs 3.0-8.9 vs 9.0-14.9 vs ≥ 15.0 months) represented a significant risk factor for prostate-specific mortality [54]. A nomogram concerning chemotherapy-naïve patients with progressive mCRPC highlighted that a short PSA-DT represented a risk factor for poor survival [55].

Although there is consensus on the relationship between PSA-DT and disease aggressiveness, there is no agreement on the cut-off level of PSA-DT able to identify mCRPC patients with different outcomes. In the TAX 327 trial, a PSA-DT < 55 days was related to shorter survival [56]. In a real-life retrospective analysis, Oudard et al. used a PSA-DT cut-off of 45 days. In their report, this PSA-DT value identified two groups of patients with a statistically significant different OS (median 16.5 and 26.4 months for shorter and longer PFS, respectively) [57]. In another retrospective study enrolling 224 mCRPC patients, the optimal cut-off level of PSA-DT for survival stratification was 70 days; patients with a PSA-DT <

70 days had a median OS of 11 months compared to the median OS of 19 months in patients with PSA-DT > 70 days [58].

A trial testing the role of a potent inhibitor of osteoclast activity, denosumab, for the prevention of skeletal disease progression in non-metastatic CRPC patients showed shorter bone metastases-free survival in patients with PSA-DT < 8 months [59].

d) Metastatic involvement

The mCRPC patients are a heterogeneous population according to several factors related to the PC metastases localisation, both before and following treatments, and the patients' characteristics. Several prognostic factors, including the number and location of bone metastases, visceral metastases, the Gleason score, performance status, baseline PSA or its decline ≥ 50% following treatment, and alkaline phosphatase, have been evaluated but not directly compared in the era of new-generation therapies [60,61]. In the case of DOC treatment, visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine were considered independent prognostic factors able to predict the response to therapy by categorisation into three risk groups: low (0 or 1 factor), intermediate (2 factors), and high (3 or 4 factors), showing significantly different OS (with a median of 25.7, 18.7, and 12.8 months, respectively) [62].

Among the aforementioned variables, the presence of visceral metastases (lung or liver metastases) is usually perceived as one the most important signs of aggressive disease and worse prognosis. The rate of visceral metastases among the patients enrolled in the mCRPC second-line pivotal studies ranged from approximately 11% in the case of new hormone agents to 25% in the case of cabazitaxel [6,8,10].

Regarding the special population of patients with visceral metastases, in the COU-AA-301 trial, the experimental treatment reduced the risk of death by 21%, corresponding to an absolute survival benefit

of 4.6 months compared to the placebo arm, which did not achieve statistical significance (HR = 0.79; 95% CI: 0.60-1.05; p = 0.102) [63].

Similarly, in the AFFIRM trial, the subgroup analysis showed a death reduction of 22% in the mCRPC patients with visceral metastases treated with enzalutamide: the median OS was 13.4 months in the experimental arm compared to 9.5 months in the control arm [8].

No analysis specifically addressing the efficacy of cabazitaxel in patients with visceral metastases is available from the TROPIC trial, although the study forest plot suggested that this new-generation taxane produced a clear survival benefit in patients with measurable disease with a 32% death reduction.

e) Symptoms

The occurrence of symptoms in mCRPC patients usually reflects a more advanced disease and/or a more aggressive disease. Nevertheless, the presence/absence of symptoms (for example, pain) influenced the treatment choice, since this variable was considered among the eligibility criteria in the first- and second-line pivotal trials. AA and enzalutamide may be used only in asymptomatic or mildly symptomatic patients when these agents are used in a first-line setting [64,65] while they can be used in all mCRPC patients regardless of the presence of symptoms when they are used in later treatment lines [6,8]. In the case of cabazitaxel, the TROPIC trial enrolled mCRPC patients with or without symptoms [10] while the ALSIMPCA trial with radium-223 required the presence of symptoms to enrol mCRPC patients [11].

In the TROPIC trial, which used the McGill-Melzack scale to rate pain presence, 46% of the patients in the cabazitaxel arm were symptomatic at the baseline; in this group of patients, the reduction of death risk was 23% in favour of those treated with cabazitaxel [10].

In the COU-AA-301 trial, which adopted the Brief Pain Inventory to identify symptomatic patients, the rate of patients with a pain score ≥ 4 at the baseline was 32.2%; in these symptomatic patients, AA administration led to an absolute median OS increase of 3.7 months (12.6 vs 8.9 months), reducing the risk of death by 32% [6].

Similar results were observed in the AFFIRM trial, which used the same scale for pain assessment. In this study, the reduction of death risk in symptomatic patients treated with enzalutamide was 29%, with an absolute increase in terms of median OS of 3.3 months [8].

The ALSYMPCA trial, which adopted the WHO ladder to assess cancer pain, enrolled only symptomatic patients (32% with a score of 3). When the agent was administered after DOC, the reduction in death risk was 30%, with a median OS of 14.4 months and 11.3 months in the experimental and control arm, respectively [66].

f) Cross-resistance among active agents

Radium-223 exerts its anticancer activity via direct cell damage by alpha-particle emission, while, as underlined before, the other life-prolonging agents in mCRPC act on AR. However, in the case of taxanes, their interference in microtubule polymerisation hinders AR nuclear migration [41] and is alternatively able to inhibit cancer cell mitosis, and in the case of new-generation hormonal agents, AR machinery is the only direct or indirect target. Regarding the specific mechanism of action of AA, this agent indirectly inhibits AR activation by blocking the autocrine production of androgens [67], but at the same time, it has been postulated to have a direct effect on AA metabolites in the AR machinery [68]. Finally, enzalutamide blocks three different levels of the AR machinery [69]. On this basis, it could be hypothesised that the risk of cross-resistance could be higher by sequencing the two new-generation hormonal agents than by sequencing one taxane and one new hormonal agent, while the results of the

TROPIC trial show that, at least in a proportion of patients, there is no cross-resistance between the two taxanes [10].

Although no prospective trials support the increased risk of cross-resistance when AA and enzalutamide are sequentially administered, several observations supported this finding. Recently, the investigators of the COU-AA-302 trial described the activity of post-progression therapies in patients treated in the AA experimental arm. The PFS of the patients who were treated with DOC as a first post-progression treatment was 7.6 months [70], while those who received enzalutamide as a first post-progression treatment was 2.8 months [71]. A retrospective report described the outcomes of 546 patients who after first-line treatment with AA or enzalutamide received DOC or the other hormone agent not administered in the first-line setting: the clinical and PSA response rates at both 3 and 6 months clearly favoured DOC [72].

A recently published systematic review and descriptive analysis explored the clinical outcomes of mCRPC patients who were treated with third-line new-generation hormonal agent after having previously received DOC and another new generation hormonal agent [73]. This review, which analysed the survival plots of 13 studies (involving 1016 patients), suggested that in patients who had previously received first-line DOC, the use of CABA and a new hormonal agent in any order seemed to offer a greater OS advantage compared to the sequential administration of both new generation hormonal agents.

More recently, an individual data analysis of more than 1,000 mCRPC patients treated with at least two life-prolonging agents after first-line DOC confirmed that after second-line treatment with a new hormonal agent, cabazitaxel may be more active than another new hormonal agent [74].

Discussion

The metastatic prostate cancer therapeutic landscape has dramatically evolved over the last decade: new clinical scenarios initiated by several trials, concluded in a very few years, made it difficult to translate the previous available evidence into current scenarios. For example, the TAX 327 trial proved the efficacy of DOC in chemo-naïve mCRPC patients in 2004, when none of the enrolled patients had previously received new-generation hormone agents, such AA or enzalutamide. Therefore, we do not have prospective data, based on randomised controlled studies, on DOC activity as a second-line treatment after the failure of AA or enzalutamide administered as a first-line treatment. Similarly, no prospective data can drive the therapeutic choice for mCSPC patients treated with AA or DOC who progress and become castration-resistant.

Very limited observations were derived from reports concerning the post-progression therapies administered to the mCSPC patients enrolled in pivotal trials. The most accurate report on these treatments concerned the GETUG-AFU 15 trial and was recently published [25]. Unfortunately, this report reflected the very limited availability of new-generation agents at the time the trial was conducted, since only 39 out of 111 evaluated patients in the DOC arm (35.1%) received such agents after castration-resistance development: 24 patients (21.6%) were treated with a DOC rechallenge, 10 (9%) with one new-generation hormone agent, four (3.6%) with radium-223, and only one with cabazitaxel. It is clear that the retrospective nature of this report and the low number of patients evaluated did not allow definitive conclusions, reflecting not just a specific sequential strategy but more simply the availability of new agents in daily clinical practise, and did not help in driving the decision-making of clinicians when one patient treated with DOC in a mCSPC setting progressed and became castration-resistant.

Nevertheless, in this context, the choice of therapy for the growing number of patients treated with DOC and ADT for mCSPC and progressing to mCRPC is something to urgently address in daily

clinical practise. There are no parameters to guide clinical decision-making in this setting and no evidence to support decision-making in cases of high-risk mCSPC patients who will receive AA before progressing to mCRPC. However, some considerations may help clinicians in these two situations after one treatment for mCSPC: the current situation of treating patients after DOC, and the future situation of treating patients after AA.

From a conceptual point of view, it is unclear whether mCSPC patients progressing after DOC should be considered similar to chemotherapy-naïve patients who should receive first-line mCRPC or similar to DOC pretreated mCRPC patients, who should receive second-line treatment. From a practical point of view, the lack of evidence from prospective controlled studies means that the choice of treatment can be driven only by personal feelings regarding drug activity based on pivotal trial data and everyday clinical experience.

In our opinion, some suggestions based on experimental and clinical data on mCRPC patients could help and drive our choices.

Suggestions for patients progressing after docetaxel administered in mCSPC

The first decision driver could be the duration of disease control in mCSPC patients treated with DOC plus ADT: median PFS in the CHAARTED trial was 20.2 months in the DOC + ADT arm and 11.7 months in the ADT arm. Accordingly, as patients whose PFS is > 20 months could conceivably have experienced the greatest benefit from DOC, they should be considered highly sensitive to the drug and, on the basis of cumulative experience with first-line DOC treatment for mCRPC, could be reasonably managed with a DOC rechallenge.

In patients whose PFS is equal to or lower than the median observed in the CHAARTED control arm, especially those experiencing a PFS largely shorter than 20 months, the addition of DOC to ADT can be considered as bringing no relevant advantage, and DOC resistance can be hypothesised.

As previously highlighted from a biological point of view, it can be thought that, in patients developing rapidly progressing mCRPC, the heterogeneity of cellular clones worsens, thus leading to an increase in resistance mechanisms by bypassing the androgen receptor pathway [35]. From a clinical point of view, some published data suggest that AA and enzalutamide are less efficacious in patients whose disease is controlled by ADT for a shorter time. A post hoc analysis from COU-AA-301 showed lower AA activity after DOC in patients with ADT exposure at the lowest quartile [75]. Similarly, data from real life suggested less efficacy of enzalutamide in patients achieving a shorter disease control with ADT [76]. Because of these biological and clinical data, we believe that cabazitaxel could be considered the best therapeutic option for mCSPC patients relapsing within 12 months of DOC treatment, even if this consideration is not supported by a randomized clinical trial. Taxanes are capable of killing androgen receptor-negative tumoral cells but can also interfere with the androgen receptor signalling pathway[77]. Moreover, it is worth noting that, in the TROPIC trial, the survival advantage of cabazitaxel was also observed in patients whose disease progressed during DOC treatment and those with short PFS[10]. However, cabazitaxel as first line therapy in mCRPC patients failed to demonstrate an improvement in OS compared to docetaxel in the FIRSTANA trial.

When PFS is between 12 and 20 months, PSA-DT may be a further guide for decision-making. PSA-DT is related to the prognosis of mCRPC patients, as a shorter PSA-DT indicates shorter survival[55]. Although there is no established PSA-DT cut-off value to distinguish patients with different survival outcomes, a short PSA-DT is seen as a sign of aggressive disease and, consequently, it is widely accepted in the oncological community that chemotherapy should be the treatment of choice. Accordingly, we believe that patients with a PSA-DT $\leq$ 90 days should receive cabazitaxel and, in all other cases (for example, patients whose PFS is 12-20 months and PSA-DT > 90 days), the choice could consider all of the available agents (cabazitaxel, AA, enzalutamide, and radium-223), with prescribing limitations for radium-223 as it can be administered only to patients with symptomatic bone

metastases without visceral or large nodal involvement. Of note, the Pharamacovigilance Risk Assessment Committee (PRAC) has recently recommended restricting the use of Radium-223 to patients who have had two previous treatments for mCRPC or who cannot receive other treatments [78].

In clinical decision-making the choice of therapeutic options has to take into account patient characteristics. Although mCSPC patients treated with chemotherapy + ADT are all highly selected and capable of receiving six courses of DOC, the therapeutic choice may be influenced by comorbidities such as significant cardiovascular disease, diabetes, or a history of seizures. In addition, certain concomitant medications may interfere with the activity of new-generation hormonal agents.

Finally, patient preferences also have to be considered as these may be influenced by the different toxicity profiles of the available agents, as well as by the burden of the side effects of previous DOC administration.

Suggestions for patients progressing after abiraterone administered in mCSPC

In patients who will be treated with AA for high-risk mCSPC and progress to mCRPC, we believe the growing evidence of the potential cross-resistance of AA and enzalutamide [47,79,80] should reasonably limit the choice between DOC and radium-223. According to recent PRAC restrictions [78], Radium 223 should be considered only for symptomatic patients not eligible for docetaxel treatment, in the absence of large nodes and/or visceral metastases.

Conclusions

It is clear that the proposed algorithms do not reflect robust evidence from prospective trials or suggestions from real-life series. In developing our decision-making algorithm, we considered only some suggestions usually involved when choosing second-line mCRPC treatment. For example, we did not consider the Gleason score, which is usually viewed as a marker of aggressiveness, because we

believe that patients with mCSPC at the time of diagnosis have aggressive disease regardless of their Gleason score.

One final issue may further limit our proposal and the applicability of second-line mCRPC rules to mCSPC patients progressing after DOC or AA. We do not know whether the adaptive response of cancer cells to the drugs used to treat mCSPC is the same as that observed during the castration-resistant phase of the disease or whether their response to subsequent agents is the same as that expected in mCRPC. However, despite the lack of evidence from prospective studies, we must propose a treatment for mCSPC patients progressing after DOC or AA, and our proposal may help in such everyday decision-making.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. CA Cancer J Clin 66:7-30, 2016
2. Hellerstedt BA, Pienta KJ: The current state of hormonal therapy for prostate cancer. CA Cancer J Clin 52:154-79, 2002
3. McCrea E, Sissung TM, Price DK, et al: Androgen receptor variation affects prostate cancer progression and drug resistance. Pharmacol Res 114:152-162, 2016
4. Autio KA, Morris MJ: Targeting bone physiology for the treatment of metastatic prostate cancer. Clin Adv Hematol Oncol 11:134-43, 2013
5. Kantoff PW, Higano CS, Shore ND, et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N. Engl. J Med 363:411-422, 2010
6. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N. Engl. J Med 364:1995-2005, 2011
7. Ryan C, Smith MR, Fizazi K, et al: Final Overall Survival Analysis of COU-AA-302, a Randomized Phase 3 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Without Prior Chemotherapy. Ann Oncol 25, 2014
8. Scher HI, Fizazi K, Saad F, et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J Med 367:1187-1197, 2012
9. Beer TM, Armstrong AJ, Rathkopf DE, et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N. Engl. J Med 371:424-433, 2014
10. de Bono JS, Oudard S, Ozguroglu M, et al: 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
11. Parker C, Nilsson S, Heinrich D, et al: Alpha emitter radium-223 and survival in metastatic prostate cancer. N. Engl. J Med 369:213-223, 2013
12. Sweeney CJ, Chen YH, Carducci M, et al: Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N. Engl. J Med 373:737-746, 2015
13. James ND, Sydes MR, Clarke NW, et al: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet, 2015
14. Fizazi K, Tran N, Fein L, et al: Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N. Engl. J Med 377:352-360, 2017
15. James ND, de Bono JS, Spears MR, et al: Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N. Engl. J Med 377:338-351, 2017
16. Gravis G, Fizazi K, Joly F, et al: Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 14:149-158, 2013
17. Gravis G, Boher JM, Joly F, et al: Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol 70:256-62, 2016
18. Kyriakopoulos CE, Chen YH, Carducci MA, et al: Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol 36:1080-1087, 2018
19. Gravis G, Boher JM, Chen YH, et al: Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies. Eur Urol 73:847-855, 2018
20. Sydes MR, Parmar MK, James ND, et al: Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial. Trials 10:39, 2009

21. Vale CL, Burdett S, Rydzewska LH, et al: Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol, 2015

22. Tucci M, Bertaglia V, Vignani F, et al: Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone-sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 69:563-573, 2016

23. Vale CL, Fisher DJ, White IR, et al: What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis. Ann Oncol 29:1249-1257, 2018

24. Sydes MR, Spears MR, Mason MD, et al: Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol 29:1235-1248, 2018

25. Lavaud P, Gravis G, Foulon S, et al: Anticancer Activity and Tolerance of Treatments Received Beyond Progression in Men Treated Upfront with Androgen Deprivation Therapy With or Without Docetaxel for Metastatic Castration-naive Prostate Cancer in the GETUG-AFU 15 Phase 3 Trial. Eur Urol 73:696-703, 2018

26. Francini E, Yip S, Ahmed S, et al: Clinical Outcomes of First-line Abiraterone Acetate or Enzalutamide for Metastatic Castration-resistant Prostate Cancer After Androgen Deprivation Therapy + Docetaxel or ADT Alone for Metastatic Hormone-sensitive Prostate Cancer. Clin Genitourin Cancer 16:130-134, 2018

27. Barata P, Emamekhoo H, Mendiratta P, et al: Treatment selection for men with metastatic prostate cancer who progress on upfront chemo-hormonal therapy. Prostate, 2018

28. Zong Y, Goldstein AS: Adaptation or selection--mechanisms of castration-resistant prostate cancer. Nat. Rev Urol 10:90-98, 2013

29. Ahmed M, Li LC: Adaptation and clonal selection models of castration-resistant prostate cancer: current perspective. Int. J Urol 20:362-371, 2013

30. van Bokhoven A, Varella-Garcia M, Korch C, et al: Molecular characterization of human prostate carcinoma cell lines. Prostate 57:205-25, 2003

31. Li P, Yang R, Gao WQ: Contributions of epithelial-mesenchymal transition and cancer stem cells to the development of castration resistance of prostate cancer. Mol Cancer 13:55, 2014

32. McDonnell TJ, Troncoso P, Brisbay SM, et al: Expression of the protooncogene bcl-2 in the prostate and its association with emergence of androgen-independent prostate cancer. Cancer Res 52:6940-4, 1992

33. Reed JC: Bcl-2 and the regulation of programmed cell death. J Cell Biol 124:1-6, 1994

34. Fesik SW: Promoting apoptosis as a strategy for cancer drug discovery. Nat Rev Cancer 5:876-85, 2005

35. Wen S, Niu Y, Lee SO, et al: Androgen receptor (AR) positive vs negative roles in prostate cancer cell deaths including apoptosis, anoikis, entosis, necrosis and autophagic cell death. Cancer Treat. Rev 40:31-40, 2014

36. van Leenders GJ, Schalken JA: Epithelial cell differentiation in the human prostate epithelium: implications for the pathogenesis and therapy of prostate cancer. Crit Rev Oncol Hematol 46 Suppl:S3-10, 2003

37. Bonkhoff H, Stein U, Remberger K: The proliferative function of basal cells in the normal and hyperplastic human prostate. Prostate 24:114-8, 1994

38. Niu Y, Chang TM, Yeh S, et al: Differential androgen receptor signals in different cells explain why androgen-deprivation therapy of prostate cancer fails. Oncogene 29:3593-604, 2010

39. Pienta KJ: Preclinical mechanisms of action of docetaxel and docetaxel combinations in prostate cancer. Semin Oncol 28:3-7, 2001

40. Bai S, Zhang BY, Dong Y: Impact of taxanes on androgen receptor signaling. Asian J Androl, 2018

41. Darshan MS, Loftus MS, Thadani-Mulero M, et al: Taxane-induced blockade to nuclear accumulation of the androgen receptor predicts clinical responses in metastatic prostate cancer. Cancer Res 71:6019-6029, 2011

42. Gan L, Chen S, Wang Y, et al: Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. Cancer Res 69:8386-94, 2009

43. Sharma A, Comstock CE, Knudsen ES, et al: Retinoblastoma tumor suppressor status is a critical determinant of therapeutic response in prostate cancer cells. Cancer Res 67:6192-203, 2007

44. Vrignaud P, Semiond D, Lejeune P, et al: Preclinical antitumor activity of cabazitaxel, a semisynthetic taxane active in taxane-resistant tumors. Clin Cancer Res 19:2973-83, 2013

45. van Soest RJ, de Morree ES, Kweldam CF, et al: Targeting the Androgen Receptor Confers In Vivo Cross-resistance Between Enzalutamide and Docetaxel, But Not Cabazitaxel, in Castration-resistant Prostate Cancer. Eur Urol 67:981-985, 2015

46. Antonarakis ES, Lu C, Luber B, et al: Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer. JAMA Oncol 1:582-591, 2015

47. Antonarakis ES, Lu C, Wang H, et al: AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N. Engl. J Med 371:1028-1038, 2014

48. Scher HI, Lu D, Schreiber NA, et al: Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer. JAMA Oncol 2:1441-1449, 2016

49. Del Re M, Biasco E, Crucitta S, et al: The Detection of Androgen Receptor Splice Variant 7 in Plasma-derived Exosomal RNA Strongly Predicts Resistance to Hormonal Therapy in Metastatic Prostate Cancer Patients. Eur Urol 71:680-687, 2017

50. Fizazi K, Scher HI, Molina A, et al: Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 13:983-992, 2012

51. Loriot Y, Massard C, Gross-Goupil M, et al: The interval from the last cycle of docetaxel-based chemotherapy to progression is associated with the efficacy of subsequent docetaxel in patients with prostate cancer. Eur. J. Cancer 46:1770-1772, 2010

52. Caffo O, Pappagallo G, Brugnara S, et al: Multiple rechallenges for castration-resistant prostate cancer patients responding to first-line docetaxel: assessment of clinical outcomes and predictive factors. Urology 79:644-649, 2012

53. Oudard S, Kramer G, Caffo O, et al: Docetaxel rechallenge after an initial good response in patients with metastatic castration-resistant prostate cancer. BJU Int 115:744-52, 2015

54. Freedland SJ, Humphreys EB, Mangold LA, et al: Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294:433-9, 2005

55. Svatek R, Karakiewicz PI, Shulman M, et al: Pre-treatment nomogram for disease-specific survival of patients with chemotherapy-naive androgen independent prostate cancer. Eur Urol 49:666-674, 2006

56. Armstrong AJ, Garrett-Mayer ES, Yang YC, et al: A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin. Cancer Res 13:6396-6403, 2007

57. Oudard S, Banu E, Scotte F, et al: Prostate-specific antigen doubling time before onset of chemotherapy as a predictor of survival for hormone-refractory prostate cancer patients. Ann Oncol 18:1828-1833, 2007

58. Semeniuk RC, Venner PM, North S: Prostate-specific antigen doubling time is associated with survival in men with hormone-refractory prostate cancer. Urology 68:565-9, 2006

59. Smith MR, Saad F, Oudard S, et al: Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 31:3800-6, 2013

60. Glass TR, Tangen CM, Crawford ED, et al: Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol 169:164-9, 2003

61. Gravis G, Boher JM, Fizazi K, et al: Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: Validation of the Glass Model and Development of a Novel Simplified Prognostic Model. Eur Urol 68:196-204, 2015

62. Armstrong AJ, Garrett-Mayer E, de Wit R, et al: Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. Clin Cancer Res 16:203-11, 2010

63. Goodman OB, Jr., Flaig TW, Molina A, et al: Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic. Dis 17:34-39, 2014

64. Ryan CJ, Smith MR, Fizazi K, et al: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16:152-160, 2015

65. Beer TM, Armstrong AJ, Rathkopf D, et al: Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. Eur Urol 71:151-154, 2017

66. Hoskin P, Sartor O, O'Sullivan JM, et al: Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol 15:1397-1406, 2014

67. Jarman M, Barrie SE, Llera JM: The 16,17-double bond is needed for irreversible inhibition of human cytochrome p45017alpha by abiraterone (17-(3-pyridyl)androsta-5, 16-dien-3beta-ol) and related steroidal inhibitors. J Med Chem 41:5375-5381, 1998

68. Li Z, Bishop AC, Alyamani M, et al: Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature 523:347-351, 2015

69. Tran C, Ouk S, Clegg NJ, et al: Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 324:787-790, 2009

70. de Bono JS, Smith MR, Saad F, et al: Subsequent Chemotherapy and Treatment Patterns After Abiraterone Acetate in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. Eur Urol 71:656-664, 2017

71. Smith MR, Saad F, Rathkopf DE, et al: Clinical Outcomes from Androgen Signaling-directed Therapy after Treatment with Abiraterone Acetate and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. Eur Urol 72:10-13, 2017

72. Oh WK, Miao R, Vekeman F, et al: Real-world Characteristics and Outcomes of Patients With Metastatic Castration-resistant Prostate Cancer Receiving Chemotherapy Versus Androgen Receptor-targeted Therapy After Failure of First-line Androgen Receptor-targeted Therapy in the Community Setting. Clin Genitourin Cancer, 2017

73. Maines F, Caffo O, Veccia A, et al: Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer. Crit Rev Oncol Hematol 96:498-506, 2015

74. Caffo O, Wissing M, Bianchini D, et al: Survival outcomes from a cumulative analysis from worldwide observational studies on sequential use of new agents (NAs) in metastatic Castration-Resistant Prostate Cancer (mCRPC) (CASTOR study). ASCO, 2018, pp 5026

75. Bellmunt J, Kheoh T, Yu MK, et al: Prior Endocrine Therapy Impact on Abiraterone Acetate Clinical Efficacy in Metastatic Castration-resistant Prostate Cancer: Post-hoc Analysis of Randomised Phase 3 Studies. Eur Urol 69:924-932, 2016

76. Loriot Y, Eymard JC, Patrikidou A, et al: Prior long response to androgen deprivation predicts response to next-generation androgen receptor axis targeted drugs in castration resistant prostate cancer. Eur J Cancer 51:1946-1952, 2015

77. Thadani-Mulero M, Nanus DM, Giannakakou P: Androgen receptor on the move: boarding the microtubule expressway to the nucleus. Cancer Res 72:4611-4615, 2012

78. Agency. EM: EMA restricts use of prostate cancer medicine Xofigo. www.ema.europa.eu/medicines/human/referrals/xofigo

79. Maines F, Caffo O, Veccia A, et al: Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer. Crit Rev Oncol Hematol, 2015

80. Attard G, Borre M, Gurney H, et al: A phase IV, randomized, double-blind, placebo (PBO)-controlled study of continued enzalutamide (ENZA) post prostate-specific antigen (PSA) progression in men with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 35:5004, 2017