Sequential use of novel therapeutics in advanced prostate cancer following docetaxel chemotherapy

Aurelius Omlin, Carmel Pezaro and Silke Gillessen Sommer

Abstract: In the last three years, five novel treatments have been shown to improve survival in metastatic castration-resistant prostate cancer (CRPC). These novel treatments have distinct mechanisms of action: tubulin-binding chemotherapy (cabazitaxel); immunotherapy (sipuleucel-T); CYP-17 inhibition (abiraterone); androgen receptor (AR) blockade (enzalutamide); and radioisotope therapy (radium-223). For a number of years, docetaxel was the only treatment with a proven survival benefit for patients with CRPC. Therefore, somewhat artificially, three treatment spaces for drug development in CRPC have emerged: pre-docetaxel; docetaxel combinations; and post-docetaxel. For patients progressing after docetaxel-based chemotherapy, treatment options available outside of clinical trials now include abiraterone, cabazitaxel and enzalutamide. Prospective data on how to best use these novel agents sequentially are not available. Clinicians face the difficult task of choosing between treatment options for individual patients to maximize patient benefit. Treatment evaluation in patients with CRPC remains challenging due to the predominance of bone metastatic disease and the lack of validated surrogate markers for survival. This review summarizes the data available with regards to sequencing of the novel treatments for CRPC.

Keywords: abiraterone acetate, androgen receptor signaling, cabazitaxel, castration-resistant prostate cancer (CRPC), docetaxel, enzalutamide, radium223, sequential treatment strategies

Introduction

In Western society, prostate cancer is a leading cause of mortality and morbidity [Jemal et al. 2010; La Vecchia et al. 2010]. Although advanced prostate cancer is generally sensitive to initial androgen deprivation therapy (ADT), responses are in most cases not durable and disease progression is inevitable. When prostate cancer progresses despite castrate levels of testosterone, termed castration-resistant prostate cancer (CRPC), markers of disease activity can include a rising prostate-specific antigen (PSA), radiographic progression or development of new metastatic lesions.

In the past decade the growing insight into the biology of advanced prostate cancer has led to unprecedented drug development. Six drugs with different mechanisms of action have been shown to prolong overall survival (OS) in CRPC patients, namely the tubulin targeting chemotherapies docetaxel and cabazitaxel, the immunotherapy sipuleucel-T, the androgen biosynthesis inhibitor abiraterone, the second generation androgen receptor (AR) antagonist enzalutamide and the alpha-emitting radiopharmaceutical radium-223 [Kantoff et al. 2010; Ryan et al. 2013b; de Bono et al. 2011; Scher et al. 2012; Parker et al. 2012, 2013; Tannock et al. 2004] (see Table 1). Patients with CRPC live longer and maintain better quality of life [Rathkopf et al. 2013; Omlin et al. 2013; Nilsson et al. 2013; Logothetis et al. 2012; Sternberg et al. 2013]. The available preclinical and clinical data regarding treatment sequencing in CRPC are discussed in the following sections.

Challenge of treatment sequencing in CRPC

In the post-docetaxel setting cabazitaxel, sipuleucel-T, abiraterone, radium-223 and enzalutamide...
have now been approved. Prospective data addressing optimal treatment sequencing are not available and head-to-head comparisons of novel therapeutics, such as for example abiraterone versus enzalutamide, have not been performed. Therefore, in clinical practice, doctors constantly face uncertainty. Furthermore, the ‘typical’ patient rarely exists and evidence obtained from large patient trials must invariably be adapted to suit the circumstances of the individual seeking treatment. Despite this ability to manage uncertainty, oncologists struggle to accept it. Trainees are taught to seek high-quality data, to use evidence to support all decisions and to abhor anecdote-based practice. Unfortunately, required evidence for important therapeutic decision-making is not always available. That is certainly the case with treatment sequencing in CRPC due to the rapid development of multiple new drugs and the lack of sequencing trials in this disease. Although the development of survival-prolonging treatments has been welcomed, it is not yet known how much incremental benefit will be obtained by the serial use of novel treatments. The successful development of several new drugs for metastatic renal cell carcinoma has already shown the difficulties of making treatment decisions based on patient and physician decisions [Sonpavde et al. 2012].

Preclinical data suggest that use of additional treatments may allow expansion of prostate cancer clones with mutations conferring resistance to subsequent therapies [Baca et al. 2013]. The selection of post-docetaxel treatments has also been limited by funding in some areas, so that clinicians and patients have been faced with a difficult ‘either-or’ choice, not currently supported by predictive biomarkers for response or resistance. Commonly expressed quandaries include the selection of the ‘optimal’ treatment sequence, the lack of clinical predictors of poor response to one or more therapies, and the appropriate duration of each therapy for best patient outcome. Unfortunately, these concerns remain difficult to fully address at present.

Despite these challenges, preliminary data are emerging regarding the safety and activity for sequentially administered therapies in men with CRPC. Although these data are generally retrospective analyses that do not yet reach the best standard of randomized trial data, they remain useful and hypothesis-generating until such time that better evidence becomes available. A number of phase III trials are ongoing (see Table 2) and will hopefully provide more robust evidence and answers.

**Current role of docetaxel**

It was only in 2004 that two large randomized phase III trials reported an OS benefit for CRPC patients treated with docetaxel-based chemotherapy. In the TAX-327 trial a total of 1006 men with CRPC were randomized 1:1:1 to prednisone combined with 3-weekly docetaxel 75 mg/m², or weekly docetaxel 30 mg/m² for 5 of 6 weeks, or mitoxantrone. It was found that 3-weekly docetaxel proved superior to the

<table>
<thead>
<tr>
<th>Rising PSA, no evidence of metastatic disease (M0)</th>
<th>CRPC first line (in patients without evidence of visceral disease)</th>
<th>CRPC second line (after docetaxel)</th>
<th>Third line or more (if treatment not used previously)</th>
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<tr>
<td>Consider clinical trial participation</td>
<td>Docetaxel</td>
<td>Cabazitaxel</td>
<td>Consider clinical trial participation.</td>
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<tr>
<td></td>
<td>Abiraterone [Level 1 evidence for asymptomatic or minimally symptomatic pts]</td>
<td>Abiraterone</td>
<td>None of the available treatments have been formally tested in third-line setting.</td>
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<tr>
<td></td>
<td>Radium-223 [in patients not ‘fit’ for docetaxel and symptomatic]</td>
<td>Enzalutamide</td>
<td>Options:</td>
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<td></td>
<td>Sipuleucel-T [asymptomatic or minimally symptomatic points]</td>
<td>Radium-223</td>
<td>Cabazitaxel</td>
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<td></td>
<td>Consider clinical trial participation</td>
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<td>Abiraterone</td>
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<td>Radium-223</td>
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<td>CRPC, castration resistant prostate cancer; PSA, prostate-specific antigen.</td>
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Table 2. Ongoing phase III clinical trials in CRPC (including STAMPEDE trial for hormone naïve patients).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Place in treatment sequence</th>
<th>Patient population</th>
<th>Primary endpoint</th>
<th>Number of patients</th>
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<tr>
<td>Abiraterone plus prednisone plus enzalutamide versus abiraterone alone</td>
<td>Pre-docetaxel</td>
<td>Metastatic CRPC, chemotherapy naïve</td>
<td>OS</td>
<td>1428</td>
<td></td>
<td>Alliance A031201 trial (ClinicalTrials.gov identifier)</td>
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<td>Orteronel plus prednisone versus placebo plus prednisone</td>
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<td>Metastatic CRPC, docetaxel-naïve</td>
<td>OS and rPFS</td>
<td>1454</td>
<td>NCT01193244</td>
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<tr>
<td>Enzalutamide versus placebo</td>
<td>Pre-docetaxel</td>
<td>Metastatic CRPC, docetaxel-naïve</td>
<td>OS and PFS</td>
<td>1680</td>
<td>NCT01212991</td>
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<tr>
<td>Ipilimumab versus placebo</td>
<td>Pre-docetaxel</td>
<td>Metastatic CRPC, docetaxel-naïve</td>
<td>OS</td>
<td>600</td>
<td>NCT01057810</td>
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<tr>
<td>PROSTVAC-V/F ± GM-CSF versus placebo</td>
<td>Pre-docetaxel</td>
<td>Metastatic CRPC, docetaxel-naïve</td>
<td>OS</td>
<td>1200</td>
<td>PROSPECT NCT01322490</td>
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<td>Arm A: ADT</td>
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<td>Arm B: ADT plus zolendronic acid</td>
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<td>Arm C: ADT plus docetaxel plus prednisone</td>
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<td>Arm D: ADT plus celecoxib</td>
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<tr>
<td>Arm E: ADT plus zolendronic acid plus docetaxel plus prednisone</td>
<td>Pre-docetaxel and docetaxel first line</td>
<td>High-risk newly diagnosed, non metastatic node negative prostate cancer OR newly diagnosed metastatic, node positive prostate cancer (hormone naïve)</td>
<td>OS</td>
<td>5000</td>
<td>STAMPEDE NCT00268476</td>
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<td>Arm F: ADT plus zolendronic acid plus celecoxib</td>
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<td>Arm G: ADT plus abiraterone plus prednisone</td>
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<td>Arm H: ADT plus radiotherapy</td>
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<td>Cabazitaxel 25 mg/m² versus 20 mg/m² versus docetaxel</td>
<td>First-line treatment</td>
<td>Metastatic CRPC requiring chemotherapy</td>
<td>OS</td>
<td>1170</td>
<td>FIRSTANA NCT01308567</td>
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<td>Orteronel versus placebo</td>
<td>Post-docetaxel, maintenance</td>
<td>Nonprogressive disease after docetaxel first-line treatment with a cumulative dose ≥300 mg/m²</td>
<td>EFS</td>
<td>192</td>
<td>NCT01707966</td>
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<tr>
<td>Cabazitaxel 25 mg/m² versus 20 mg/m²</td>
<td>Second-line, post-docetaxel</td>
<td>CRPC, second-line chemotherapy, prior abiraterone allowed</td>
<td>OS</td>
<td>1200</td>
<td>PROSELICA NCT01308580</td>
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Table 2. (Continued)

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<thead>
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</thead>
<tbody>
<tr>
<td>Cabazitaxel plus OGX-011 (custirsen) versus cabazitaxel alone</td>
<td>Second-line, post-docetaxel</td>
<td>metastatic CRPC, second-line chemotherapy, prior abiraterone or enzalutamide allowed</td>
<td>OS</td>
<td>630</td>
<td>AFFINITY</td>
<td>NCT01578655</td>
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<tr>
<td>Orteronel plus prednisone versus placebo plus prednisone</td>
<td>Second-line, post-docetaxel</td>
<td>CRPC progressing after docetaxel, prior abiraterone exposure is excluded</td>
<td>OS(^a)</td>
<td>1083</td>
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<td>NCT01193257</td>
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<tr>
<td>Ipilimumab versus placebo following radiotherapy</td>
<td>Second-line, post-docetaxel</td>
<td>CRPC progressing after docetaxel</td>
<td>OS(^b)</td>
<td>800</td>
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<td>NCT00861614</td>
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<tr>
<td>Cabozantinib versus mitoxantrone plus prednisone</td>
<td>Third-line, post-docetaxel and abiraterone or enzalutamide</td>
<td>Metastatic CRPC progressing after docetaxel and abiraterone or enzalutamide</td>
<td>Confirmed pain response at week 12</td>
<td>246</td>
<td>COMET-2</td>
<td>NCT01522443</td>
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<tr>
<td>Cabozantinib versus prednisone</td>
<td>Third-line, post-docetaxel and abiraterone or enzalutamide</td>
<td>Metastatic CRPC progressing after docetaxel (cumulative dose of minimum 225 mg/m(^2)) and abiraterone or enzalutamide</td>
<td>OS</td>
<td>960</td>
<td>COMET-1</td>
<td>NCT01605227</td>
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ADT, androgen deprivation therapy; CRPC, castration resistant prostate cancer; EFS, event free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; OS, overall survival; PFS, progression free survival; rPFS, radiographic progression free survival.

\(^a\)Trial unblinded based on Independent Data Monitoring Committee (IDMC) recommendations. Primary endpoint of improved overall survival not met. www.takeda.com July 26, 2013.

\(^b\)Trial reported at the ECC conference in Amsterdam September 2013 no overall survival benefit.

mitoxantrone arm, resulting in a median OS of 18.9 months compared with 16.5 months [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.62–0.94] [Tannock et al. 2004]. Maximum PSA declines of ≥50% occurred in 45% (3-weekly docetaxel) and 48% (weekly docetaxel), but only in 32% of patients in the mitoxantrone arm. The updated survival results confirmed a 2.9-month survival benefit with 3-weekly docetaxel (HR 0.79, 95% CI 0.67–0.93) [Berthold et al. 2008].

The second phase III trial randomized 770 men in a 1:1 ratio to estramustine, an alkylating agent derived from estradiol, with docetaxel 60 mg/m\(^2\), or to mitoxantrone plus prednisone. Similarly to TAX-327 the docetaxel arm compared favourably with a median OS of 17.5 months compared with 15.6 months with mitoxantrone (HR 0.8, 95% CI 0.67–0.97) [Petrylak et al. 2004]. However, the combination of the docetaxel and estramustine was not adopted as standard therapy due to the appearance of lower activity in this indirect comparison relative to docetaxel 75 mg/m\(^2\) in TAX-327 and the increased gastrointestinal toxicity, neutropenic sepsis and death on study.

**Docetaxel combination trials**

These two docetaxel trials set the regimen of docetaxel and prednisone as standard treatment for CRPC. Subsequent clinical trials have shown that combining docetaxel with other agents is generally associated with increased toxicity and equal or even inferior survival when compared with the standard regimen. A total of nine large phase III
docetaxel-based combination trials have been reported since 2004 and in all studies the primary endpoint was not met [Antonarakis and Eisenberger, 2013]. In the ASCENT trial (docetaxel plus calcitriol), the GVAX trial (docetaxel plus GVAX immunotherapy) and the MAINSAIL trial (docetaxel plus lenalidomide), median OS was significantly shorter in the combination arm [Scher et al. 2011; Small et al. 2009; Petrylak et al. 2012]. In the other six phase III trials the median OS was not significantly different when comparing the docetaxel combination treatment with the control arm [Kelly et al. 2012; Quinn et al. 2012; Fizazi et al. 2013; Araujo et al. 2013; Tannock et al. 2013; James et al. 2013].

A further combination trial (SYNERGY: docetaxel plus OGX-011 [ClinicalTrials.gov identifier: NCT01188187]) and a head-to-head comparison trial (FIRSTANA: docetaxel versus cabazitaxel 25 mg/m² or 20 mg/m² [ClinicalTrials.gov identifier: NCT01308567]) have completed accrual. The results of these trials will be informative to define the role of docetaxel as first-line chemotherapy for CRPC, but at present the standard regimen remains docetaxel 75 mg/m² administered 3-weekly.

Sequential use of docetaxel
With regards to the sequential use of docetaxel, preliminary data from a small cohort study of 35 patients suggested that prior abiraterone exposure might impact docetaxel activity. In this cohort, docetaxel treatment resulted in ≥50% PSA declines in only 26% (95% CI 13–43%) of patients with a median OS of 12.5 months (95% CI 10.6–19.4). Of the eight patients who did not respond to abiraterone (defined as maximum PSA decline on abiraterone of <50%), none responded to docetaxel chemotherapy [Mezynski et al. 2012]. A smaller case series of 14 patients who received docetaxel after prior abiraterone and ketoconazole reported maximum PSA declines of ≥50% in six patients (43%) and a median time to progression (TTP) on docetaxel of 4.2 months (range 2.0–9.7 months) [Aggarwal et al. 2012].

The observed docetaxel activity in both retrospective studies was lessened compared with the TAX-327 trial data, which might be explained by some degree of cross-resistance between abiraterone and docetaxel. This hypothesis is supported by preclinical data indicating that taxanes can impact AR nuclear translocation and AR-related transcriptional activity [Darshan et al. 2011]. Due to the very small cohort sizes these data need to be interpreted with caution. Prospectively collected data from larger cohorts will clarify the activity of docetaxel in abiraterone resistant and refractory patients.

Abiraterone

First- versus second-line abiraterone
The activity of abiraterone when used before or after docetaxel chemotherapy (so-called ‘first’ or ‘second’ line as a proven therapy for CRPC) has never been directly compared. Instead, it is necessary to extrapolate data from the post-docetaxel COU-301 and pre-docetaxel COU-302 abiraterone studies [Ryan et al. 2013b; de Bono et al. 2011]. Although participants in the studies were similarly aged, the COU-302 population was less symptomatic, with a lower burden of disease. Patients with visceral metastases were specifically excluded from COU-302. Importantly, the trials employed similar treatment and monitoring schedules. As expected, comparison of OS, which was the primary endpoint in the COU-301 and the coprimary endpoint of the COU-302 trials, shows marked differences in survival. Median OS in the postchemotherapy setting was 15.8 months on abiraterone versus 11.2m on placebo (HR 0.74, 95% CI 0.64–0.86) [Fizazi et al. 2012]. In the earlier prechemotherapy setting, OS was 35.3 months on abiraterone versus 30.1 months on placebo (HR 0.75, 95% CI 0.61–0.94) [Ryan et al. 2013]. Considering the secondary activity endpoints in COU-301, the time to PSA progression was 10.2 months, radiographic progression-free survival (PFS) was 5.6 months and 38% of participants achieved ≥50% maximum decline of PSA. In the earlier setting of COU-302, abiraterone treatment resulted in a time to PSA progression of 11.1 months, radiographic PFS was 16.5 months and 62% patients had ≥50% PSA decline. These data echo the phase II trials of abiraterone, which suggested higher rates of PSA decline and soft tissue responses when administered to chemotherapy-naïve patients [Loriot et al. 2013].

Third-line abiraterone
The activity of abiraterone after docetaxel and enzalutamide has been reported in two cohort studies. In a series of 38 patients from two centres in Europe, third-line abiraterone resulted in confirmed ≥50% and ≥30% PSA declines in three (8%) and seven (18%) patients, respectively.
From the start of abiraterone the median PFS was 2.7 months (95% CI 2.3–4.1) and median OS was 7.2 months (95% CI 5.0–not reported). In contrast, prior enzalutamide treatment resulted in ≥50% and ≥30% PSA declines in 21 (55%) and 24 (63%), respectively. It was found that one of the 17 patients (6%) who did not respond to enzalutamide had a subsequent ≥50% PSA decline on abiraterone. Of note, many of these patients had more advanced disease and a poorer performance status than the population in the COU-301 trial [de Bono et al. 2011; Loriot et al. 2013].

In 30 patients from four North American centres, third-line abiraterone resulted in ≥50% PSA declines in 3% and ≥30% PSA declines in 11% of patients [Noonan et al. 2013]. The median PFS and OS were 3.6 months (95% CI 2.5–4.7) and 11.6 months (95% CI 6.6–16.7), respectively. The response to prior enzalutamide included PSA declines of ≥50% and ≥30% in 60% and 70% respectively. Of the nine patients with <30% PSA decline on enzalutamide, two (22%) had a subsequent ≥30% PSA decline on abiraterone. This cohort of patients also had poorer functional status parameters at commencement of abiraterone.

Taken together these data suggest that the activity of abiraterone is reduced after exposure to both enzalutamide and docetaxel. However, PSA is a poor marker of both immediate and longer-term treatment benefit. Predictive biomarkers would substantially improve the ability to appropriately select patients for third-line abiraterone.

Currently there are few clinical predictors of abiraterone activity. Subgroup analysis of the COU-AA-301 trial demonstrated benefit from abiraterone regardless of patient characteristics such as age, pain level and performance status, disease characteristics including presence of visceral metastases and type of disease progression, number of prior chemotherapies or geographical region [de Bono et al. 2011]. A later exploratory subgroup analysis evaluated the impact of the response to docetaxel. Of 797 included patients, docetaxel was discontinued for progressive disease (45%), completion of planned treatment (37%), toxicity (12%) and other reasons (5%). In patients who progressed on docetaxel, the median survival from start of abiraterone was 14.2 months (95% CI 12.0–15.8) compared with 17.0 months (95% CI 15.6–18.2) in the patients that stopped for other reasons. However, this analysis failed to distinguish between patients who were primarily refractory to docetaxel and those who initially responded and subsequently progressed [Chi et al. 2012].

A subgroup analysis of the COU-AA-301 trial evaluated the prognostic value of serum androgens (ultrasensitive measurements of testosterone, androstenedione and dehydroepiandrosterone sulfate) and found a strong association of serum androgen levels with OS (testosterone HR 0.64, 95% CI 0.53–0.77) [Ryan et al. 2013a]. The ultrasensitive measurement of serum androgens may be a useful stratification factor for clinical trials of similar agents in the future.

As yet, there are insufficient data on abiraterone after cabazitaxel or other novel agents to comment on the comparative efficacy. In the absence of solid data, fit later-line patients should generally be given the opportunity to trial proven therapies, with close monitoring and discontinuation after an appropriate trial in the absence of clinical benefit.

**Abiraterone combination studies**

The mild toxicity profile and substantial activity of single-agent abiraterone has encouraged testing of combination therapies. More than 20 abiraterone combination trials are currently open, adding chemotherapy agents, novel anti-androgens, inhibitors of the phosphoinositide 3-kinase (PI3K) / AKT / mammalian target of rapamycin (mTOR) pathway, immunotherapeutics, multitargeting tyrosine kinase inhibitors against vascular endothelial growth factor (VEGF), MET and Src, inhibitors of the heat-shock protein chaperone proteins and 5α reductase inhibitors (see www.clinicaltrials.gov for details). Reported data include a phase II trial of abiraterone and sipuleucel-T, in which concurrent treatment was compared to sequential sipuleucel-T followed by abiraterone. Both strategies resulted in similar immune responses as judged by upregulation of CD54 and had similar adverse event rates [Small et al. 2013]. Preliminary data on a phase I trial of combined cabazitaxel and abiraterone was reported at the American Society of Clinical Oncology (ASCO) 2013 Annual Meeting. The full monotherapy dose of both agents was delivered, with no observed change in cabazitaxel clearance. Preliminary evidence of activity included ≥50% PSA declines in four of the ten enrolled patients [Massard et al. 2013].
Enzalutamide and novel antiandrogens

There are currently only very limited data evaluating the sequential administration of enzalutamide after abiraterone and docetaxel. However, clinical trials have tested enzalutamide in several clinical states of prostate cancer. The only published phase III clinical data are from the AFFIRM trial where 1199 men with CRPC and disease progression after docetaxel were randomized in a 2:1 ratio to enzalutamide or placebo. Patients with prior exposure to abiraterone were excluded on this trial. Median OS was significantly longer in the enzalutamide arm when compared with placebo (18.4 months versus 13.6 months, HR 0.63, 95% CI 0.53–0.75) and enzalutamide was also superior with regards to the secondary endpoints such as ≥50% PSA decline (54% versus 2%), soft tissue responses (29% versus 4%) and quality of life improvement (43% versus 18%) [Scher et al. 2012].

For docetaxel-naïve patients, the results of the PREVAIL trial (enzalutamide versus placebo; 1680 patients [ClinicalTrials.gov identifier: NCT01212991]) are pending. However, the phase I/II clinical trial of enzalutamide included 65 chemotherapy-naïve patients and maximum PSA declines of ≥50% were reported in 62% of patients with soft tissue responses in 36% of patients [Scher et al. 2010]. These preliminary activity data suggest higher enzalutamide activity in docetaxel-naïve patients. Preliminary results in an even earlier, hormone-naïve patient population were recently presented and showed maximum PSA declines of ≥80% at week 25 in 93% of the 67 enrolled patients (95% CI 86–99%) [Smith et al. 2013].

Third-line enzalutamide

Preliminary retrospective data on enzalutamide activity after docetaxel and abiraterone showed a time to tumor progression of 15 weeks (range 7–22 weeks) in the 10 evaluable patients [Stevenson et al. 2013]. No activity data with regards to maximum PSA declines or soft tissue responses were presented.

A further retrospective cohort analysis in 35 patients who received enzalutamide after prior docetaxel and abiraterone reported PSA declines of ≥50% in 29% of patients, a median PFS of 4 months (95% CI 2.0–6.0) and a median OS of 7.1 months (95% CI 6.2–8.1) [Schrader et al. 2013]. Complete cross-resistance was not observed and 3 of 19 (16%) patients who had not responded to abiraterone achieved a PSA declines of ≥50% on enzalutamide.

These results have to be interpreted with caution since they were derived from a very small cohort of advanced patients. With the approval of enzalutamide in the United States and in Europe it is likely that there will be further data on the clinical activity of enzalutamide after abiraterone. Nevertheless, the antitumor activity in the setting of heavily pretreated and advanced CPRC patients is likely to be limited and may not reflect the overall activity of sequential treatment.

ARN-509

For the promising second-generation antiandrogen ARN-509, preliminary activity data suggested limited activity when administered after abiraterone. Maximum PSA declines of ≥50% at week 12 occurred in 29% patients previously exposed to abiraterone but in 88% of abiraterone-naïve patients [Rathkopf et al. 2012].

Enzalutamide combinations

A phase I clinical trial combining enzalutamide and docetaxel at full doses showed no untoward toxicity in 22 patients and no significant effect of enzalutamide on docetaxel pharmacokinetics [Fleming et al. 2013]. A combination phase I clinical study of abiraterone and enzalutamide is currently ongoing [ClinicalTrials.gov identifier: NCT01650194].

For the first-generation antiandrogens (bicalutamide, flutamide), mutations in the ligand-binding domain (LBD) of the AR can confer agonist activity [Taplin et al. 1999]. Recently a novel mutation in the AR-LBD was described in preclinical models that resulted in agonistic activity with both enzalutamide and ARN-509 [Balbas et al. 2013].

Radium223

The phase III ALSYMPCA trial randomized 921 patients in a 2:1 ratio to radium223, a novel α-emitting radionuclide (50 kBq/kg IV delivered 4-weekly, maximum 6 treatments) or matching placebo. The trial population included 43% of patients that refused or were considered unfit for chemotherapy and 57% of patients with prior docetaxel exposure. Radium223 was superior when compared with placebo, with a median OS of 14 months compared with 11.2 months in the control arm (HR 0.695, 95% CI 0.55–0.88) [Parker et al. 2013]. Radium223 was associated with low
frequencies of myelosuppression with grade 3/4 neutropenia (about 3% versus 2%) and grade 3/4 thrombocytopenia (about 6% versus 3%) participants, respectively.

Of particular interest, radium\textsuperscript{223} appeared equally tolerable in patients exposed to docetaxel compared with docetaxel-naïve patients. Preliminary results showed a preserved survival benefit in docetaxel-naïve (median OS: 16.1 months radium\textsuperscript{223} versus 11.5 months placebo, HR 0.745, 95% CI 0.562–0.987) and in docetaxel pretreated patients (median OS: 14.4 months radium\textsuperscript{223} versus 11.3 months placebo, HR 0.71, 95% CI 0.565–0.891) [Vogelzang et al. 2013]. Grade 3/4 adverse events were minimally higher in the docetaxel pretreated patients including anemia and not much different to the patients that received placebo instead of radium\textsuperscript{223} (14% versus 11% in docetaxel-naïve patients and 14% versus 12% in the placebo groups) neutropenia (3% versus 1%; 1% in both placebo groups) and thrombocytopenia (9% versus 3% and 3% versus 1% in the placebo groups).

**Combination studies**

A phase I clinical trial that tested the combination of radium\textsuperscript{223} and docetaxel in 17 patients found significant hematologic toxicity, which did not allow administration of full doses of both agents. The doses explored in the ongoing expansion phase are docetaxel 60 mg/m\textsuperscript{2} every 3 weeks and radium\textsuperscript{223} 50 kBq/kg every 6 weeks for a maximum of 5 applications [Morris et al. 2013].

**Cabazitaxel**

Cabazitaxel is a taxane chemotherapy which demonstrated potent antitumor activity in docetaxel-sensitive cancer cell lines, with additional activity in cell lines rendered docetaxel resistant due to either P-glycoprotein (P-gp) overexpression [Mita et al. 2009] or multidrug resistance mechanisms [Hunter et al. 1993]. Cabazitaxel was initially tested versus mitoxantrone and prednisone as a second-line CRPC treatment in patients with disease progression on or after docetaxel chemotherapy. The phase III TROPIC study showed significant benefit for cabazitaxel/prednisone with median OS of 15.1 months versus 12.7 months (HR 0.70, 95% CI 0.59–0.83). Substudy analysis showed the benefit even in patients who progressed during docetaxel treatment; however, no distinction was made between patients who were truly docetaxel refractory and those with secondary resistance [de Bono et al. 2010]. All of the reported subgroups appeared to derive benefit from cabazitaxel. A subgroup analysis presented in 2012 suggested a benefit for both patients with visceral metastases (OS HR 0.88, 95% CI 0.64–1.22) and those with poorly differentiated tumors (OS 15.2 months versus 12.7 months, $p < 0.0001$) [Oudard et al. 2012]. Furthermore cabazitaxel was also shown to prolong 2-year survival compared with mitoxantrone (15.9% of patients on cabazitaxel and 8.2% of patients on mitoxantrone alive at 2 years; HR 2.11, 95% CI 1.33–3.33) [Bahl et al. 2013].

**First-line cabazitaxel**

Cabazitaxel will be directly compared with docetaxel in the randomized, open-label, multicentre, phase III FIRSTANA study previously discussed (see Table 2).

**Third-line cabazitaxel**

Preclinical data have suggested that both docetaxel and abiraterone may target the AR signaling pathway [Zhu et al. 2010]. The activity of third-line cabazitaxel after docetaxel and abiraterone is therefore of great interest. Thus far the largest series presented has been a multicentre collaboration including 89 patients. These patients received a median of 4.8 months (range 1–55 months) of abiraterone treatment followed by an average of six cycles of cabazitaxel (range 1–15). Whilst on cabazitaxel 44 patients (49%; 95% CI 39–60%) had ≥50% PSA declines and soft tissue responses were reported in seven patients (20%; 95% CI 8–37%) [Pezaro et al. 2013]. A smaller cohort of 24 patients has also been reported. In this cohort the median PSA decline was 30% (95% CI 11.8–54.2%) and median survival from start of cabazitaxel was 8.2 months (95% CI 3.3–13), but PSA declines ≥50% and soft tissue responses were not reported [Sella et al. 2013]. Prospective data are not yet available, but these retrospective cohorts suggest that cabazitaxel retains significant activity when used in the third-line setting. There are not yet published data on the activity of cabazitaxel after enzalutamide.

**Combination studies**

Several cabazitaxel combination studies are in progress, including a phase III study with custirsen.
Earlier phase studies include combinations with abiraterone [ClinicalTrials.gov identifier: NCT01511536], tasquinimod [ClinicalTrials.gov identifier: NCT01513733] and the chemotherapeutic agents mitoxantrone [ClinicalTrials.gov identifier: NCT01594918] and carboplatin [ClinicalTrials.gov identifier: NCT01505868], although the potential for overlapping myelosuppression may limit the ability to deliver chemotherapy-duos successfully.

Conclusion
Within less than a decade multiple survival-prolonging treatments have become available for patients with CRPC. Although these treatments have distinct mechanisms of action, the activity when used sequentially appears reduced, which may be explained by cross-resistance and also clonal evolution [Baca et al. 2013].

Based on the available data, no specific sequence of post-docetaxel treatments can be recommended. All survival-prolonging treatments are valid options, taking into account the performance status of the patient and drug availability. Patients and clinicians should be aware that response rates may be lessened in more advanced or heavily treated patient populations. Clinical trial participation remains a key priority for these patients. Recommendations on the sequential use of novel agents are limited by the lack of prospective data and are based on small retrospective cohort studies. Furthermore accessibility of drugs, patient comorbidities and patient/physician preferences impact treatment decisions. The increasing information on the genetic heterogeneity of prostate cancer may be helpful for molecular disease characterization and to understand mechanisms of treatment resistance. It is also envisaged that predictive markers can be discovered and validated to make rationale treatment decisions.

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