Treatment of mCRPC in the AR-axis-targeted therapy-resistant state


Background: The increased use of the androgen receptor axis-targeted (ARAT) agents abiraterone and enzalutamide in first- and second-line treatment of metastatic castration-resistant prostate cancer (mCRPC) has improved patient outcomes, but resistance to these agents is inevitable. Early identification of patients with primary or secondary resistance to ARAT therapy is of increasing clinical concern.

Design: PubMed and conference proceedings were searched for studies of agents used after progression on abiraterone or enzalutamide. The key search terms (or aliases) used a combination of mCRPC and abiraterone or enzalutamide, and results were limited to clinical trials and comparative or validation studies.

Results and conclusion: This systematic review assembles current evidence and provides an approach to treatment using available clinical factors. Issues of patient selection, use of laboratory and clinical biomarkers to identify patients at risk of poor outcomes, and the timing and sequencing of available treatment options are addressed. Our findings reveal a lack of high-level evidence regarding predictive factors and treatment of patients with resistance to ARAT therapy, and a need for further research in this area. In the meantime, we suggest practical strategies to guide management of ARAT treatment-resistant patients based on available data.

Key words: castration-resistant, prostate cancer, treatment sequencing, abiraterone, enzalutamide, taxanes

introduction

Prostate cancer (PC) is a major global health concern, as the most common malignancy among men in economically developed countries and second to lung cancer worldwide [1]. In 2012, an estimated 1.1 million (15% of all cancers diagnosed in men) new PC cases were diagnosed worldwide, and 307,000 (6.6%) men died of the disease, making it the fifth leading cause of death from cancer in men [2].

The androgen receptor (AR) is a nuclear hormone receptor predominately dependent on activation by dihydrotestosterone, a ligand produced through intracellular conversion of testosterone, to induce nuclear localization and target gene transcription [3]. The AR is commonly involved in driving PC development and progression, and many agents used to treat PC target the AR signaling axis. Androgen deprivation therapy (ADT) by medical or surgical means [4-8] has been used as the main component of first-line PC therapy in the metastatic state. Although disease regression and stability may occur for varying lengths of time, disease progression is inevitable and reactivation of AR-axis signaling has been identified as an important driver of this process [9]. The loss of response to ADT, leading to castration-resistant prostate cancer (CRPC), is associated with compensatory mechanisms allowing post-castration activation of the AR, including AR gene amplification, mutation, incomplete blockade of ligand-dependent AR activation, and aberrant AR co-regulator activity, among other mechanisms [10-14].

With the recent development and widespread adoption of the androgen biosynthesis inhibitor abiraterone acetate (hereafter referred to as abiraterone) [15-17] and the novel antiandrogen enzalutamide [18, 19] for the treatment of metastatic castration-resistant prostate cancer (mCRPC), these agents have become the most commonly used AR-axis-targeted (ARAT) therapies in this setting. Both abiraterone and enzalutamide have been associated with improvements across a spectrum of clinical outcomes and high response rates of prolonged duration, particularly for chemotherapy-naïve patients. Other non-ARAT agents approved for treatment of mCRPC in recent years include cabazitaxel [20], a second-generation taxane designed to overcome docetaxel resistance, the immunotherapeutic agent sipuleucel-T [21] and the bone-targeting radiotherapy Radium-223 [22].
Despite these mCRPC treatment advances, primary resistance to ARAT therapy and the development of secondary resistance remain clinical challenges. In the pivotal trials with abiraterone and enzalutamide, primary resistance was observed in both chemotherapy experienced and naïve mCRPC patients [15–19]. In patients previously treated with chemotherapy, the proportion of patients showing radiographic progression and prostate-specific antigen (PSA) progression within the first 3 months of treatment was $\sim$35% and 15%, respectively, for abiraterone [15] and 25% and 10%, respectively, for enzalutamide [18]. In chemotherapy-naïve populations, radiographic progression and PSA progression within the first 3 months was $\sim$5% and 8%, respectively, for abiraterone [17] and 5% and 3%, respectively, for enzalutamide [19].

Proposed mechanisms of resistance to abiraterone and enzalutamide include alternate signaling pathways to induce steroid synthesis, AR gene amplification, increased expression of ligand-independent AR splice variants [23, 24], and mutations that confer resistance to AR antagonists and promiscuous activation by alternative ligands, including AR antagonists, glucocorticoids, or progesterone (Figure 1) [24–28]. Despite distinct mechanisms of action, abiraterone and enzalutamide both target AR-axis signaling [15–19] and share mechanisms associated with treatment resistance [23, 24]; therefore, there is potential for cross resistance.

There is level 1 evidence supporting the establishment of ARAT agents and other therapies as first- or second-line treatment for mCRPC, yet robust clinical data to guide the optimal sequencing of these therapies are lacking. The best available evidence to inform patient selection, duration of treatment, and survival is retrospective. Our review focuses on treatment options for mCRPC; therefore, ARAT therapy will hereafter be used to specifically indicate abiraterone and enzalutamide. We provide a systematic review and interpretation of available clinical data addressing the diagnosis and treatment of ARAT therapy-resistant mCRPC.

**methods**

PubMed (to 12 November 2014) and the proceedings of American Society of Clinical Oncology (ASCO; 2013–2014) meetings, the Annual Congress of the European Society for Medical Oncology (ESMO; 2013–2014), and the European Cancer Congress (ECC; 2013) were searched for studies of agents used after progression on ARAT therapies (specifically abiraterone and enzalutamide). The key search terms (or aliases) mCRPC, abiraterone, and enzalutamide were used, and results were limited to clinical trials and comparative or validation studies (Figure 2). A supplemental bibliographic search of recent review articles and directed searches of ASCO GU 2015 for updated reports of specific studies was also conducted. A total of 447 records were identified from selected sources.

**findings**

A total of 70 prognostic/predictive studies were identified (24 assessing biomarkers; 46 assessing clinical/biological factors; Figure 2). Relevant treatment outcomes were identified from a total of 44, predominately retrospective, studies (Figure 2), with some assessing multiple treatment cohorts (total cohorts $n = 60$). For pragmatic reasons, outcomes for cohorts assessing fewer than 15 patients ($n = 14$) were excluded from the analysis due to their highly variable nature, resulting in a final data set of 46 treatment cohorts.
predictive biomarkers

Predictive markers of treatment response are key tools for identifying patients who are likely to be resistant to therapy. One should note that the possible usefulness of these markers is largely agent-specific and may not be generalized to other therapies until validated. Laboratory biomarkers of interest in predicting response or resistance to ARAT therapy for mCRPC have focused on aberrations in AR gene or protein expression [28–36].

AR amplification occurs in 50% or more CRPC patients [37], and has been associated with both response and resistance to ARAT therapy. Increased AR copy number following initial ADT has been associated with improved response to subsequent combined androgen blockade [36], while more recent data have shown that AR copy number gain in circulating tumor DNA (ctDNA) is associated with poor response to the AR agents abiraterone and enzalutamide [33, 38]. AR mutations, particularly in the ligand-binding domain, that confer resistance to AR antagonists or activation by glucocorticoids or progesterone have also been explored for association with response to ARAT therapy, with some studies indicating an association with disease progression and treatment resistance [25, 27, 28, 33, 38].

Other potential biomarkers include nuclear AR [29, 39] and cytoplasmic CYP17 expression [29]. High nuclear AR expression combined with ≥10% cytoplasmic CYP17 expression in bone metastases has been significantly correlated with improved outcomes following treatment with abiraterone plus prednisone [29], and following enzalutamide therapy [30]. However, further studies are necessary to validate the correlation between these biological factors and resistance to therapy.

Recently, compelling data have emerged on the expression of the AR splice variant AR-V7, which lacks the ligand-binding domain of the receptor [31, 40]. Patients initiating treatment with either abiraterone (n = 31) or enzalutamide (n = 31) were prospectively enrolled in a single-center study to assess association between AR-V7 status and treatment outcomes [31]. Analysis of AR-V7 expression in circulating tumor cell (CTC) RNA showed that men receiving abiraterone who were positive for AR-V7 expression had lower rates of PSA response, defined as a ≥50% PSA decline (0 versus 68%, P = 0.004), as well as shorter median PSA progression-free survival (PFS; 1.3 months versus not reached; P < 0.001), median clinical or radiographic PFS (2.3 months versus not reached; P < 0.001), and median overall survival (OS; 10.6 months versus not reached, P = 0.006) than those who were AR-V7 negative. Likewise, men receiving enzalutamide who were positive for AR-V7 expression showed lower rates of PSA response (0 versus 53%, P = 0.004), and shorter median PSA–PFS (1.4 versus 6.0 months; P < 0.001), median clinical or radiographic PFS (2.1 versus 6.1 months; P < 0.001), and median OS (median, 5.5 months versus not reached; P = 0.002) [31]. A similar, albeit smaller, prospective study (n = 37) was conducted to assess taxane activity in these patients [41]. Although small numerical differences in favor of AR-V7-negative status were apparent, differences were not statistically significant for PSA response (41 versus 65%, P = 0.19), PSA–PFS (4.5 versus 62 months, HR 1.72, P = 0.32) or median PFS (5.1 versus 6.9 months, HR 2.65, P = 0.11) in AR-V7-positive compared with AR-V7-negative patients.

Although the results of these AR-V7 biomarker studies are promising, findings must be interpreted with caution given that they were derived from small, single-center trials conducted in heterogeneous and heavily pretreated patient populations where treatment was not selected in a randomized fashion. Additionally, the possibility remains that AR-V7 is generally prognostic rather than predictive of response to ARAT therapy, given the likelihood that the taxane AR-V7 study was insufficiently powered to detect differences in treatment outcomes. It is therefore unclear how these findings apply in less heavily...
treated populations and in settings where processes for detection and analysis of CTCs are not standardized.

Large-scale, prospective validation of potential biomarkers is necessary before these cellular and molecular signatures can be used to guide treatment strategy. Prospective evaluation of several laboratory biomarkers are underway, where correlative studies are integrated into multi-center clinical trials randomizing patients to treatment with ARAG agents or chemotherapy (clinicaltrials.gov: NCT02125357 and NCT02254785). These types of trials will provide robust data that are critical to validate candidate biomarkers and assess clinical utility.

**prognostic and predictive clinical factors and models**

Given the substantial heterogeneity of disease outcomes and absence of validated laboratory biomarkers, identifying patients with particularly poor prognosis and those potentially resistant to ARAG therapy can help determine which patients are susceptible to treatment failure, and allow consideration of alternative treatment options as early as possible. A total of 46, primarily retrospective, studies investigating either individual factors or prognostic models were identified (Figure 2).

These factors include the duration of response to prior ADT, PSA response, Gleason score, baseline serum androgen levels, and chromogranin A levels (summarized in Table 1); however, none has been validated as predictive of response to ARAG treatment.

Among the individual prognostic factors investigated for association with outcomes to ARAG therapy, the duration of response to prior ADT has been of interest based on the assumption that patients with poor response or rapid progression on first-line ADT are unlikely to respond to further AR-directed therapies (Table 1). Two retrospective analyses of institutional cohorts have indicated a relationship between the degree of response to prior ADT and response to AR-targeted therapy (including ARAG agents and other hormonal therapies, e.g. antiandrogen, diethylstilboestrone, estramustine, ketoconazole) in chemotherapy-exposed populations [42, 43]. These studies suggest that shorter durations of previous sensitivity to ADT (<16 versus ≥16 months) [42] and shorter responses to surgical or chemical castration therapy (<12 versus ≥12 months) [43] indicate a poor likelihood of response to ARAG agents. Data on treatment with taxanes demonstrate a reduced time to biochemical progression [43], reduced time to progression and shorter OS among patients with <1 year response to ADT, although similar rates of PSA response [43, 57] and clinical benefit [57] were observed regardless of the duration of response to prior ADT or time to CRPC. Finally, retrospective analysis of data from the TROPIC trial show that OS was shorter in cabazitaxel-treated patients with a shorter duration of prior hormonal therapy [58]. The relationship between shorter response to prior hormonal therapy and poor likelihood of response to ARAG agents may indicate resistance across therapies targeting the AR axis, a plausible hypothesis considering their shared mechanisms of treatment resistance. However, given a similar trend of reduced benefit of taxanes with shorter duration of prior hormonal therapy, it is unclear whether the duration of prior ADT should be considered in treatment decisions. Even so, pending more robust clinical data, a recently published European Consensus, have indicated that a short duration of response (<1 year) to first-line ADT may be useful in identifying patients with an increased risk of primary resistance to AR-axis-targeted agents [59].

Given the limitations of individual prognostic factors, research is underway to develop and validate prognostic models based on multiple clinical factors. A study of the COU-AA-301 database of mCRPC patients pretreated with docetaxel-assessed clinical factors [lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance status, presence or absence of liver metastases, serum albumin and alkaline phosphatase (ALP) levels and time from the start of ADT to initiation of therapy at baseline to identify independent prognostic factors for OS (Table 1) [54]. Patients were assigned to risk groups based on the number of baseline factors, good (0 or 1), intermediate (2 or 3), and poor (4–6). Patients in the poor risk group who were treated with abiraterone had a lower median OS compared with those in the good risk group (6.1 versus 21.3 months) [54]. The differences in median OS in poor prognosis patients treated with abiraterone compared with placebo appeared to be modest, emphasizing that poor prognosis cannot be interpreted as predictive of poor response to abiraterone. This prognostic model has been validated in both population-based and independent retrospective cohort analyses [60, 61].

Both neutrophil-lymphocyte ratio (NLR) and extent of metastatic disease have also been studied as a factors associated with poor response to ARAG therapy and assessed in prognostic models. A recent study by Leibowitz–Amit et al. [55] sought to identify factors associated with PSA response to abiraterone, and validate this association in an independent cohort (Table 1). The group identified an institutional cohort of 108 abiraterone-pretreated mCRPC patients. A univariate analysis of potential factors to predict response to abiraterone therapy demonstrated that a score derived from the sum of NLR ≤5 and restricted metastatic spread was significantly associated with PSA response to abiraterone therapy (P = 0.007). Validation with an independent cohort of 245 mCRPC patients verified the predictive capacity of the score and demonstrated an association with OS. Patients with a score of 2 (NLR > 5 and extensive metastatic spread, defined as visceral involvement or combined bone and lymph node disease) had a poor response to abiraterone therapy (P = 0.003). A recently developed prognostic model, incorporating NLR, was evaluated in a cohort of chemotherapy-naïve mCRPC patients (n = 357) treated with docetaxel (Table 1) [56]. Multi-variable analysis indicated that liver metastases, low hemoglobin, high ALP, LDH, and NLR were associated with decreased survival. In conclusion, considerable research has been conducted to elucidate the underlying mechanisms of clinical resistance to ARAG therapy in the hope of identifying new treatment approaches and potential predictive factors. Potential biomarkers, such as AR-V7 splice variant expression and other AR gene aberrations (e.g., mutation, copy number increase) [31, 33, 38] and clinical and laboratory factors, such as short duration of response to initial ADT, early response, features of poor prognosis, androgen levels by ultrasensitive assays, and NLR (Table 1), hold promise for considerable clinical utility [42–45, 48–51, 54–56, 60, 61]. Presently, however, caution must be used when applying these hypothesis-generating findings clinically, highlighting the need for further validation.
Although treatment with greater lines of therapy (3 versus 2) has been associated with improved OS [62], the optimal sequencing of agents following docetaxel and ARAT therapy is not well-defined. Table 1.

Table 1. Prognostic/predictive clinical factors in the treatment of mCRPC

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Associated outcome</th>
<th>Study detail</th>
<th>Study population</th>
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<tbody>
<tr>
<td>Individual factors</td>
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<tr>
<td>ADT response &lt;16 months</td>
<td>↓ PSA response ↓ PFS</td>
<td>AR-axis targeted agents</td>
<td>Retro analysis, institutional cohort [42]</td>
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<tr>
<td>Response to surgical or chemical castration &lt;12 months</td>
<td>↓ PSA response ↓ PFS</td>
<td>AR-axis targeted agents</td>
<td>Retro analysis, MC cohort [43]</td>
</tr>
<tr>
<td>Early PSA response</td>
<td>↑ OS ↑ PFS</td>
<td>Abiraterone</td>
<td>Enzalutamide</td>
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<tr>
<td>Abiraterone-associated PSA kinetics, ↑ PSA decline</td>
<td>↑ OS ↑ rPFS</td>
<td>Abiraterone</td>
<td>Retro analysis of phase III data (COU-AA-301 &amp; COU-AA-302) [46, 47]</td>
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<tr>
<td>↑ Gleason score (≥8; poorly differentiated tumor)</td>
<td>↓ Response to abiraterone ↓ OS benefit</td>
<td>Abiraterone + pred versus pred (chemotherapy-naïve)</td>
<td>Retro analysis of phase III data (COU-AA-301 &amp; COU-AA-302) [49]</td>
</tr>
<tr>
<td>↑ Baseline serum androgens (T, androstenedione, DHEA)</td>
<td>↑ OS</td>
<td>Abiraterone</td>
<td>Retro analysis of phase III data [50]</td>
</tr>
<tr>
<td>DHEA ≥ LOQ</td>
<td>↑ PSA response ↑ (r)PFS</td>
<td>Abiraterone</td>
<td>Phase II [51]</td>
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<tr>
<td>CgA &gt; 3x UNV</td>
<td>↓ PFS ↓ OS</td>
<td>Abiraterone</td>
<td>Enzalutamide</td>
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<tr>
<td>Models</td>
<td>Poor prognosis</td>
<td>Abiraterone (docetaxel pretreated)</td>
<td>Retro analysis of phase III data [54]</td>
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<td>Prognostic Model - Variables</td>
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<tr>
<td>ECOG PS 2</td>
<td>Liver metastases</td>
<td>Short duration LHRH agonist therapy to start of abiraterone (≤36 months)</td>
<td>Low albumin</td>
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<tr>
<td>Prognostic score—variables</td>
<td>↓ PSA response&lt;sup&gt;d&lt;/sup&gt; ↓ OS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Abiraterone</td>
<td>SC cohort (n = 108) [55]</td>
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<tr>
<td>NLR &gt; 5</td>
<td>Visceral or multiple metastatic sites</td>
<td>Prognostic score—variables</td>
<td>Liver metastases</td>
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</tbody>
</table>

<sup>a</sup>PSA decline >50% from baseline during the first 4 weeks of therapy.
<sup>b</sup>PSA >30% in the first three months of treatment.
<sup>c</sup>PSA decline ≥50% below baseline maintained for ≥3 weeks.
<sup>d</sup>In exploratory analysis.
<sup>e</sup>Each variable individually associated with reduced OS.

ALP, alkaline phosphatase; Cab, cabazitaxel; CgA, chromogranin A; DHEA, dehydroepiandrosterone; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LN, lymph node; LOQ, limit of quantitation; MC, multi-center; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival; Pred, prednisone; PSA, prostate-specific antigen; Retro, retrospective; rPFS, radiographic PFS; SC, single center; T, testosterone; TTPP, time to PSA progression; ULN, upper limit of normal; UNV, upper normal value.

treatment

Although treatment with greater lines of therapy (3 versus 2) has been associated with improved OS [62], the optimal sequencing of agents following docetaxel and ARAT therapy is not well-defined. third-line outcomes for ARAT therapy or chemotherapy following progression on docetaxel and ARAT therapy. Outcomes for ARAT therapy or cabazitaxel as third-line treatments are available from multiple retrospective analyses and early access
### Table 2. Third-line treatment outcomes in chemotherapy-pretreated patients after progression on abiraterone or enzalutamide

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence</th>
<th>n</th>
<th>PSA decline ≥ 50% (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
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<tr>
<td><strong>Outcomes for enzalutamide following progression on docetaxel and abiraterone</strong></td>
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<tr>
<td>Brasso et al. [63]</td>
<td>D-A-E</td>
<td>137</td>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.3</td>
</tr>
<tr>
<td>Cheng et al. [64]</td>
<td>D-A-E</td>
<td>122</td>
<td>26</td>
<td>–</td>
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<tr>
<td>Stevenson et al. [65]</td>
<td>D-A-E</td>
<td>69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
<td>3.5&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>–</td>
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<tr>
<td>Azad et al. [66]</td>
<td>D-A-E</td>
<td>68</td>
<td>22</td>
<td>4.6&lt;sup&gt;f&lt;/sup&gt;</td>
<td>10.6</td>
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<tr>
<td>Scholz et al. [67]</td>
<td>D-A-E</td>
<td>63&lt;sup&gt;g,h&lt;/sup&gt;</td>
<td>29 (PSA decline ≥30%)</td>
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<tr>
<td>Badrising et al. [68]</td>
<td>D-A-E</td>
<td>61</td>
<td>21</td>
<td>2.8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7.3&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Caffo et al. [69]</td>
<td>D-A-E</td>
<td>49</td>
<td>20</td>
<td>3</td>
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<tr>
<td>Bianchini et al. [70]</td>
<td>D-A-E</td>
<td>39</td>
<td>12.8&lt;sup&gt;i&lt;/sup&gt;</td>
<td>2.8</td>
<td>–</td>
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<tr>
<td>Schrader et al. [71]</td>
<td>D-A-E</td>
<td>35</td>
<td>28.6&lt;sup&gt;j&lt;/sup&gt;</td>
<td>–</td>
<td>7.1&lt;sup&gt;k&lt;/sup&gt;</td>
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<td>Vera-Badillo et al. [72]</td>
<td>D-A-E</td>
<td>26</td>
<td>27</td>
<td>4.9&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>Thomsen et al. [73]</td>
<td>D-A-E</td>
<td>24</td>
<td>17</td>
<td>–</td>
<td>4.8</td>
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<tr>
<td>Thomson et al. [74]</td>
<td>D-A-E</td>
<td>23&lt;sup&gt;n&lt;/sup&gt;</td>
<td>39.1</td>
<td>–</td>
<td>8.5</td>
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<td>Sandhu et al. [75]</td>
<td>(D)-A-E&lt;sup&gt;n&lt;/sup&gt;</td>
<td>23</td>
<td>17&lt;sup&gt;i&lt;/sup&gt;</td>
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<td>Bournakis et al. [76]</td>
<td>D-ABS-E&lt;sup&gt;p&lt;/sup&gt;</td>
<td>20</td>
<td>40</td>
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<td><strong>Outcomes for abiraterone following progression on docetaxel and enzalutamide</strong></td>
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<td>Loriot et al. [77]</td>
<td>D-E-A</td>
<td>38</td>
<td>8</td>
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<tr>
<td>Noonan et al. [78]</td>
<td>D-E-A</td>
<td>30</td>
<td>4</td>
<td>3.5&lt;sup&gt;l&lt;/sup&gt;</td>
<td>11.3&lt;sup&gt;d&lt;/sup&gt;</td>
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<td><strong>Outcomes for cabazitaxel following progression on docetaxel and ARAT therapy</strong></td>
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<tr>
<td>Caffo et al. [69]</td>
<td>D-A-C</td>
<td>88</td>
<td>28</td>
<td>4</td>
<td>–</td>
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<tr>
<td>Pezaro et al. [79]</td>
<td>D-A-C</td>
<td>89</td>
<td>46&lt;sup&gt;l&lt;/sup&gt;</td>
<td>5.5&lt;sup&gt;j&lt;/sup&gt;</td>
<td>12&lt;sup&gt;j&lt;/sup&gt;</td>
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<tr>
<td>Al Nakouzi et al. [80]</td>
<td>D-A-C</td>
<td>79</td>
<td>35</td>
<td>4.4</td>
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<td>D-A-C</td>
<td>69&lt;sup&gt;j&lt;/sup&gt;</td>
<td>31.8&lt;sup&gt;n&lt;/sup&gt;</td>
<td>2.6</td>
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<td>Sonpavde et al. [82]</td>
<td>D-A-C</td>
<td>36</td>
<td>–</td>
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<td>–&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>Sella et al. [83]</td>
<td>D-A-C</td>
<td>24</td>
<td>31.5</td>
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<td>Saad et al. [84]</td>
<td>D-A-C</td>
<td>21</td>
<td>42.9</td>
<td>5.9&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>Oudard et al. [32]</td>
<td>D-A/E-C</td>
<td>68</td>
<td>–</td>
<td>6&lt;sup&gt;g&lt;/sup&gt;</td>
<td>–&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>Pezaro et al. [85]</td>
<td>D-A/E-C&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41</td>
<td>39</td>
<td>4.6</td>
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<table>
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<tr>
<th>Study</th>
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<td>D-E-C</td>
<td>16</td>
<td>25</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Outcomes for docetaxel following progression on docetaxel and abiraterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azad et al. [86]</td>
<td>D-A-D</td>
<td>49</td>
<td>37</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*aPSA evaluable patients: n = 122.*

*bMedian duration of radiographic PFS in the 34 patients who underwent regular radiographic follow-up.*

*c69 patients had prior abiraterone, 57 of which received abiraterone just prior to enzalutamide.*

*dConverted to months using 4.35 weeks/month.*

*eMedian time to progression for 44 patients that had stopped enzalutamide due to PSA progression at the time of the report.*

*fMedian time to radiologic/clinical progression.*

*gAfter a median follow-up of 12.5 weeks in 63 patients evaluable for PSA response.*

*h55 patients received previous docetaxel.*

*i4 additional patients had unconfirmed PSA decline ≥ 50%; 3 with short lived response and 1 where treatment was ongoing at time of report.*

*jPSA decline >50%.*

*kReported as mean OS.*

*lMedian time to treatment failure.*

*mSome patients had other prior therapy: cabazitaxel (35%), dexamethasone (30%), and Stilboestrol (52%).*

*nMedian biochemical PFS of 2.8 months.*

'o15 patients received prior docetaxel.*

*pAndrogen biosynthesis inhibitors (ABS): abiraterone, 75%; oteronel, 35%; ketoconazole, 5%; more than one, 15%.*

*qTime from start of abiraterone to time of PSA progression (PSA increase of 25% from nadir and a minimum of 2 ng/ml), radiographic progression, and/or symptomatic progression.*

*rn = 74 evaluated for PSA response, determined from max PSA change in waterfall plot.*

*sEstimated from graph, no numerical data available.*

*t1 patient (1.4%) received enzalutamide or placebo before abiraterone–cabazitaxel; 5 patients (7.2%) received enzalutamide or placebo between abiraterone and cabazitaxel.*

*uPartial response defined as a PSA decrease of ≥50% compared to baseline in at least two separate PSA measurements 3 weeks apart.*

*vMedian OS of 17.0 months reported, defined as the number of days between start of second-line therapy (cabazitaxel or abiraterone) and death or censoring, regardless of therapies afterwards.*

*wMedian OS of 11.8 months reported, measured from date of initiation of post-D second-line treatment to date of death, censoring patients who were still alive at last contact.*

*xMedian time to PSA progression.*

*yMedian clinical and/or progression-free survival; data estimated from graph.*

*zMedian overall survival of 22 months from start of next life-extending therapy after docetaxel; data estimated from graph.*

+*5 patients received sequential abiraterone and enzalutamide prior to cabazitaxel.*

A, abiraterone; ABS, androgen biosynthesis inhibitor; C, cabazitaxel; D, docetaxel; E, enzalutamide; OS, overall survival; PSA, prostate-specific antigen; PFS, progression-free survival.
programs (EAPs; Table 2). A total of 16 retrospective cohort analyses assessed the effectiveness of a second ARAT therapy after progression on prior docetaxel and ARAT treatment (Table 2) [63–78]. Enzalutamide was the most investigated agent in this setting (docetaxel followed by enzalutamide, D-A-E; n = 14 cohorts) [63–76]. Rates of ≥50% PSA decline data were available for the majority of D-A-E cohorts (n = 13) and were highly variable, ranging from 12% to 40%. Median PFS for three-line enzalutamide ranged from 2.8 to 4.9 months (n = 7 cohorts) [63, 65, 66, 68–70, 72], while median OS outcomes ranged from 4.8 to 10.6 months (n = 6 cohorts) [63, 66, 68, 71, 73, 74]. Abiraterone outcomes in this setting were examined in only two studies (docetaxel followed by enzalutamide, followed by abiraterone, D-E-A) [77, 78], with rates of ≥50% PSA decline of 4% and 8%, respectively. Survival outcomes for third-line abiraterone were reported for both studies, with median PFS of 2.7 months and 3.5 months and median OS of 7.2 months and 11.5 months, respectively.

Cabazitaxel outcomes have been investigated in a total of 10 retrospective analyses in docetaxel and ARAT therapy-pretreated patients (docetaxel–abiraterone–cabazitaxel or docetaxel–enzalutamide–cabazitaxel [D-A/E-C] sequences; Table 2) [32, 69, 79–85]. Findings from these cohort analyses also show substantial variability, with ≥50% PSA decline data ranging from 25% to 46% (n = 8 cohorts; Table 2). Median PFS for third-line cabazitaxel were reported for eight D-A/E-C cohorts, and ranged from 4 to 5.9 months [32, 69, 79–81, 84, 85], while median OS was reported for four cohorts analyses, with values ranging from 8.2 to 15.8 months [79, 80, 83, 85]. Data on the use of docetaxel rather than cabazitaxel is limited, and outcomes from a single study examining retreatment with docetaxel (docetaxel followed by abiraterone, then docetaxel, D-A-D; n = 49) suggest activity in this context (≥50% PSA decline of 37%) [86].

**Table 3. Second-line treatment outcomes in chemotherapy-naive patients previously treated with abiraterone**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of analysis/Data set</th>
<th>N</th>
<th>Median treatment duration (months)</th>
<th>PSA decline ≥ 50% (%)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azad et al. [86]</td>
<td>Retro MC Cohort</td>
<td>37</td>
<td>3</td>
<td>47</td>
<td>–</td>
</tr>
<tr>
<td>Smith et al. [88]</td>
<td>Phase III post-hoc</td>
<td>53</td>
<td>5</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td>Zafeiriou et al. [90]</td>
<td>Retro SC Cohort</td>
<td>30</td>
<td>–</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>Cheng et al. [64]</td>
<td>Retro MC Cohort</td>
<td>28</td>
<td>–</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>Outcomes for abiraterone following progression on abiraterone</td>
<td>Smith et al. [88]</td>
<td>Phase III post-hoc</td>
<td>55</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>de Bono et al. [94]</td>
<td>Phase III post-hoc</td>
<td>265</td>
<td>3</td>
<td>47</td>
<td>–</td>
</tr>
<tr>
<td>Aggarwal et al. [93]</td>
<td>Retro SC Cohort</td>
<td>23</td>
<td>4.3</td>
<td>48</td>
<td>12.4</td>
</tr>
</tbody>
</table>

脜Cohort of patients who received enzalutamide following discontinuation of initial abiraterone in COU-AA-302 study; patients were chemotherapy-naive prior to treatment with A, and 67% (n = 22) received intervening chemotherapy prior to subsequent enzalutamide.

脜67% reported as having positive response during subsequent therapy, PSA values.

脜Cohort of patients who received cabazitaxel following discontinuation of initial abiraterone in COU-AA-302 study; patients were chemotherapy-naive prior to initial treatment with abiraterone, and 69% (n = 38) received intervening chemotherapy prior to subsequent cabazitaxel.

脜44% reported as having ‘positive response’ during subsequent therapy, PSA values.

脜4 patients received cabazitaxel following abiraterone, not docetaxel.

脜Other hormonal or investigational drugs, including enzalutamide, were allowed prior to treatment with docetaxel.

MC, multi-center; OS, overall survival; PSA, prostate-specific antigen; Retro, retrospective study; SC, single center.
Docetaxel outcomes were assessed in a total of seven studies of ARAT therapy-pretreated, chemotherapy-naïve populations (A–D; Table 3) [86, 89–94]. Results from six of these studies included rates of ≥50% PSA decline ranging from 26% to 48% [86, 89, 91–94], and median OS outcomes for two studies were reported as 12.5 and 12.4 months, respectively [91, 93]. Studies of the use of alternate treatment options in the second-line, chemotherapy-naïve setting, such as the androgen biosynthesis inhibitor ketoconazole, the HSP90 inhibitor AT13387, and the next-generation AR inhibitor ODM-201, have also been undertaken, although limited data are available [51, 95–98].

Retrospective analyses of mCRPC treatment data have described outcomes for a variety of second- and third-line treatments in both the chemotherapy-experienced and naïve settings (Tables 2 and 3). However, such analyses are prone to multiple biases and cross trial comparisons are discouraged. Despite this, there are some consistent trends that may help guide therapy in the absence of randomized data. There is a trend toward reduced response to ARAT treatment after prior ARAT therapy, which may reflect a degree of cross-resistance [70, 71, 77, 78] arising from common mechanisms of resistance, such as increased expression of splice variants or AR amplification [31, 33, 38, 99]. Despite controversial pre-clinical and early clinical evidence suggesting cross-resistance between ARAT therapy and taxane chemotherapy [80, 85, 86, 91, 100–104], most clinical data suggest continued activity of both second-line docetaxel and third-line cabazitaxel in ARAT therapy-pretreated patients (Tables 2 and 3), confirming the importance and relevance of chemotherapy in ARAT treatment-resistant patient populations.

discussion


treatment sequencing

There are multiple treatment options available for ARAT therapy-resistant mCRPC [15, 17–19, 87]. When developing an individualized therapeutic strategy, patient factors such as age, co-morbid illnesses, functional status, agent tolerability, and clinical factors associated with poor response to ARAT therapy (Table 1), in conjunction with patient preferences, should be considered to guide treatment selection and sequencing. Between 3% and 25% of mCRPC patients may exhibit primary resistance to ARAT therapy [15, 17–19] and close monitoring of response.

Figure 3. Sequencing of mCRPC therapies.
to treatment is important for early identification. Lack of PSA decline or PSA progression within 3 months of start of treatment suggests primary resistance to an ARAT therapy [59], indicating the need for a timely switch to an alternate ARAT therapy, or to chemotherapy while a patient’s performance status remains favorable. Although primary or acquired resistance to either abiraterone or enzalutamide does not preclude a response to the other, resistance across agents is a possibility and close monitoring of treatment response is an important consideration when sequencing ARAT therapy [59].

Based on currently available prospective and retrospective data and our clinical experience, we suggest the following treatment algorithm to guide the treatment of patients with AR therapy-resistant mCRPC disease (Figure 3). Although not specifically detailed throughout the algorithm, enrollment in a clinical trial is recommended whenever feasible, and radium-223 is considered an appropriate option for patients with symptomatic bone metastases and no significant soft tissue disease at all levels, including those who are chemotherapy-ineligible. For first-line mCRPC patients progressing on ADT for PC, treatment with ARAT therapy is preferred for the majority of patients. However, docetaxel can be considered for patients with good performance status who are able to tolerate chemotherapy, suspected of ARAT treatment resistance (e.g., prior response to ADT < 1 year), symptomatic or have visceral metastatic disease.

For those receiving ARAT therapy in first-line, retrospective data suggest better responses to second-line docetaxel (Table 3), although an ARAT therapy switch (i.e., enzalutamide following first-line abiraterone) may also be considered for patients with good response to prior ARAT therapy, >1 year response to prior ADT, asymptomatic or minimally symptomatic disease or have no visceral disease. In third-line, docetaxel is suggested for those who remain chemotherapy-naive, while cabazitaxel is recommended for those pretreated with docetaxel.

Among patients receiving first-line docetaxel, second-line ARAT therapy is preferred (Figure 3). However, treatment with cabazitaxel can be considered in patients with symptomatic disease, a poor response to prior ADT (<1 year), a prior prolonged response to docetaxel, or visceral disease. For third-line therapy following ARAT treatment, cabazitaxel is preferred based on retrospective evidence that suggests a trend toward greater response to cabazitaxel compared with ARAT therapy (Table 2). However, an ARAT agent switch can be considered for asymptomatic or minimally symptomatic patients with a good response to prior ARAT therapy, good response to prior ADT (>1 year), and no visceral disease. For all patients progressing on third-line therapy and eligible for continued treatment, the therapeutic agent not yet given remains an option.

treatment challenges: AR-negative/neuroendocrine prostate cancer

Effective inhibitors of AR-axis signaling may drive adaptive cellular responses and lead to an anaplastic, small cell or neuroendocrine phenotype characteristic of particularly aggressive and treatment-resistant mCRPC [105–107]. An increased proportion of neuroendocrine cells is found in high-grade and late-stage prostate tumors and is particularly common in CRPC. Neuroendocrine prostate cancer (NEPC) demonstrates a reduction or loss of AR-signaling, as indicated by the loss of AR expression and target gene transactivation (e.g., loss of PSA expression), as well as neuroendocrine cell-specific histological markers (e.g., CGA, synaptophysin, neuron-specific enolase) [108].

The association of NEPC with high-risk and poor prognosis, combined with lack of AR expression, indicates high likelihood of resistance to ARAT therapy and more probable response to chemotherapy. The optimal treatment strategy for patients with NEPC must take into account individual patient and tumor characteristics, including the potential for mixed adenocarcinoma/neuroendocrine tumors that may retain AR expression and therefore have the potential for response to hormonal or ARAT therapy [109]; however, patients with this PC variant commonly present with symptomatic disease and visceral (e.g., the liver, lung) metastases [105, 110]. For these high-risk patients with aggressive disease, first- and second-line platinum-based chemotherapy combinations have demonstrated robust initial, but not durable, responses with ultimately poor OS [111]. Much research to identify molecular targets and develop targeted agents for treatment of NEPC is underway (e.g., a phase II trial of the aurora kinase A inhibitor MLN8237 (NCT01799278)).

conclusion

The introduction of second-generation ARAT agents for treatment of first- and second-line mCRPC has improved outcomes, and the therapeutic landscape for PC continues to evolve as the benefits of these therapies are evaluated for earlier stages of disease. However, in mCRPC, resistance to ARAT agents is inevitable and identification of a clinically validated predictive biomarker remains elusive. Available retrospective data suggest that taxanes are a preferred treatment choice following ARAT therapy, although a switch to an alternate ARAT agent can be considered in select patients. Continued prospective research into predictive factors and optimal treatment sequencing for ARAT therapy-resistant mCRPC is warranted.

acknowledgements

We thank Deanna McLeod of Kaleidoscope Strategic for editorial assistance in preparing the review.

funding

This work was supported by an unrestricted educational grant from Sanofi Canada. Kaleidoscope Strategic, an independent medical information management firm, assisted in data collection and analysis, administrative support, and writing; the lead medical writer is named as an author according to ICMJE criteria. The opinions presented in the paper represent those of the authors and not of the sponsor; none of the clinical authors were paid for writing this review. The sponsor did not contribute to the design or development of the article and did not see the drafts or the final manuscript prior to submission. No grant numbers apply.

Disclosure

KC has received honoraria from, and served as a consultant for, Amgen, Astellas, Boehringer Ingelheim, Bayer, Janssen, Lily,
references


Annals of Oncology

Volume 26 | No. 10 | October 2015
doi:10.1093/annonc/mdv267


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