New agents for prostate cancer

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The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has been revolutionized by the arrival of multiple novel agents in the past 2 years. Immunotherapy in the form of sipuleucel-T, androgen axis inhibitors, including abiraterone acetate and enzalutamide, a chemotherapeutic agent, cabazitaxel, and a radiopharmaceutical, radium-223, have all yielded incremental extensions of survival and have been recently approved. A number of other agents appear promising in early studies, suggesting that the armamentarium against castrate-resistant prostate cancer is likely to continue to expand. Emerging androgen pathway inhibitors include androgen synthesis inhibitors (TAK700), anrogen receptor inhibitors (ARN-509, ODM-201), AR DNA binding domain inhibitors (EPI-001), selective AR downregulators or SARDs (AZD-3514), and agents that inhibit both androgen synthesis and receptor binding (TOK-001/galeterone). Promising immunotherapeutic agents include poxvirus vaccines and CTLA-4 inhibitor (ipilimumab). Biologic agents

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targeting the molecular drivers of disease are also being investigated as single agents, including cabozantinib (Met and VEGFR2 inhibitor) and tasquinimod (angiogenesis and immune modulatory agent). Despite the disappointing results seen from studies evaluating docetaxel in combination with other agents, including GVAX, anti-angiogenic agents (bevacizumab, afibercept, lenalidomide), a SRC kinase inhibitor (dasatinib), endothelin receptor antagonists (atrasentan, zibotentan), and high-dose calcitriol (DN-101), the results from the trial evaluating docetaxel in combination with the clusterin antagonist, custirsen, are eagerly awaited. New therapeutic hurdles consist of discovering new targets, understanding resistance mechanisms, the optimal sequencing and combinations of available agents, as well as biomarkers predictive for benefit. Novel agents targeting bone metastases are being developed following the success of zoledronic acid and denosumab. Finally, all of these modalities do not appear curative, suggesting that clinical trial enrollment and a better understanding of biology remain of paramount importance.

Key words: prostate cancer, novel agents

introduction

Until 2010, the only systemic regimen known to extend survival in men with metastatic castration-resistant prostate cancer (mCRPC) was docetaxel-based chemotherapy [1, 2]. Since April 2010, five new agents have been approved in the United States based on an extension of survival including sipuleucel-T, cabazitaxel, abiraterone acetate (AA), enzalutamide, and radium-223 [3–7]. Sipuleucel-T (for minimally symptomatic disease), radium-223 (for docetaxel-ineligible or post-docetaxel symptomatic bone metastases without visceral metastases), and AA are available for both chemo naive and post-docetaxel patients, while cabazitaxel and enzalutamide are currently available only for post-docetaxel patients in the United States.

Despite the dramatic expansion in the therapeutic armamentarium, all of the aforementioned agents provide incremental gains and extend median survival by 3–5 months. Hence, there is a need to better understand the biology of the disease and to develop more effective agents. This review highlights the ongoing efforts to make further gains, following the success of the first wave of new agents we have summarized earlier.

molecular mechanisms underlying prostate cancer growth, survival, and propagation

Prostate cancer is fueled by the androgen axis even after progression on androgen deprivation (Figure 1). Tumor growth occurs as a result of synthesis of sufficient amounts of intratumoral androgens to allow continued ligand-mediated activation of AR, or aberrant AR signaling [8]. Prostate cancer cells adapt to castration by intratumoral synthesis or conversion of adrenal androgens to testosterone and DHT and, subsequently, derive a growth advantage. Many enzymes involved in androgen synthesis are highly upregulated in castrate-resistant prostate cancer (CRPC) compared with those with androgen-sensitive prostate cancer [9]. The pivotal enzymes in androgen synthesis are among others the CYP17 enzymes (CYP17 hydroxylase and CYP17, 20 lyase), which catalyze the conversion of pregnenolone and progesterone to the weak androgens, dehydroepiandrosterone (DHEA) and androstenedione, respectively. Both DHEA and androstenedione are eventually converted to testosterone, and then to dihydrotestosterone (DHT), the most potent androgen. Recently, CRPC has been shown to express gain-of-stability mutation in 3ß-hydroxysteroid dehydrogenase type 1 (3ßHSD1), which mediates conversion of DHEA to DHT [10]. This gain of stability mutation renders 3ßHSD1 resistant to ubiquitination and degradation, resulting in its profound accumulation in the cytoplasm, leading to an accelerated conversion of DHEA to DHT, and persistent activation of AR.

Mechanisms underlying aberrant AR signaling include increased AR gene expression, either due to AR gene amplification, an increased rate of transcription of AR gene, or from the increased stability of the AR transcript [11, 12]. One emerging mechanism is AR gene rearrangement, resulting in constitutively active truncated AR splice variants (AR-Vs) [13]. AR-Vs lead to AR protein variants capable of mediating ligand-independent AR signaling. Less frequently, somatic mutations of AR are known to result in promiscuous ARs, which are activated by antiandrogens and other endogenous steroids (such as progesterone or deoxycorticosterone) [14, 15]. Sequencing studies have shown prevalence of mutation in both ligand binding and N-terminal domains of the AR coding region [15]. Using a reporter-based mutagenesis screen, a novel AR mutant (AR F876L) was recently identified in enzalutamide-sensitive cell lines, as well as xenografts models with prolonged exposure to enzalutamide [16]. Acquisition of AR F876L mutation converts enzalutamide and ARN-509 into AR agonist, and induces treatment resistance in vitro as well as in vivo [16–18]. Using structural modeling, it has been determined that AR F876L allows the repositioning of the helix in AR (helix 12) to an agonist-like conformation that permits coactivation recruitment when tumor cells are treated with enzalutamide. Interestingly, bicalutamide remained an antagonist in these AR-mutant cells. Most importantly, the Sawyer’s group has synthesized compounds (i.e. DR103) that might restore the position of helix 12 into the antagonist form which inhibited the growth of prostate cancer cell lines expressing both wild-type and F876L-mutant AR [16].

Other hallmark pathways of carcinogenesis may be invoked to aid ligand-independent aberrant AR signaling in prostate cancer progression [19]. For example the loss of tumor suppressor genes, p53 and PTEN, appears to be common and may drive multiple downstream pathways. An autopsy study of metastatic sites of heavily pretreated mCRPC demonstrated that proteins that interact with AR, such as the ERG gene fusion product, FOXA1, MLL2, UTX, and ASXL1, were mutated, although the overall mutation rate was low [20]. Additionally, stromal–epithelial crosstalk in the prostate cancer microenvironment has been implicated in the facilitation of prostate cancer progression [21]. These data establish the critical role of AR signaling and the selection for
aberrations in AR occurring in CRPC, and thus provide the rationale for targeting the androgen synthesis pathway, and components of aberrant AR signaling in its treatment. Pathways independent of the androgen-AR axis also may drive tumor growth [19]. For example the role of the microenvironment and immune system has been validated by improved outcomes with sipuleucel-T and radium-223.

**emerging androgen synthesis and signaling inhibitors**

**CYP17 inhibitors**

Orteronel (TAK-700) is a CYP17 inhibitor with more specificity for 17.20 lyase over 17 hydroxylase [22]. Following the promising phase I data in mCRPC, the phase II portion included four additional dose cohorts of chemonaive patients (300 mg b.i.d. without prednisone; higher doses with prednisone 5 mg b.i.d.) [22]. Serum prostate specific antigen (PSA) response rates at 12 weeks were 63%, 50%, 41%, and 60% in the 300 mg b.i.d., 400 and 600 mg b.i.d. + prednisone, and 600 mg qds groups, respectively. Of 51 patients with measurable disease, 10 had partial responses and 22 had stable disease (SD). Median testosterone and DHEA-sulfate (DHEA-S) levels decreased in all groups, but testosterone appeared to be a more reliable marker of lyase inhibition. Mean circulating tumor cells (CTCs) decreased from 16.6 to 3.9 per 7.5 ml at 12 weeks. The common grade ≥3 adverse events (AEs) were fatigue (12%) and hypokalemia (8%).

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**Figure 1.** Biology of castration-resistant prostate cancer and potential molecular targets for therapy.
In a separate phase II trial, 38 men with nonmetastatic CRPC were treated with orteronel 300 mg twice daily without corticosteroids [23]. At 3 months of treatment, the median serum testosterone declined by 89% to 0.78 ng/ml. The median serum ACTH increased by 171%, along with a decrease in median serum cortisol (21%), which remained within normal range. The median time to PSA progression and progression free survival (PFS) were both 13.8 months. The median serum PSA declined by 83%, and 32% of men achieved a PSA ≤0.2 ng/ml. One- and 2-year metastasis-free rates were 94% and 69%, respectively.

Despite these promising results, in a recently reported phase III trial of men with mCRPC with prior docetaxel therapy, treatment with TAK-700 plus prednisone did not meet the primary end point of improved OS when compared with the control arm, with prednisone alone (hazard ratio (HR) 0.894, P = 0.226). However, there was an advantage for TAK-700 plus prednisone for the secondary end point, radiographic PFS, over the control arm (HR 0.755, P = 0.00029). In addition, there were no safety concerns [24]. Notably, AA was approved while this trial was accruing patients, and post-trial treatment of these men with AA could have confounded the effect of TAK-700 on overall survival (OS). Another phase III trial in the pre-docetaxel setting has recently completed accrual (Table 1).

**VT-464 (Viamet), is a novel oral CYP17 inhibitor with a higher selectivity for 17, 20-lyase over 17-hydroxylase. In animal models, VT-464 induces androgen suppression without a concomitant increase of upstream steroids or cortisol suppression, thus providing the opportunity to be potentially used without concomitant steroids [25]. VT-464 is currently undergoing phase I development.**

**Androgen receptor inhibitors**

**ARN-509.** Like enzalutamide, ARN-509 is an oral novel AR antagonist that binds to AR, and blocks nuclear translocation of AR, binding of AR to androgen response elements, and recruitment of coactivators by the AR. In a murine xenograft model of mCRPC, ARN-509 showed greater antitumor activity than enzalutamide, for a given dose and plasma concentration. Furthermore, ARN-509 achieved significantly lower steady-state brain levels than those observed with enzalutamide, suggesting its lower seizurogenic potential [26]. A phase I trial accrued 30 men with mCRPC and reported promising activity of ARN-509 [27]. At 12 weeks, 42% of patients displayed ≥50% PSA declines and fluoro-dihydro-testosterone (FDHT)-PET imaging demonstrated AR blockade at 4 weeks across multiple doses. ARN-509 was safe and exhibited linear pharmacokinetics. A phase II evaluation showed that at 12 weeks, the PSA response was 91% in therapy-naïve and 60% in post-AA mCRPC patients and 89.5% in nonmetastatic CRPC patients [28, 29]. A phase III trial of ARN-509 is currently accruing men with nonmetastatic CRPC (Table 1).

**ODM-201.** This is a novel pure oral AR antagonist that does not penetrate the blood–brain barrier in preclinical models. In a phase I/II study, treatment with ODM-201 was well tolerated and was associated with a high activity in mCRPC, including those with prior treatment with docetaxel and a CYP17 inhibitor [30]. Overall, 136 patients were accrued (phase I: 24; phase II: 112). No dose-limiting toxicity was found in the phase I part. Seventy-eight of 108 (70%) assessable patients experienced a PSA decline during the first 12 weeks, including a >50% PSA drop in 44 of 108 (41%). No seizures were observed.

**AZD3514.** This is an oral drug which inhibits AR signaling through two distinct mechanisms, an inhibition of ligand-driven nuclear translocation of AR, and downregulation of androgen receptor levels. Preclinically, AZD3514 has been shown to have antitumor activity in both androgen-sensitive and castration-resistant prostate tumors [31]. In a first-in-man phase I trial, 49 men with CRPC were treated with escalating dose levels of AZD3514 [32]. Encouraging responses were seen, even in those with prior disease progression on AA, including: PSA decline of ≥30% in 11 of 49 (23%), PSA decline of ≥50% in 7 of 49 (14%), and objective soft tissue responses in 2 of 26 (8%) men with measurable disease. The most common toxicities were nausea and vomiting, and were manageable with oral antiemetics. None met the definition of dose limiting toxicity.

**EPI-001.** The N-terminal domain (NTD) is essential for transcriptional activity of the AR. EPI-001 covalently binds to the NTD, inhibits protein–protein interactions necessary for transcriptional activity of the AR and its splice variants, and reduces the growth of CRPC in xenografts. EPI-001, which is currently awaiting clinical development, has the potential to be efficacious in CRPC progressing on treatment with enzalutamide, where AR-Vs are believed to play an increasing role as driver of tumor progression [33].

These novel androgen receptor inhibitors have the potential to provide valuable additional therapeutic options, owing to their varied mechanism of actions, and possibly nonoverlapping adverse effect profiles.

**Dual androgen synthesis and signaling inhibitor**

**TOK-001 (galeterone) is an oral steroid analog that concomitantly inhibits CYP17, binds with and inhibits AR, and reduces AR levels. In a phase I study of chemo-naïve men with CRPC, TOK-001 was well tolerated and demonstrated clinical activity. Of 49 patients, 22% demonstrated a >50% PSA decline and an additional 26% had PSA declines of 30%–50% [34]. Based on these preliminary results, a phase II study is currently accruing patients with CRPC (Table 1).**

**Individualized development of androgen synthesis inhibitors**

The TMPRSS2–ERG fusion gene, a fusion of the ETS transcription factor family gene (ERG), with the promoter of the highly expressed transmembrane protease serine 2 (TMPRSS2) gene, is the most frequent genomic rearrangement found in prostate cancer, and may contribute to the progression of prostate cancer, despite low androgen levels [35]. Concordance has been shown between ERG gene status in primary treatment-naïve tumor tissue, fresh CRPC biopsies, and the CTCs, suggesting that rearrangement of ERG may be an earlier event in prostate carcinogenesis [36]. The TMPRSS2–ERG fusion usually results in the merging of TMPRSS2 exon 1 or 2 sequences to exon 2, 3, or 4 ERG sequences, with frequent deletion of the chromosomal region between TMPRSS2 and ERG on chromosome 21 [37]. In a cohort of 445 conservatively managed patients with prostate cancer, ERG status was predictive of cause-specific survival [37].
Table 1. Ongoing phase III trials investigating novel agents for mCRPC

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Arms</th>
<th>Population</th>
<th>Primary end point</th>
<th>Comments</th>
<th>Clinical trial ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17</td>
<td>TAK-700 + P Placebo + P</td>
<td>Docetaxel pretreated</td>
<td>OS</td>
<td>Preliminary results showed no improvement in the primary end point of OS, but significant improvement in rPFS (a secondary end point). Post-trial treatment with abiraterone may have confounded OS data.</td>
<td>NCT01193257</td>
</tr>
<tr>
<td>CYP17,17.20 lyase activity</td>
<td>TAK-700 + P versus Placebo + P</td>
<td>Chemonaive</td>
<td>OS, rPFS</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT01193244</td>
</tr>
<tr>
<td>AR</td>
<td>ARN-509 Placebo</td>
<td>Chemonaive</td>
<td>OS, PFS</td>
<td>Results showed significant improvement in the primary endpoints of OS, and rPFS.</td>
<td>PREVAIL NCT01212991</td>
</tr>
<tr>
<td>Clusterin mRNA</td>
<td>Custirsen + CBZ-P Placebo + CBZ-P</td>
<td>Nonmetastatic chemonaivea</td>
<td>Metastasis-free survival</td>
<td>Accrual: ongoing</td>
<td>SATURN NCT01083615</td>
</tr>
<tr>
<td>Clusterin mRNA</td>
<td>Custirsen + DP Placebo + DP</td>
<td>Chemonaive</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>SYNERGY NCT01188187</td>
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<td>Immune response</td>
<td>PROSTVAC ± GM-CSF versus placebo</td>
<td>Asymptomatic or minimally symptomatic chemonaive disease</td>
<td>OS</td>
<td>Accrual: ongoing.</td>
<td>PROSPECT NCT01322490</td>
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<td>c-MET and VEGFR2</td>
<td>Cabozantinib Prednisone</td>
<td>Docetaxel and abiraterone pretreated relatively asymptomatic disease</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT01605227</td>
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<tr>
<td>c-MET and VEGFR2</td>
<td>Cabozantinib MP</td>
<td>Docetaxel and abiraterone pretreated symptomatic disease</td>
<td>Pain response</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT01522443</td>
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<tr>
<td>Src-family kinases</td>
<td>Dasatinib + DP Placebo + DP</td>
<td>Chemonaive disease</td>
<td>OS</td>
<td>Results showed no improvement in OS, the primary end point.</td>
<td>READY NCT00744497</td>
</tr>
<tr>
<td>Immune-modulatory protein S100A9</td>
<td>Tasquinimod Placebo</td>
<td>Asymptomatic or minimally symptomatic chemonaive disease</td>
<td>PFS</td>
<td>Accrual: completed; results: pending.</td>
<td>NCT01234311</td>
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<tr>
<td>Immune-modulatory protein S100A9</td>
<td>Ipilimumab Placebo, (following a single dose of radiotherapy)</td>
<td>Docetaxel pretreated stable disease</td>
<td>PFS</td>
<td>Currently accruing.</td>
<td>NCT01732549</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab Placebo, (following a single dose of radiotherapy)</td>
<td>Asymptomatic or minimally symptomatic chemonaive disease</td>
<td>OS</td>
<td>Preliminary results showed no improvement in OS, the primary end point. Prespecified subset analyses suggested improved efficacy of ipilimumab in men with lower disease burden.</td>
<td>NCT00861614</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab Placebo, (following a single dose of radiotherapy)</td>
<td>Asymptomatic or minimally symptomatic chemonaive disease</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>CA-184-095 NCT01057810</td>
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<tr>
<td>Microtubules</td>
<td>CBZ-P</td>
<td>Chemonaive disease</td>
<td>OS</td>
<td>Accrual: completed; results: pending.</td>
<td>FIRSTANA NCT01308567</td>
</tr>
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</table>

mCRPC, metastatic castration-resistant prostate cancer; P, prednisone; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival; D, docetaxel; M, mitoxantrone; CBZ, cabazitaxel; P, prednisone; VEGFR, vascular endothelial growth factor receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4.

*aOnly trial in nonmetastatic castration-resistant prostate cancer setting.
Prostate cancers with no ERG alterations showed favorable cause-specific survival (90% survival at 8 years). In contrast, prostate cancer with 2+Edel (duplication of retained 3′-ERG and concomitant deletion of 5′-ERG sequences) exhibited poor cause-specific survival (HR = 6.10, 95% confidence interval 3.33–11.15, P < 0.0001, 25% survival at 8 years). Other categories of ERG alteration (Edel and Espplit) were associated with intermediate or good prognosis. These findings were further validated in the COU-AA-302 phase III trial where 1195 chemonaive men with mCRPC were randomized in a 2:1 ratio to receive AA with prednisone versus prednisone alone [38]. Men who received AA with prednisone and who had 2+Edel prostate tumors, had a significantly improved radiographic PFS and time to PSA progression, compared with those with ERG nonarranged tumors. However, ERG rearrangement status did not correlate with outcome in the control arm. These data suggest that 2+Edel status may predict response to AA in chemonaive patients with mCRPC.

COU-AA-301 was a randomized, phase III trial comparing AA plus prednisone (n = 797) versus placebo plus prednisone (n = 398) in men with mCRPC, with prior docetaxel treatment. In a retrospective study of men enrolled on the COU-AA-301 trial, clinical parameters were analyzed for association with OS through a univariate Cox proportional hazards regression model [39]. Following clinical parameters were significantly correlated with a poor prognosis: Eastern Cooperative Oncology Group (ECOG) performance status of 2, presence of liver metastases, time from start of initial luteinizing hormone releasing hormone (LHRH) agonist therapy to start of AA treatment of ≤36 months, low albumin, high alkaline phosphatase, and high lactate dehydrogenase (LDH) levels. In a previous analysis of this trial, baseline serum androgen levels were prognostic for OS, but not predictive for benefit from AA [40].

emerging immunotherapeutic agents

poxvirus-based vaccines

Vaccinia viruses have been extensively studied, due to their ease of production and feasibility of integrating tumor DNA into their genome. Fowlpox viruses have been used in sequence with vaccinia viruses to produce radiation-enhancing vaccines. Vaccinia viruses have been extensively studied, due to their ease of production and the possibility of integrating tumor DNA into their genome. Fowlpox viruses have been used in sequence with vaccinia viruses to produce radiation-enhancing vaccines. Vaccinia viruses have been extensively studied, due to their ease of production and the possibility of integrating tumor DNA into their genome. Fowlpox viruses have been used in sequence with vaccinia viruses to produce radiation-enhancing vaccines.

Ipilimumab is a fully human monoclonal antibody that inhibits CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), a surface T-cell checkpoint receptor, and is approved for melanomas [42]. In the setting of mCRPC, a phase I/II trial explored ipilimumab as monotherapy and in combination with radiotherapy [43]. Use of radiotherapy was based on the preclinical data suggesting that radiation enhances immune response by upregulation of tumor antigens [44–47]. In the dose escalation stage, 33 patients (≥60 cohort) received ipilimumab with or without radiotherapy. Of these, the 10-mg/kg cohorts were expanded to 50 patients (ipilimumab monotherapy (n = 16), and ipilimumab + radiotherapy (n = 34). Common immune-related AEs (irAEs) among the 50 patients receiving 10 mg/kg ± radiotherapy were diarrhea (54%), colitis (22%), rash (32%), and pruritus (20%). Of these, grade 3 or 4 irAEs included colitis (16%) and hepatitis (10%). Among patients receiving 10 mg/kg ± radiotherapy (n = 46), eight had PSA declines of ≥50% lasting for 3 to >13 months. Among 28 tumor assessable patients, 1 had complete response (time to response 2.5 months, censored at 11.3 months), and 6 had SD lasting for 2.8–6.1 months.

Two large placebo-controlled phase III trials of ipilimumab, preceded by radiotherapy, have completed accrual in chemonaive or post-docetaxel mCRPC patients. Results of the phase III trial in post-docetaxel mCRPC setting were recently reported. Men were randomized (1:1) to receive bone-directed radiotherapy at 8 Gy before either 10 mg/kg ipilimumab (n = 399) or placebo (n = 400) every 3 weeks for four doses, followed by one dose every 3 months [48]. The primary end point was OS. In the intent-to-treat analysis (n = 799), median OS with ipilimumab was not significantly improved compared with that with placebo (11.2 versus 10 months; HR = 0.85; 95% CI 0.72–1.00; P = 0.053). Treatment-related AEs were common and were mostly immune-related, as reported previously [42]. Prespecified subset analyses showed that ipilimumab may be most active in men with lower disease burden, which suggest that immunotherapy should be tested early in men with CRPC. Furthermore, optimal patient selection and appropriate follow-up even after progression are critical for trials evaluating vaccines and other immunotherapeutic agents for CRPC [49].

antibody conjugates

The naked anti-PSMA antibody, J591, has demonstrated marginal antitumor activity [50]. Radioimmunoconjugates of J591 and radio-pharmaceuticals (Y-90, Lu-177) have demonstrated more promising activity and tolerable thrombocytopenia [51–55]. An ongoing phase II trial is evaluating 127Lu-J591 in nonmetastatic CRPC with rapidly rising PSA (PSA-DT <8 months and PSA ≥2 ng/ml) and/ or PSA ≥20 ng/ml. Additionally, antibody-drug conjugates targeting six-transmembrane epithelial antigen of the prostate (STEAP)-1 or PSMA linked to the potent antimitotic agent, MMAE, exhibited anti-tumor activity in recent phase I trials [56, 57].

agents targeting metastasis, invasion, angiogenesis, proliferation, and cell survival

Hepatocyte growth factor (HGF) and its receptor c-Met are over expressed in prostate cancer and promote metastasis. The HGF...
often acts synergistically with vascular endothelial growth factor (VEGF) on endothelial cells, as well as several other cellular signaling pathways, including Ras/MEK pathway and PI3K/AKT pathway [58, 59]. Cabozantinib (XL-184) inhibits receptor tyrosine kinases of c-MET and VEGF, in addition to those of RET, KIT, AXL, and FLT3. In a phase II trial, of 171 men with mCRPC treated with cabozantinib, 87% had bone metastasis, and 43% were docetaxel pretreated. Activity was particularly promising in the bone metastasis context, with 68% of patients showing complete or partial resolution of lesions on bone scan, and 67% of men showing improvement in pain [60]. In a retrospective analysis, ≥30% reduction in bone scan lesion area, CTC conversion (>5 to ≤4/7.5 ml of blood), and improved pain intensity after 6 weeks of treatment with cabozantinib, was associated with an OS benefit [61]. Treatment with cabozantinib frequently correlated with diminished FDHT uptake. Interestingly, these declines were matched by diminished FDG PET/CT uptake only 50%–60% of the time, and correlated even less frequently with PSA declines [62]. Cabozantinib is currently being evaluated in two phase III trials dedicated to docetaxel-pretreated patients (Table 1).

Custirsen (OGX-011) is an antisense oligonucleotide that targets clusterin, a chaperone, stress-induced protein, which may be responsible for resistance to docetaxel. In a randomized phase II trial, weekly i.v. custirsen plus docetaxel extended median survival compared with docetaxel alone (23.8 versus 16.9 months) [63]. Based on these promising data, separate phase III trials are evaluating custirsen in combination with docetaxel or cabazitaxel (Table 1).

Heat Shock Protein 27 (Hsp27) chaperones AR, which enhances transactivation of AR-regulated genes. OGX-427 is a second generation antisense agent that inhibits Hsp27 expression [64]. In a randomized phase II trial, chemonaive patients with minimal or no symptoms were randomized to receive OGX-427 with prednisone 5 mg PO b.i.d., or prednisone only. Preliminarily, among 44 randomized patients, 12 of 17 (71%) OGX427-treated patients were progression free at 12 weeks compared with 6 of 15 (40%) prednisone alone patients. A ≥50% PSA decline occurred in 11 of 22 (50%) versus 4 of 20 (20%), and measurable disease response occurred in 4 of 9 (44%) versus 0 of 12 patients. Moreover, favorable CTC conversion occurred in 12 of 22 (55%) versus 7 of 17 (41%) patients. Another phase II trial is evaluating the antitumor effects of OGX-427 in continuing AA and prednisone treatment in men with mCRPC who have PSA progression [65]. The addition of OGX-427 is expected to restore sensitivity to AA and improve survival outcomes. Ganetespib is a novel small molecule inhibitor of Hsp90 with promising activity in prostate cancer cell lines. However, as a single agent, ganetespib did not improve PFS in a phase II trial in metastatic CPRC [66]. Combination therapy is being considered.

Tasquinimod is an oral quinoline-3-carboxamide derivative with both antiangiogenic (upregulates thrombospondin) and immunomodulatory properties (targets S100A9 [MRP-14], which is expressed on myeloid-derived suppressor cells). In a randomized placebo-controlled, randomized phase II trial in chemonaive patients, tasquinimod demonstrated an improvement in median PFS (7.6 versus 3.3 months) [67]. A phase III placebo-controlled trial is evaluating tasquinimod as maintenance therapy in docetaxel-responding patients (Table 1).

LHRH-R, the receptor for LHRH, is highly expressed on CRPC cells, and thus is a potential target for drug development. AEZS-108 is a LHRH-cytotoxic hybrid in which doxorubicin is linked to a LHRH agonist, and may have promise as a more efficacious and less toxic therapy in tumor-expressing receptors for LHRH than standard systemic chemotherapy. AEZS-108 has shown promising clinical activity in a phase I trial, and a phase II trial of AEZS-108 is currently accruing [68].

**continuing role for chemotherapeutic agents**

The success of cabazitaxel, following docetaxel, may warrant the continued evaluation of chemotherapeutic agents for mCRPC [4]. An ongoing phase III trial is comparing cabazitaxel with docetaxel, which may potentially change the choice of first-line chemotherapy (Table 1). Recently, an ECOG sponsored phase III trial (CHAARTED Trial) was reported in a media release (December 5, 2013) to demonstrate an extension of survival with a combination of androgen deprivation therapy (ADT) and upfront docetaxel therapy compared to ADT alone in men with metastatic high volume castration-sensitive prostate cancer [69]. Additionally, patients with progression following novel androgen inhibitors appear to be poorly responsive to docetaxel, suggesting the need for better chemotherapy in this setting [70]. In this retrospective study, docetaxel resulted in a PSA decline of ≥50% in only nine patients (26%). The median OS was 12.5 months and all patients who failed to achieve a PSA fall on abiraterone and were deemed abiraterone-refractory were also docetaxel-refractory (n = 8) [70]. The proper sequencing of chemotherapy and androgen inhibitors also requires further study given the absence of validated predictive biomarkers. Retrospective studies suggest that the sequence of androgen inhibitors following second-line cabazitaxel chemotherapy may allow the exposure to more lines of therapy and potentially yield longer survival [71–73].

Eribulin mesylate, a nontaxane halichondrin B analog microtubule inhibitor, has demonstrated activity in CRPC, is accompanied by an excellent toxicity profile, and does not require steroid premedication [74]. In a single-arm phase II trial, 108 men with mCRPC were treated with eribulin mesylate. PSA decreases of ≥50% were achieved in 22.4% and 8.5% of taxane-naïve (n = 58) and taxane-exposed (n = 50) patients, respectively. Neutropenia was the most common grade 3/4 AE, seen in 22.4% of taxane-naïve and 40% of taxane-exposed men. Grade 3 peripheral neuropathy was not seen in any taxane-naïve patient, and occurred in only 6% of taxane-pretreated patients, [74]. A role for the development of more potent platinum drugs with a better therapeutic index may be warranted, alone or in combination with taxanes.

**conclusion**

All of the therapeutic advances in mCRPC have conferred incremental gains and the disease remains incurable. The biology and mechanisms of resistance appear heterogeneous. Furthermore, advances are required in the objective measurement of disease.
burden and the identification of predictive biomarkers. While the Prostate Cancer Working Group (PCWG)-2 guidelines provide a framework, novel imaging techniques are imperative for intermediate measures of disease volume [75]. In the setting of immunotherapy, guidelines endorse the assessment of tumor burden as a continuous variable considering index, as well as new lesions [76, 77]. CTC alterations appear useful in the setting of chemotherapy and AA, but require validation in the context of other classes of agents, and to switch therapy [78, 79].

Until the discovery of validated molecular biomarkers predictive for the efficacy of specific agents, an attempt to sequentially administer all agents known to extend survival is likely prudent. No effort should be spared in providing access to clinical trials evaluating promising new agents. Indeed, phase II trials are evaluating rational combinations of biologic agents based on a better understanding of tumor biology, which may lead to phase III trials.

disclosure

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Prophylaxis of infectious complications with colony-stimulating factors in adult cancer patients undergoing chemotherapy—evidence-based guidelines from the Infectious Diseases Working Party AGIHO of the German Society for Haematology and Medical Oncology (DGHO)

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Background: Current evidence on myelopoietic growth factors is difficult to overview for the practicing haematologist/oncologist. International guidelines are sometimes conflicting, exclude certain patient groups, or cannot directly be applied to the German health system. This guideline by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO) gives evidence-based recommendations for the use of G-CSF, pegylated G-CSF, and biosimilars to prevent infectious complications in cancer patients undergoing chemotherapy, including those with haematological malignancies.

Methods: We systematically searched and evaluated current evidence. An expert panel discussed the results and recommendations. We then compared our recommendations to current international guidelines.

Results: We summarised the data from eligible studies in evidence tables, developed recommendations for different entities and risk groups.

Conclusion: Comprehensive literature search and expert panel consensus confirmed many key recommendations given by international guidelines. Evidence for growth factors during acute myeloid leukaemia induction chemotherapy and pegfilgrastim use in haematological malignancies was rated lower compared with other guidelines.

Key words: cancer, evidence-based guideline, febrile neutropenia, G-CSF, infection, supportive care

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