Clinical Perspective

Issues and unmet needs in advanced prostate cancer

Koen Slabbaert¹,² & Hein Van Poppel*²

Practice Points

- Luteinizing hormone-releasing hormone-agonists and -antagonists are the mainstay of advanced prostate cancer.
- If a patient has prostate-specific antigen-progression with castration-resistant prostate cancer, we now have new hormonal therapeutic possibilities to control the androgen receptor.
- Several new therapeutic agents have been developed and are already available or are used in Phase III trials: these are luteinizing hormone-releasing hormone antagonists, which give a faster decline in testosterone without testosterone surge, abiraterone and MDV3100.
- Cabazitaxel is the new drug in chemotherapy for castration-resistant prostate cancer. It is more powerful compared to mitoxantrone and docetaxel, and it is US FDA approved as second-line chemotherapy in metastatic castration-resistant prostate-cancer patients who have failed to improve on docetaxel.
- Since these new drugs are available, luteinizing hormone-releasing hormone-agonists or -antagonists can be offered with antiandrogens, followed by Sipuleucel-T and docetaxel, and even after docetaxel failure cabazitaxel or abiraterone are available.

SUMMARY The development of new therapeutic agents in advanced prostate cancer has developed in past years. Several new drugs have been created and find their place in between the classic luteinizing hormone-releasing hormone-agonists, antiandrogens and chemotherapeutic agents. The demand for new drugs was especially high because of the poor prognosis for patients with castration-resistant prostate cancer. Degarelix, abiraterone, TAK-700 (orteronel), cabazitaxel, Sipuleucel-T and MDV3100 are examples of new drugs that give hope of better survival for prostate cancer patients.

¹R.Z. Tienen, Department of Urology, Kliniekstraat 45, 3300 Tienen, Belgium
²U.Z. Gasthuisberg – Department of Urology, Herestraat 49, 3000 Leuven, Belgium
*Author for correspondence: Tel.: +32 16 34 69 30; Fax: +32 16 34 69 31; hendrik.vanpoppel@uzleuven.be
Prostate cancer is the most prevalent cancer in males and the second cause of cancer-related death. Prostate cancer is caused by an androgen-dependent tumor and in metastatic disease the first treatment step is to use hormonal therapy.

The past & the present
Since prostate cancer screening with digital rectal examination and prostate-specific antigen (PSA) testing has been widespread in the last 20 years, it has been possible to detect more cases of prostate cancer at an early stage, which in most incidences can be cured by surgery or radiotherapy. In selected cases with localized small volume and well- or medium-differentiated prostate tumors, active surveillance can be an option. Recently, there has been a paradigm shift in the management of locally advanced prostate cancer with the application of radical surgery with extended lymph node resection instead of radiotherapy combined with hormonal therapy. While years ago surgery was cancelled when an invaded lymph node was found, nowadays extensive radical surgery with an extended lymph node dissection is proposed with a better outcome and improved progression-free and cancer-specific survival could be an option. Recently, there has been a paradigm shift in the management of locally advanced prostate cancer with the application of radical surgery with extended lymph node resection instead of radiotherapy combined with hormonal therapy.

As with other oncological diseases we have noticed a quick progression in the development of new therapeutic agents in the treatment of advanced prostate cancer in the past 10 years. Until a few years ago we only had the luteinizing hormone-releasing hormone (LHRH)-agonists (which have been used since 1984) and the steroidal and nonsteroidal antiandrogens (AAs). The estrogens, with the synthetic version diethylstilbestrol, and orchietomy were used in the past but the estrogens had too many side-effects, such as higher cardiovascular (CV) morbidity and mortality. Before the LHRH-agonists became available a bilateral subcapsular orchietomy was performed in metastatic disease, but it was an irreversible treatment. The potential reversibility of the LHRH-agonists has led to its success and its worldwide use. However, there are disadvantages with the use of the agonists, such as the testosterone surge at initiation and the microsurges at each subsequent injection. On the other hand, surgical castration was very efficient in the short term: within 3 h after the surgical procedure the testosterone level dropped below castrate level [3].

Most patients with advanced prostate cancer will experience a good response to the androgen deprivation therapy (ADT), but the response is not durable; this is dependent upon several factors, but mostly on the aggressiveness of the prostate cancer, translated by a higher Gleason score. In 2002 a meta-analysis published in Cancer, including almost 7000 patients showed no statistical significant difference in survival after 2 years of follow-up comparing patients treated with combined androgen blockade versus patients treated with monotherapy, but at 5 years there was a statistically significant difference in favor of combined androgen blockade [4].

Eventually all patients will develop hormone-refractory prostate cancer, nowadays called castration-resistant prostate cancer (CRPC). This status of a castrated man should be confirmed by a castrate serum testosterone level (testosterone <50 ng/dl or <1.7 nmol/l) and three consecutive PSA rises – at least more than 50% of the nadir level – measured with at least a 2-week interval in patients who stopped any nonsteroidal AA at least 4–6 weeks before the first PSA rise. This definition is according to the 2011 EAU guidelines on prostate cancer but is not the only standard definition for CRPC. Many trials used any serial increase, and a greater than 25% increase in PSA is sometimes used to initiate a new therapy because it correlates with poor outcome.

The side effects of ADT are well known: in the short term, erectile dysfunction, loss of libido and hot flashes; in the long-term, osteoporosis, loss of muscle mass, sarcopenic obesity, tiredness, anemia, gynecomastia, diabetes, CV disease, depression and other psychological effects. Despite the increased CV morbidity, the American Heart Association stated that candidates for ADT who have known cardiac problems do not need to be referred to an internist prior to treatment and they need no specific testing. The decision to give ADT is most appropriately made by physicians administering ADT, and patients receiving ADT should see primary-care physicians for periodic evaluation [9].

In most cases hormonal therapy is given continuously, but one can also give it as an intermittent treatment [6]. Since the 1980s
many urologists have used intermittent androgen suppression (IAS) to reduce the adverse effects of continuous androgen deprivation. The latest reports on SWOG (subanalysis) and SEUG trials have shown that it is equal to continuous androgen suppression (CAD) when comparing time to castration resistance and cancer-specific survival, but it has less adverse effects, it provides a better quality of life, especially for sexual function, and the cost is lower. The initial (induction) cycle must last between 6 and 9 months, otherwise testosterone recovery is unlikely. At the ASCO meeting of 2011 a Phase III randomized trial of intermittent versus CAD for PSA progression after radical therapy was presented. In this trial the researchers compared overall survival (OS) in both groups as primary end point. Secondary end points were quality of life, hormone resistance, cholesterol/HDL/LDL, length of nontreatment periods, testosterone-levels and potency recovery. Concerning OS there was no difference between IAS and CAD, but IAS patients had a better quality of life in physical function, a decrease in fatigue, urinary problems and hot flashes, and an increase in desire for sexual activity and erectile function. The time-to-progression to hormone resistance was significantly longer in the IAS arm [7].

A few questions remain unanswered: how to select the right patients for this therapy? What is the optimal duration of the therapy? And when to restart therapy after the off-period? There are a few trials where treatment was resumed if the PSA rose over 10 ng/ml and was stopped when it decreased to less than 4 ng/ml [8,9].

ADT is effective as long as the PSA levels are low and serum testosterone is below castration level, which means less than 50 ng/dl. If there is PSA progression when a patient is on monotherapy with either an AA or with a LHRH-agonist, most patients respond to complete androgen blockade (AA + LHRH-agonist) for a few months to a few years, depending on the aggressiveness of the tumor. If there is progression on one AA it is possible to switch to another AA, and sometimes changing the LHRH-analog can also yield a temporary lowering of the PSA level [10]. If the patient has PSA progression on complete androgen blockade (AA + LHRH-agonist) one can stop the AA and obtain an AA withdrawal effect in 15–40% of cases, lasting between 3 and 12 months [11–13].

The present & the future

LHRH-agonists: degarelix & abarelix

In 2001–2002 a new, potent and long-acting gonadotropin-releasing hormone (GnRH) antagonist (degarelix) was developed and tested [14]. At the time, abarelix was another FDA-approved pure LHRH-antagonist, but its administration was reported to give significant allergic reactions and anaphylaxis in a small number of patients [15]. GnRH-antagonists differ from the agonists by directly blocking of the GnRH receptor. The advantage of this medication is that there is no testosterone surge as seen with the LHRH-agonists, thus avoiding a potential clinical flare. This can be important in patients with extensive bone metastases and/or threatening spinal cord compression, or very advanced local disease with possible bladder outlet obstruction. The disadvantage for the LHRH-antagonists that are currently available is that they need to be administered monthly, while for LHRH-agonists, 3 and 6 months depot preparations are available. Degarelix was extensively tested in Phase III trials and became available for patients at the end of 2010. In Phase III randomized controlled trials, degarelix was compared with monthly leuprolide: it was safe and there was no flare. Because there is no flare, there’s no need for an oral nonsteroidal AA at initiation of the treatment with degarelix. The GnRH antagonist was shown to provoke an immediate and sustained drop in serum testosterone, comparable to surgical castration, and a more rapid and prolonged decrease of PSA.

Chemotherapy: mitoxantrone, paclitaxel, docetaxel & cabazitaxel

When a patient is at the CRPC stage one might consider chemotherapy. The patient still remains on LHRH. Many medical oncologists will prefer to wait to start chemotherapy until the patient becomes symptomatic. Chemotherapy with mitoxantrone and prednisone have never shown a survival benefit, but had an obvious palliative benefit on the symptoms. The median life expectancy for this group was only 12–18 months, but newer taxane-based chemotherapy has become available and other new drugs that proved to be efficacious in taxotere-resistant patients are under investigation to be used at an earlier stage to delay chemotherapy.

Mitoxantrone with prednisone gave a statistically significant improvement in pain relief, had
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quite a high PSA response rate and a longer time-to-progression but did not have a longer OS [16]. Taxanes such as paclitaxel and docetaxel were shown to have a PSA response in the range of 40 to 70%. Docetaxel combined with estramustine showed a PSA-response rate of 74% [17], whereas paclitaxel combined with estramustine gave a lower PSA-response rate of 48% and paclitaxel alone gave only 25% of PSA-response rate [18]. In this context docetaxel is more potent compared with paclitaxel. The best survival gain was seen in the 3-weekly regime of docetaxel. A weekly docetaxel scheme was not better in terms of survival compared with mitoxantrone. A concept of intermittent docetaxel is an option, and at present there is no consensus about the number of cycles: in most studies 10–12 cycles are administered in a 3-weekly regimen. Docetaxel every 3 weeks also improved response rates in terms of pain and quality of life [19]. Another Phase III trial from the South-West Oncology Group (9916) was reported at about the same time, confirming these results. There were two study arms: estramustine and docetaxel or mitoxantrone and prednisone. There was an improvement in OS in the docetaxel and estramustine arm compared with the mitoxantrone arm [20]. And thus docetaxel with prednisone became the standard chemotherapy for CRPC.

In 2010, cabazitaxel, a new taxoid, demonstrated a better OS compared with mitoxantrone in a patient group with progressive disease after administration of docetaxel and was therefore recently approved by the FDA [21]. Cabazitaxel is a third generation taxane drug. In the TROPIC-trial cabazitaxel plus prednisone was compared with mitoxantrone plus prednisone in docetaxel-refractory prostate cancer patients [21]. Response Evaluation Criteria In Solid Tumors (RECIST) was used to define progression in patients with measurable disease on a CT-scan, or by two consecutive PSA rises at least one week apart. All patients received 10 mg oral prednisone daily. The primary end point was OS, the second end point was progression-free survival (PFS). In the cabazitaxel group the median survival was 15.1 versus 12.7 months in the mitoxantrone group: median survival benefit was 2.4 months. Median PFS was 2.8 months in the cabazitaxel group and 1.4 months in the mitoxantrone group. Side effects of cabazitaxel are neutropenia and diarrhea. Death due to myelosuppression was observed in 5% of patients in the cabazitaxel arm compared with 2% in the mitoxantrone arm. The FDA approved cabazitaxel as a second-line chemotherapy in metastatic CRPC (mCRPC) patients who have failed on docetaxel.

 Immunotherapeutic drugs

The field of CRPC is now rapidly changing with the development of new drugs: Sipuleucel-T (Dendreon, WA, USA), ipilimumab and ProstVac® as immunotherapeutic agents, and abiraterone acetate, MDV 3100 and TAK-700 (orteronel) as new hormonal therapies.

Sipuleucel-T is an immunotherapeutic drug. A vaccine is created from the patients’ autologous peripheral blood mononuclear cells, isolated by leukapheresis, and is then reinfused to induce an effective immune response against human prostatic acid phosphatase, an antigen that is highly expressed in prostate cancer tissue. There have been three randomized, double-blind, controlled, multicenter Phase III studies which have shown an OS benefit of approximately 4 months. The first two studies enrolled 225 patients with asymptomatic mCRPC [22,23]. The third study, called the IMPACT-study enrolled 512 patients with asymptomatic or minimally symptomatic mCRPC [24]. All patients needed to stop corticosteroids 4 weeks prior to study entry. The observed side effects were mild including chills, fever and flu-like syndrome. In the first two studies by Small and Higano an analysis showed a median survival benefit of 4.3 months [22,23]. In the IMPACT trial (Kantoff et al.), the median survival benefit was 4.1 months in the patient group treated with Sipuleucel-T compared with placebo; median survival was 25.8 months in the Sipuleucel-T group versus 21.7 months in the placebo group [24]. The 3-year survival probability was 31.7% in the Sipuleucel-T group versus 23.0% in the placebo group. There was almost no PSA response (2.6%) and no difference in the time to objective disease progression between the two groups. Sipuleucel-T was approved by the FDA because of the results of the IMPACT trial with a survival benefit of 4 months in the group that received Sipuleucel-T in a large chemonaive patient group with mCRPC. In 2010 and 2011 new trials with other forms of immunotherapy like a poxviral-based PSA-targeted vaccine (PROSTVAC-VF) and ipilimumab have been started. Kantoff et al. showed a median survival benefit of 8.5 months in a Phase II trial with PROSTVAC-VF and an extended 3-year
survival [29]. A Phase III study with PROSTVAC-Tricom poxvirus-based prostate cancer 'vaccine' is planned in men with CRPC.

**New hormonal therapies**

In the domain of endocrine treatments we mention the development of abiraterone acetate, TAK-700 and MDV 3100. At the stage of CRPC, it became clear that the tumor remains hormone driven: extragonadal synthesis of androgens including the intratumoral biosynthesis of androgens must contribute to progression of CRPC. For that reason targeting the androgen receptor can help to maintain the disease control. CYP17 is an enzyme that controls two key reactions in the biosynthesis of androgens and estrogens. Abiraterone is a selective cytochrome P450 17 inhibitor. MDV3100 is a new antagonist of the androgen receptor and a second generation AA. Furthermore TAK-700 and TOK-001 are now being studied in clinical trials.

After having shown promising results in Phase I and II trials, abiraterone acetate – a potent, selective and orally available CYP17 inhibitor – was tested in Phase III trials in men with progression after docetaxel-based chemotherapy as well as with chemo-naive CRPC. Approximately 1200 patients were randomized to receive either 1000 mg abiraterone acetate or placebo. To prevent adrenal suppression symptoms, all patients received 5 mg prednisone orally twice daily. Primary end point was OS, secondary end points were time to PSA progression, PFS (RECIST), and the PSA response rate. In the abiraterone group OS was longer compared with the placebo-prednisone group: 14.8 months versus 10.9 months, respectively. Time to PSA-progression was 3.6 months longer in favor of abiraterone: 10.2 versus 6.6 months. PFS was prolonged with 2 months in the abiraterone group: 5.6 versus 3.6 months. The PSA response rate was 29% in the abiraterone-prednisone arm versus 6% in the placebo-prednisone arm. All these results proved that there is still a hormone response in CRPC. Side effects of abiraterone acetate–prednisone included fluid retention, hypertension and hypokalemia. In April 2011 abiraterone acetate plus prednisone was approved by FDA in patients with mCRPC who had previously received chemotherapy. A new trial with abiraterone acetate plus prednisone versus placebo-prednisone in chemo-naive patients with CRPC who are asymptomatic or mildly symptomatic has recruited and awaits its analysis in early 2012.

MDV3100 is a new potent AA with a triple action: it blocks the testosterone binding to the androgen receptor (AR), it impedes movement of the AR to the nucleus of the prostate cancer cells (nuclear translocation) and it inhibits binding to DNA. In a Phase I and II trial in 140 treated patients Scher et al. showed that an antitumor effect was observed in chemo-naive and in postchemotherapy CRPC patients: there was a decline in serum PSA of 50% or more in 56% of patients, and there was a response in the soft tissue and stabilization of bone disease [25]. There are now two trials running: the PREVAIL trial is testing chemo-naive patients and the Phase III AFFIRM study includes patients with progression after docetaxel. Results from both trials are awaited and if the data is confirmed an extra tool in the management of CRPC will become available.

TAK-700 (orteronel) is an oral inhibitor of the 17,20-lyase enzyme, a key enzyme in androgen biosynthesis. In the Phase I/II study all of the patients, who were all mCRPC patients, receiving at least 300 mg orteronel bidaily combined with 5 mg prednisone bidaily showed a decrease in PSA. Since January 2011 the Phase III trial is open and is recruiting patients: in the C21004 only chemo-naive patients are included, while in the C21005 study mCRPC patients who are progressive during or following docetaxel-based therapy are included. Awaiting trial results (Table 1).

**Bone-targeting agents**

In prostate cancer the bone metastases are of the osteoblastic type. The development of these metastases relies on a complex mechanism between osteoblasts, osteoclasts, tumor cells and signaling molecules. Zoledronic acid and its mechanism are well known: it is a bisphosphonate that minimizes bone resorption and it decreases the risk of bone fractures. In practice it is an effective treatment of skeletal complications and it reduces bone pain [27]. Recently denosumab has been developed and commercialized: it is a human monoclonal antibody with specificity for RANK-L, which is a regulator in the intracellular signaling pathways to control osteoclast formation, function and survival. Denosumab improves bone quality and
<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of action</th>
<th>Trial(s)</th>
<th>Toxicities</th>
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<tr>
<td><strong>Androgen biosynthesis inhibitor</strong></td>
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<td>Abiraterone</td>
<td>Oral, irreversible selective inhibitor of cytochrome P17, a key enzyme in the androgen and estrogen synthesis</td>
<td>In chemotherapy-naive, postketokonazole and postdocetaxel (e.g., Cougar trial)</td>
<td>Hypokalemia, hypertension, peripheral edema and fatigue</td>
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<tr>
<td>TAK 700 (orteronel)</td>
<td>Oral inhibitor of the 17,20-lyase enzyme, a key enzyme in androgen biosynthesis</td>
<td>C21004, C21005</td>
<td>Fatigue, anorexia, nausea/vomiting and constipation</td>
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<td><strong>Androgen-receptor inhibitor</strong></td>
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<td>MDV3100</td>
<td>Triple-acting, oral AR antagonist: MDV3100 inhibits testosterone binding to the AR, blocks movement of the AR to the nucleus of prostate cancer cells and inhibits binding of DNA</td>
<td>PREVAIL trial: Phase III in chemotherapy-naive patients with progressive mCRPC AFFIRM-trial</td>
<td>Fatigue, seizure and rash</td>
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<td><strong>Endothelin antagonist</strong></td>
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<td>Atrasentan</td>
<td>Competitive inhibitor of ET-1</td>
<td>SWOG 0421</td>
<td>Peripheral edema, nasal congestion and headache</td>
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<td>Zibotentan</td>
<td>Competitive inhibitor of ET-1</td>
<td>ENTHUSE</td>
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<td><strong>Antiangiogenic therapies</strong></td>
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<td>Bevacizumab (Avastin*)</td>
<td>VEGF-specific antibody Decreases tumor perfusion, vascular volume, microvascular density, interstitial fluid pressure and the number of viable, circulating endothelial and progenitor cells</td>
<td>Bevacizumab, thalidomide and docetaxel Docetaxel and thalidomide MAINSAIL trial</td>
<td>Thrombosis, wound-healing complications, bleeding, gastrointestinal perforation, renal toxicity, proteinuria and hypertension</td>
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<td>Thalidomide</td>
<td>Antiangiogenic properties Inhibits the production of IL-6 Activates apoptotic pathways</td>
<td></td>
<td>Teratogenic effects, somnolence, constipation, deep vein thrombosis and peripheral neuropathy</td>
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<td>Aflibercept (Zaltrap)</td>
<td>VEGF trap: broad-spectrum angiogenesis inhibitor with a unique mechanism of action. This fully human fusion protein binds all forms of VEGF-A, as well as VEGF-B and PIGF, additional angiogenic growth factors that appear to play a role in tumor angiogenesis and inflammation. It has been shown to bind VEGF-A, VEGF-B and PIGF with higher affinity than their native receptors</td>
<td>VENICE trial (aflibercept in combination with docetaxel in castration-resistant prostate cancer)</td>
<td>Rectal ulceration, proteinuria, hypertension, hoarseness and anorexia</td>
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<td><strong>Immunotherapy</strong></td>
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<td>Sipuleucel-T (Provenge)</td>
<td>Autologous cellular immunotherapy: activates T cells that proliferate to target prostate cancer cells, and it stimulates an immune response against prostate cancer</td>
<td>IMPACT trial</td>
<td>Acute infusion reactions, cerebrovascular events, chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasms, dizziness, headache, hypertension, muscle ache, nausea and vomiting</td>
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<td>Ipilimumab (Yervoy™)</td>
<td>Amplifies the immune response and directs it to the target</td>
<td>Trials in chemotherapy-naive patients and postdocetaxel therapy</td>
<td>Diarrhea, pruritus, rash and colitis</td>
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<td><strong>Third-generation taxane</strong></td>
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<td>Cabazitaxel</td>
<td>Microtubule inhibitor: binds to free tubulin, which is used during mitosis to form two daughter cells. Promotes assembly of tubulin into stable microtubules and at the same time it inhibits disassembly. This prevents mitosis, as well as other interphase cellular functions. Has activity in tumor cells that are both sensitive and resistant to docetaxel</td>
<td>TROPIC trial</td>
<td>Neutropenia, myelosuppression, diarrhea, death, fatigue and asthenia</td>
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<td><strong>RANK-ligand inhibitor</strong></td>
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<tr>
<td>Denosumab</td>
<td>RANK-ligand inhibitor</td>
<td>ClinicalTrials.gov NCT00321620</td>
<td>Osteonecrosis of the jaw and hypocalcemia</td>
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AR: Androgen receptor; ET-1: Endothelin peptide-1; mCRPC: Metastatic castration-resistant prostate cancer.
density and reduces the incidence of new vertebral fractures compared with placebo. Fizazi et al. presented a randomized, double-blind study in which the research group compared denosumab with zoledronic acid for the treatment of bone metastases in men with CRPC [28]. They concluded that denosumab was better than zoledronic acid for prevention of skeletal-related events, and potentially represents a novel treatment option in men with bone metastases from CRPC, but in the denosumab group there were slightly more serious adverse events and there was a higher risk for hypocalcemia. The risk of osteonecrosis of the jaw occurred infrequently (2% in the denosumab group versus 1% in the zoledronic acid group). OS and disease progression were not significantly better in the denosumab group. PSA-response did not differ between the two treatment arms.

### Other trials

There are also trials with angiogenesis inhibitors like bevacizumab (Avastin®, Genentech/Roche, Switzerland), aflibercept (VENICE-study), tasquinimod, thalidomide among others. The MAINSAIL-trial is a Phase III study to evaluate efficacy and safety of docetaxel and prednisone with or without lenalidomide, an antiangiogenic drug, in patients with CRPC and will include patients until the end of 2011. The Phase II CALBG trial with bevacizumab combined with docetaxel and estramustine showed promising results initially, but a lot of patients had to leave the trial early because of disease progression or due to toxicity. In the randomized, double-blind, placebo-controlled CALBG 90401 trial, there was no increase in OS in the bevacizumab plus docetaxel and prednisone group and this combination was even associated with a higher incidence of morbidity and mortality [29]. Ipilimumab (Yervoy™, Bristol-Myers Squibb, NY, USA) is currently in Phase III clinical trials in chemo-naive and postdocetaxel chemotherapy-recurrent forms of mCRPC patients; the primary end point is OS. There is evidence that ipilimumab has significant activity in the earlier stage prostate cancer but these data are to be confirmed in larger trials. The SYNERGY trial is also a randomized, controlled, international Phase III trial: they will enroll approximately 800 men with CRPC who have disease progression and require first-line docetaxel chemotherapy with or without Custirsen (OGX-011/TV-1011). Atrasentan and zibotentan are endothelin antagonists and are inhibitors of endothelin peptides, but the results of these studies were disappointing: atrasentan did not improve time-to-progression neither did it improve OS.

### Conclusion

In advanced prostate cancer the limitations of therapy with LHRH-agonists, AAs, ketokonazole and docetaxel chemotherapy is changing rapidly with the development of several new therapeutic agents. In the advanced prostate cancer setting we now have LHRH-antagonists, which provide a faster decline in testosterone without testosterone surge. Especially in the stage of CRPC, we will soon have more drugs available (e.g., abiraterone, MDV3100) to postpone chemotherapy. On the other hand, nowadays we can use the new chemotherapeutic agent cabazitaxel, which is more powerful than mitoxantrone and docetaxel and is FDA approved as second-line chemotherapy in mCRPC patients who have failed on docetaxel. These new drugs improve the outcome in mCRPC. The gold standard treatment until 2010 was LHRH-agonists and AAs followed by docetaxel in the symptomatic mCRPC. Since these new drugs have become available, we can offer LHRH-agonists or -antagonists, with AAs, followed by Sipuleucel-T and docetaxel, and after docetaxel failure we still have cabazitaxel or abiraterone available. Several trials are now running with these new drugs to find out what the responses are in chemo-naive CRPC patients and in the postdocetaxel chemotherapeutic situation. This is important in order to decide the right timing in the use of these new drugs in the series of already available therapies. The availability of clinical trial centers could help to prognosticate and to design patient-tailored therapies. The development of these new drugs improves the prognosis of CRPC patients and offers them a longer survival by postponing progression.

### Future perspective

Nowadays prostate cancer is diagnosed in an early stage in a lot of men, and can be treated with curative intent. However, in more advanced and aggressive cases we need hormonal therapies to control tumor growth. At a certain time the prostate cancer escapes the
hormonal control of LHRRH-agonists and then the patient is in a CRPC stage. Until recently palliative chemotherapy was the only option after hormonal failure and PSA progression. With the development of new therapeutic agents we create a larger army against prostate cancer. In the near future the right timing of these new agents will be scheduled as the results of these trials become available. We expect that even more agents will appear in trials with fewer side effects and greater efficacy. In the coming years we will have more therapeutic tools to help treat advanced prostate cancer so we can postpone death and make it even more a chronic disease adding extra years of life.

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