REVIEW ARTICLE

# Metastatic Castrate-resistant Prostate Cancer: When and How to Treat?

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ABSTRACT

The treatment of metastatic castrate-resistant prostate cancer has dramatically changed over the last decade. Six new agents have been showed to increase overall survival: docetaxel, cabazitaxel, abiraterone, enzalutamide, sipuleucel-T, and radium-223. Another important goal in the treatment of this disease is to decrease bone complications due to distant metastases or treatment-induced osteoporosis. Bisphosphonates (ie zoledronic acid) and denosumab, a recombinant monoclonal antibody that binds to the receptor activator of nuclear factor-κB ligand inhibitor, are approved for use in this indication. The availability of newer drugs raises questions about when treatment should be initiated or changed and in what sequence they should be administered in order to produce the best outcome. This review explores these newer agents and offers insight into molecules currently under development.

**Keywords:** hormonal therapy; immunotherapy; metastatic castrate-resistant prostate cancer; androgen resistance; chemotherapy

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Prostate cancer is the most common male cancer and the second most common cause of cancer-related death in men in the USA[1] and the UK.[2] In Europe, approximately 24 per 100,000 men also die from the disease annually. Prostate cancer is hormone dependent and androgen deprivation therapy (ADT) is the cornerstone treatment for recurrent or metastatic disease. Unfortunately, within an average of 1–4 years, resistance to androgen blockade generally occurs leading to castrate-resistant prostate cancer (CRPC). Until 2004, the number of therapeutic agents available to treat CRPC was highly limited. The availability of six new molecules in recent years has, however, positively impacted on patient outcomes, including survival. Increased focus on the complications of metastatic castrate-resistant prostate cancer (mCRPC), particularly due to bone metastases, is also reducing the overall morbidity associated with this disease.

In this paper, we review the concept of "castration resistance," examine its principal causes, and explore criteria that can assist in defining disease progression and appropriate treatment strategies. We also discuss recent therapeutic advances in this ever-changing field.

## 1. MECHANISMS OF ANDROGEN RESISTANCE

It is well established that prostate cancer growth is largely dependent on the androgen signaling pathway.[3] ADT, either through orchiectomy or the use of gonadotropin releasing hormone (GnRH)-agonists or antagonists, remains the mainstay of first-line treatment in locally advanced or metastatic prostate cancer. Unfortunately, resistance to hormonal treatment always occurs despite optimal castration.

For prostate cancer cells to survive and proliferate in an environment deprived of androgen, they must either adapt the androgen receptor (AR) pathway to the androgen-deprived conditions or create alternative growth pathways.[4] Both of these mechanisms are commonly reported in the literature as either AR dependent, subclassified as ligand dependent and ligand independent, or as mechanisms which support tumor growth by bypassing the AR (Fig. 1).

Ligand-dependent castration resistance refers to tumor growth in the presence of a ligand. In approximately, 30% of castrate-resistant tumor cells, the AR gene remains amplified and supports tumor growth despite low concentrations of the naturally circulating ligands testosterone (T) and dihydrotestosterone (DHT).[5,6] It is thought that tumor cells in this environment become hypersensitive to the low level of androgens present in blood, enabling them to continue androgen-dependent growth.[7,8] Moreover, this phenomenon is associated with AR stability and nuclear localization.[9] The use of AR antagonists, such as bicalutamide and flutamide, does not seem to reverse tumor growth in this situation but may, in fact, enhance it.[10]

Tumor cells may also acquire resistance via genetic mutation leading to the aberrant activa-

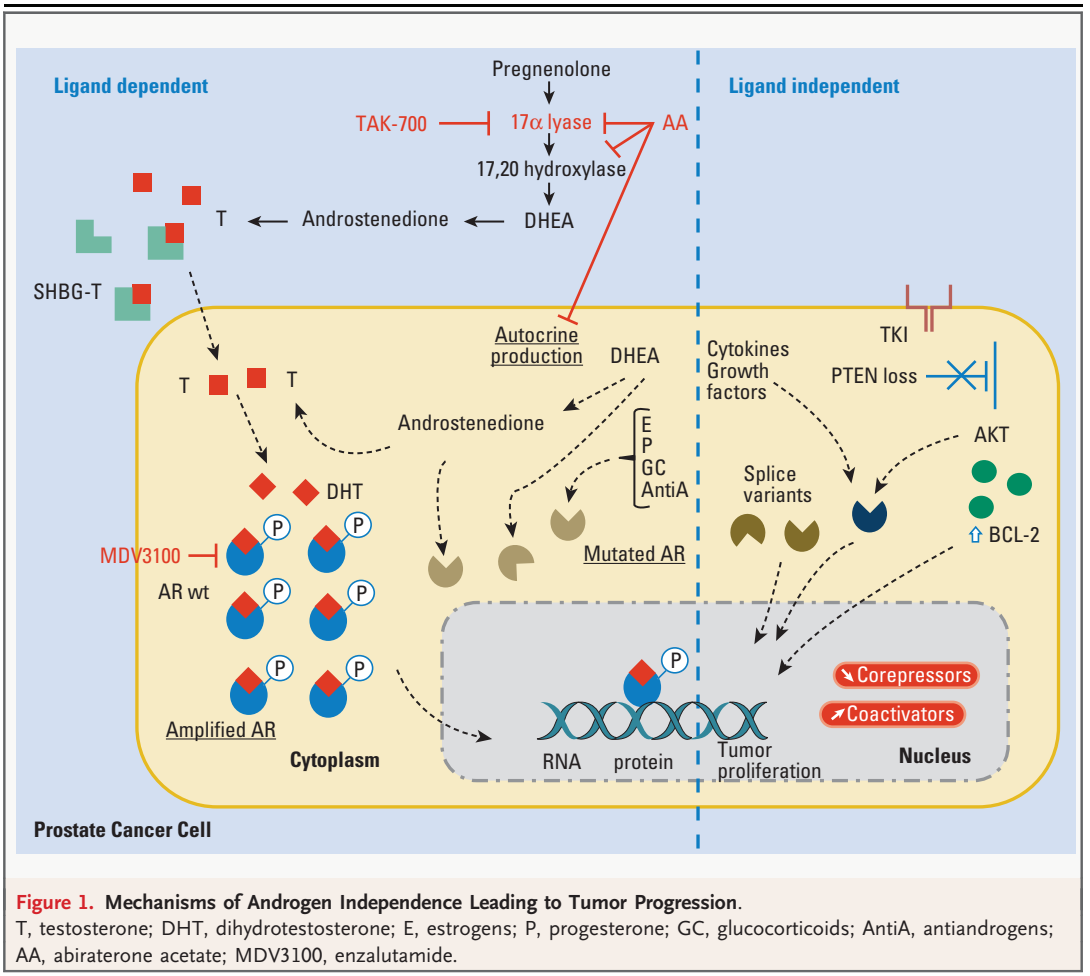


**Figure 1. Mechanisms of Androgen Independence Leading to Tumor Progression.**
T, testosterone; DHT, dihydrotestosterone; E, estrogens; P, progesterone; GC, glucocorticoids; AntiA, antiandrogens; AA, abiraterone acetate; MDV3100, enzalutamide.

tion of androgen signaling.[11] Although rare, genetic mutation of the AR can confer increased functional activity to the AR. The AR then becomes capable of binding with natural and nonclassical ligands including estrogen, progesterone, adrenal androgens, corticosteroids,[12] DHT metabolites,[13] and androgen antagonists.[14] This binding further stimulates the AR and thus promotes tumor growth.

In addition, the concentration of intratumoral androgen has been found to be higher than expected in androgen-depleted situations and appears to be present in sufficiently enough levels to activate intracytoplasmic ARs leading to gene expression.[15] Montgomery et al.[16] demonstrated that tumor cells contain transcripts that encode enzymes involved in the synthesis of T and DHT from cholesterol precursors, adding weight to the idea that androgens could come from locally converted adrenal androgens. This autocrine pathway contributes to AR activation despite castrate levels of serum testosterone.

Ligand-independent resistance refers to tumor growth through the activation of the AR in the absence of a ligand. Constitutively active splice variants of AR are able to regulate expression of genes promoting tumor cell growth without androgen binding.[17] AR-regulatory proteins, activators, or repressors[18] are recruited when AR binds to its ligand leading to transcription modulation. Upregulation of AR coactivators,[19] such as hsp27[20] or Her2Neu tyrosine kinase,[21] has been associated with the development of castration resistance. Also, the deregulation of other growth factors, including the insulin-like growth factor and the epidermal growth factor, seems to directly activate the AR or its coactivators.

Finally, prostate cancer cells may acquire independence from AR signaling by activating alternative survival mechanisms that bypass the AR pathway. These bypass mechanisms, many of which are under investigation, include the RAS/MAPK pathway, transforming growth factor-β, Wnt/β-catenin pathway, hepatocyte growth factor, fibroblast growth factor (FGF) pathway, and insulin-like growth factor (IGF) system. The phosphatidylinositol 3-kinase (PI3K)/AKT signal transduction pathway is also a key oncogenic pathway activated in many human cancers, including prostate cancer. The phosphatase and tensin homolog deleted on chromosome 10 (PTEN) gene is a tumor suppressor gene and is the main inhibitor of the PI3K/AKT pathway. Deletion of PTEN and hence activation of PI3K/AKT has been shown to modulate AR activity, thus supporting tumor growth in CRPC.[22,23]

As a result of these findings, patients who fail hormonal therapy are now referred to as castrate resistant as opposed to hormone resistant.

## 2. PROSTATE CANCER WITH NEUROENDOCRINE DIFFERENTIATION

Adenocarcinomas account for 90% of all prostate cancers.[24] Pure neuroendocrine (NE) prostate cancer, otherwise known as small-cell prostate cancer, is a rare entity and occurs in less than 1% of all prostate cancer patients.[16] NE cells often express NE markers detected by immunohistochemistry such as chromogranin A, synaptophysin, and neuron-specific enolase. Unlike patients with prostatic adenocarcinoma, the prostate-specific antigen (PSA) is not usually elevated in patients with small-cell prostate cancer. However, most NE prostate cancers are adenocarcinomas undergoing NE differentiation. These tumors are associated with lower PSA levels despite an advanced stage at presentation, aggressive disease, visceral metastases, and poorer outcome.[25] Prostate cancers seem to acquire NE characteristics as ADT is administered.[26] Furthermore, NE cells do not express AR, explaining the hormone-independent nature of theses tumors.[27–29] This differentiation is probably another mechanism which confers castration resistance. Small-cell prostate cancers are not expected to respond to classic hormonal therapy nor to taxanes. The treatment of choice is the same as for NE tumors from other origins and includes cisplatin- and etoposide-based regimens.[30] Mixed tumors, however, should be treated with castration therapy and standard first-line prostate cancer chemotherapy. The impact of treatment on survival remains unclear but most patients have a much shorter survival (under a year) than those with prostatic adenocarcinoma.

## 3. DIAGNOSIS, PROGRESSIVE DISEASE, AND INDICATIONS FOR TREATMENT

Knowing when to initiate treatment often challenges physicians as standard parameters, such as Response Evaluation Criteria in Solid Tumors (RECIST), used in general oncology are often not

applicable to prostate cancer. Treating prostate cancer requires knowledge of the natural history of the disease, depends on clinical presentation and also on the patient's wishes. The disease can be categorized into different subgroups according to the presence or not of clinically detectable metastatic disease. Most patients (90%)[31] will only develop bone metastases while others will present with nodal involvement or visceral metastases. As patients do not necessarily develop the same complications individually adapted treatment regimens should be offered. The best moment to initiate treatment once a patient develops mCRPC is still, however, a matter of debate. Physicians should be guided in their decision-making process by the appearance or worsening of disease symptoms, the development of new distant metastases and/or an increase in PSA doubling time.[32]

The Prostate Cancer Working Group 2 (PCWG2) identified key criteria (Table 1) to aid in the design of clinical trials and these can also be used in clinical practice.[33] The generally accepted definition of progressive disease (PD) is progression in the presence of castrate levels of T (T < 50 ng/dL) after the withdrawal of antiandrogen therapy. This can be based on (1) biochemical recurrence, defined as an increase in PSA confirmed by a second PSA value measured 1 week after the first; (2) development of bone metastases, defined as two or more bone lesions on bone scan and confirmed by computed tomography scan or magnetic resonance imaging in case of doubt; or (3) progression of nodal or visceral lesions according to RECIST criteria independent of any PSA evolution.

The diagnosis of PD in patients undergoing treatment for mCRPC also poses an additional challenge. Measurements and/or investigations in the first 12-week period need to be interpreted with caution. It is well known that during this time an increase in PSA, a flare-up on bone scan or an increase in pain can be observed, only to be followed by an objective response.[34]

## 4. METASTATIC CRPC

### 4.1. NON AR TARGETING AGENTS

#### *4.1.1. Chemotherapy*

Despite no survival benefit, mitoxantrone plus low-dose prednisone was a standard treatment in mCRPC for many years as the combination provided pain relief and reduced the PSA.[36,37] In 2004, two phase-III studies were published that demonstrated statistically significant survival benefits when docetaxel was administered to patients in this setting.

**Table 1. Suggested Criteria for Disease Progression According to the PCWG2.[35]**

| Variable | Sufficient criteria | Insufficient criteria when present alone |
|---|---|---|
| | Suggested criteria for treatment initiation in mCRPC | |
| PSA | PSA increase with PSA-DT < 6 months[35] | Increase in PSA |
| Bone | Appearance of new lesions on bone scan | |
| Soft tissue | Progression according to RECIST 1.1 criteria | |
| Symptoms | Apparition/worsening of disease symptoms (ie pain) | |
| | Suggested criteria for treatment discontinuation/change in clinical practice[6] | |
| PSA | | Increase in PSA |
| Bone | Appearance of two new lesions on bone scan: if new lesions appear in the first 12 weeks of treatment, 2 additional lesions must be found on a confirmatory bone scan performed at least 6 weeks later | |
| Soft tissue | PD according to RECIST 1.1 [≥20% increase in the sum of the largest diameters of the targeted lesions or appearance of new lesion (s)]: lymph nodes' greatest diameter should be ≥2cm. | |
| Symptoms | Pain worsening: pain progression could be ignored in the first 12 weeks of treatment in the absence of compelling evidence of disease progression | |

Abbreviations: PSA, prostate-specific antigen; PSA-DT, prostate-specific antigen doubling time; RECIST, Response Evaluation Criteria in Solid Tumors.

In the pivotal TAX 327 study, docetaxel, given every 3 weeks, was compared with docetaxel weekly or mitoxantrone.[38] While weekly docetaxel showed no significant survival advantage compared with mitoxantrone, median survival was increased by 2.9 months (19.2 months vs. 16.3 months, $p = 0.004$) in the group treated with docetaxel every 3 weeks.[39] Three weekly docetaxel also decreased pain and PSA levels and improved quality of life. The incidence of grade 3 or 4 neutropenia was superior in the 3-weekly docetaxel group compared to the mitoxantrone group (32% vs. 22%, respectively). Other low-grade toxicities that occurred in at least 15% of patients in the 3-weekly docetaxel group included alopecia, fatigue, diarrhea, nail changes, sensory neuropathy, stomatitis, tearing, and peripheral edema.

The second phase III study compared the combination of docetaxel and estramustine to mitoxantrone and prednisone. The overall survival (OS) of patients treated with docetaxel and estramustine was 17.5 months compared to 15.6 months ($p = 0.02$) for mitoxantrone and prednisone.[40] The addition of estramustine to docetaxel is controversial. A meta-analysis suggested that it could improve OS when combined with chemotherapy but the number of patients treated with docetaxel in the meta-analysis was low.[41] We conducted a trial comparing docetaxel to docetaxel plus estramustine. No significant differences in outcome were found and estramustine only increased toxicity, particularly gastrointestinal adverse events.[42] Therefore, in our opinion, estramustine should not be used in the routine management of mCRPC.

In 2010, cabazitaxel, a semisynthetic tubulin-binding taxane, was validated in patients who progressed during or after docetaxel-based therapy. The phase-III, randomized TROPIC trial compared cabazitaxel in combination with prednisone to mitoxantrone and prednisone.[43] Median OS in the cabzitaxel group was 15.1 months versus 12.7 months in patients who received mitoxantrone. Cabazitaxel also produced better results in terms of time to PSA increase and time to tumor progression, but pain reduction was similar in both groups. Unfortunately, no quality of life data was recorded. Toxicities were mainly hematological. Fifty percent of patients in the cabazitaxel arm experienced grade 3 or more neutropenia and 8% had febrile neutropenia. The most recorded nonhematological grade 3 or 4 toxicity was diarrhea (6%). Interestingly, cabazitaxel did not increase polyneuropathy, nail changes, or alopecia compared with mitoxantrone. A post hoc analysis of the TROPIC trial also demonstrated that from the time of the first docetaxel dose, cabazitaxel extended survival to 29 months. Therefore, with chemotherapy (docetaxel and cabazitaxel) alone, the median OS expected in patients with mCRPC has increased from 12.5 months to 29 months.[44]

Doubt exists over the optimal dose of cabazitaxel. The TROPIC trial administered cabazitaxel at a dose of 25 mg/m$^2$ but results from two other trials, PROSELICA and FIRSTANA, are eagerly awaited to see if 20 mg/m$^2$ can reduce toxicity but still maintain efficacy.

#### *4.1.2. Targeting the immune system*

Sipuleucel-T, an autologous cellular immunotherapy, prolongs survival in asymptomatic or minimally symptomatic mCRPC. The Sipuleucel-T vaccine is made from peripheral blood mononuclear cells from which antigen-presenting cells are obtained during leukapheresis. The mononuclear cells are cultured (and thus activated) ex vivo with a fusion protein of prostatic acid phosphatase linked to a granulocyte–macrophage colony stimulating factor that helps the antigen-presenting cells to mature. The product is then reinjected intravenously three times per month. In the phase III imunotherapy prostate adenocarcinoma treatment (IMPACT) trial, 513 patients with asymptomatic or minimally symptomatic mCRPC were randomized to either sipuleucel-T or placebo.[45] OS was superior in the treatment arm by 4.1 months (25.8 months vs. 21.7 months, $p = 0.02$). Interestingly, progression-free survival (PFS) was not improved in the treatment arm, probably due to the longer time needed for immunotherapy to induce tumor regression.

Other immunotherapies are under investigation. A phase II trial using a pox viral-based vaccine, Prostvac-VF, has shown promising results versus placebo.[46] Targeting immune checkpoints provides another interesting way to challenge the immune system. The cytotoxic T-lymphocyte antigen 4 checkpoint receptor plays a role in downregulating T-cell response and can be blocked with ipilimumab. Ipilimumab has demonstrated objective responses and decreases in PSA in phase II trials. Ongoing phase III trials

in mCRPC should determine its place in the treatment of mCRPC.[47]

#### 4.2. ANDROGEN-AXIS TARGETING AGENTS

##### *4.2.1. Abiraterone acetate*

As previously described, mCRPC develops despite castrate conditions and remains partially sensitive to hormones, making the development of agents that target the hormonal axis attractive. Abiraterone acetate (AA) is an irreversible inhibitor of 17 α-hydroxylase/C17,20-lyase (CYP 17), an enzyme that plays a critical role in the production of glucocorticoids and extragonadal as well as intratumoral androgens.

Two phase III trials have confirmed the efficacy of AA in the treatment of patients with mCRPC. The COU-AA-301 trial showed that in docetaxel pretreated patients, the combination of AA and prednisone significantly improved OS compared with prednisone alone (14.5 vs. 10.9 months, $p < 0.001$).[48] The COU-AA-302 study sought to determine whether AA plus prednisone could provide clinical benefit to patients who had not received chemotherapy.[49] A statistically significant benefit in radiologic PFS (median not reached in the AA plus prednisone group vs. a median of 8.3 months in the prednisone alone group; $p < 0.001$), and a trend toward increased OS (median OS not reached vs. 27.2 months with a 25% decrease in the risk of death in the AA group; $p$ = NS) encouraged the independent monitoring committee to unblind the study and allow crossover. Updated results at the third interim analysis have shown that the median time to radiographic progression doubled from 8.3 months to 16.5 months for the prednisone and combination arms, respectively, $p<0.0001$, and that OS increased from 30.1 months with prednisone alone to 35.3 months with the combination ($p = 0.0151$, although the difference did not cross the prespecified boundary for significance, $p = 0.0035$).[50]

The use of AA and prednisone in the chemonaive setting also demonstrated quality of life benefits and confirmed the acceptable toxicity profile of this treatment. The main toxicities observed were fluid overload or edema (28%), hypertension (22%), and hypokalemia (17%). All were manageable with prednisone treatment. Monitoring of aminotransferase levels is required as transient, but sometimes severe, elevation of these enzymes has been observed.

##### *4.2.2. Enzalutamide – MDV 3100*

Enzalutamide is an oral, pure AR antagonist. Unlike the first generation of AR antagonists, it does not promote AR translocation, DNA binding, or coactivator recruitment. Enzalutamide demonstrated efficacy regardless of prior chemotherapy in phase I and II trials.[51] The phase III, double-blind, placebo-controlled randomized trial, a study evaluating the efficacy and safety of the Investigational drug MDV3100 (AFFIR)M, evaluated whether enzalutamide could improve survival in patients pretreated with docetaxel.[52] Patients in the enzalutamide group increased their median OS by 4.8 months compared to placebo (median OS of 18.4 vs. 13.6 months respectively; $p<0.001$). Furthermore, significant benefits were seen in PSA and radiologic response, PFS, response rates, and quality of life scores. The most common adverse events were fatigue (34%), hot flashes (20%), and diarrhea (21%). Patients treated with enzalutamide experienced more seizures, especially if they had preexisting conditions. The interim analysis of the PREVAIL trial, evaluating enzalutamide in patients who have not yet received chemotherapy, is expected this year.

##### *4.2.3. Other androgen-axis targeting agents*

Several new promising antihormonal agents are under investigation. Orteronel (TAK700), a nonsteroidal agent that targets CYP17A1 and selectively inhibits the 17,20-lyase, has demonstrated substantial activity on PSA levels in phase I/II trials.[53] It is currently under investigation in phase III trials in chemotherapy pretreated and in chemo-naive patients. The next-generation CYP17 inhibitor, galeterone (TOK-001), also antagonizes the AR and reduces AR levels in prostate cancer cells. It is being examined in the phase I/II androgen receptor modulation optimized for response 1 (ARMOR1) trial.[54] Finally, the new androgen inhibitor, ODM-201, seems to have interesting antitumor activity in preclinical and phase I data.[55]

#### 4.3. BONE TARGETING AGENTS

Bone metastases exert a major negative impact on the quality of life of patients with mCRPC. Bone metastases are associated with skeletal-related events (SREs), including pathological fractures and spinal cord compression, resulting in the need for bone radiotherapy and orthopedic surgery.[56] Preventing complications from bone

metastases is essential and should be done early in the disease as pain related to bone disease has been correlated with poorer outcomes.[57] Biphosphonates, receptor activator of nuclear factor-κB ligand (RANK-L) inhibitors and radionucleotides are welcome therapeutic additions to treat such complications.

*4.3.1. Antiresorptive agents*

Bisphosphonates induce osteoclast apoptosis and lead to the inhibition of tumor-related osteolytic activity.[58] Despite the belief that bisphosphonates may themselves exert antitumoral effects, they have not proven to have any impact on survival.[59] Therefore, no evidence exists to support the use of these molecules in the adjuvant or nonmetastatic setting.

A phase III trial demonstrated that zoledronic acid was efficacious in delaying the onset of SREs when compared with placebo.[60] SREs occurred in 33% of patients in the experimental group versus 44% in the placebo group ($p = 0.021$). The median time to the first SRE was also not reached in the treatment arm but was 321 days in the placebo arm ($p = 0.011$). Zoledronic acid is well tolerated but requires monthly intravenous administration, renal function monitoring and dose adjustments in the presence of renal impairment. The recently presented phase III Zeus trial failed to demonstrate a benefit of zoledronic acid in preventing the incidence of bone metastases when given to patients with high-risk nonmetastatic prostate cancers.[61]

Denosumab is a fully human monoclonal antibody that inhibits the nuclear factor-κB ligand (RANK-L), thereby inhibiting osteoclastic maturation.[62] A phase III trial compared denosumab to standard therapy with zoledronic acid in mCRPC.[63] Median time to the first SRE was 20.7 months in the denosumab arm and 17.1 months in the zoledronic acid arm ($p = 0.0002$). More hypocalcemia (12.8%) occurred in the denosumab group. Both treatments were associated with osteonecrosis of the jaw but its incidence was rare (zoledronic acid 0.8% vs. denosumab 2.3%). Denosumab has advantages in that it is given as a subcutaneous injection and its administration does not depend on renal function. A phase III trial evaluated denosumab in the nonmetastatic setting and demonstrated an increase in bone metastasis-free survival of 4.2 months. Unfortunately, there was no survival benefit.[64]

*4.3.2. Radiopharmaceuticals*

Other bone-targeted therapies include radiopharmaceuticals that target osteoblastic activity. B-emitters such as samarium-153 ($^{153}$Sm) and strontium-89 ($^{89}$St) have been demonstrated to reduce pain due to bone metastases.[65,66] Studies of these agents have not demonstrated any OS advantages and data in terms of SLE prevention have not been recorded.[67] B-emitters are also associated with hematological toxicities and their use in routine practice is therefore limited.

Another radiopharmaceutical, radium-223 chloride ($^{223}$Ra, Alpharadin[68]), is an alpha-emitter that is able to deliver higher-quality radiation to a more localized area than its predecessors. The alpharadin in symptomatic prostate cancer patients (ALSYMPCA) trial randomized patients with symptomatic bone metastases due to metastatic prostate cancer to either $^{223}$Ra or placebo. Patients were either unfit for docetaxel or had received docetaxel as first-line treatment. The results showed an OS benefit with a median OS of 14.0 months in the treatment group versus 11.2 months in the placebo group, ($p = 0.00185$). Time to the first SRE was also statistically significantly in favor of $^{223}$Ra compared with placebo (13.6 months vs. 8.4 months, respectively; $p = 0.00046$). In addition, patients treated in the $^{223}$Ra arm experienced only minor toxicity and had fewer adverse events compared with patients in the placebo arm. Grades 3 and 4 neutropenia and thrombopenia, the limiting toxicities of samarium-153 and strontium-89, were observed in only 2% and 4% of patients, respectively.

## 5. OTHER AND FUTURE THERAPIES

Other targets are currently under investigation in mCRPC. Trials have examined various molecules in combination with docetaxel but none have shown any clinical benefit. Agents targeting angiogenesis, such as bevacizumab[69] and aflibercept,[70] have also been disappointing and did not enhance efficacy in mCRPC when combined with chemotherapy. A quinoline-3-carboxamide derivative, tasquiminod, seems to have activity in minimally symptomatic disease. This molecule offers antiangiogenesis and antitumoral characteristics and has demonstrated some benefit in phase II trials.[71]

The SYNERGY trial is a randomized phase III study evaluating the ability of custirsen

(OGX-O11) to improve survival when added to first-line docetaxel. Custirsen is an antisense oligonucleotide which inhibits the cytoprotective chaperone clusterin which, when overexpressed, results in resistance to treatment. Custirsen has demonstrated survival benefits in a phase II trial in combination with docetaxel.[72]

One of the most promising new agents is cabozantinib, which inhibits both c-Met and vascular endothelial growth factor receptor 2. A phase II trial demonstrated efficacy in terms of regression of soft tissue lesions (72% of patients), improved bone scan (68%), diminished bone pain, and reduction in bone turnover markers. PFS was also increased.[73] Ongoing phase III trials are evaluating cabozantinib in terms of survival (COMET-1) and as a pain-palliating agent (COMET-2).

## 6. CONCLUSIONS

The landscape of CRPC has radically changed. The use of new agents has enabled the median survival to double in a very short time. However, uncertainty remains with regards to treatment sequencing (Fig. 2). At the time of writing, there is no strong data to guide clinicians on the most appropriate sequential use of these agents. Studies have categorized treatments into the "pre-docetaxel" or "post-docetaxel" setting and also in terms of symptomatic or asymptomatic disease. Future trials will need to incorporate clever designs that evoke clear strategies according to the stage and biology of the disease.

Many questions remain. For example, could some treatments, such as immunotherapy, be more effective when the disease burden is at its lowest, as in the nonmetastatic setting? AR and androgen synthesis inhibitors are validated in the second-line setting but recent studies have demonstrated their potential first-line (before chemotherapy), which also raises questions about which treatment we should chose first. In other words, how do we accurately distinguish which mCRPC patients will benefit from AA or other hormonal manipulations as front-line therapy from those who will require rapid initiation of chemotherapy?

Conflicting results exist regarding the activity of cabazitaxel after AA.[74,75] Modest activity of abiraterone after enzalutamide and docetaxel has also been reported.[76,77] These two examples again illustrate the need to develop reliable biomarkers for treatment activity so that we can effectively choose the best option for our patients.

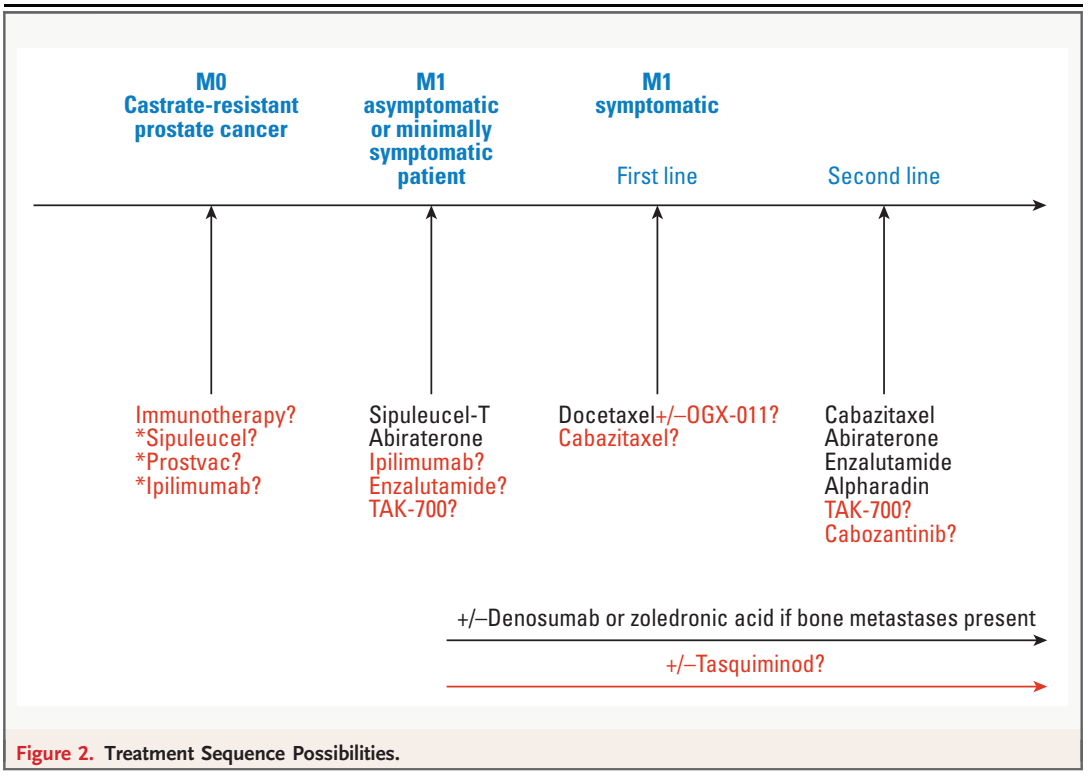


**Figure 2.** Treatment Sequence Possibilities.

Finally, common markers of activity, such as PSA or PFS, are being challenged by recent findings. Some molecules, such as Sipuleucel-T, might have an effect on OS but not on PFS.[29] Others, like cabozantinib, may demonstrate a positive effect on bone scan that does not correlate with a reduction in the PSA.[57]

In conclusion, many questions remain, making the treatment of prostate cancer an exciting and rapidly evolving field.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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