# Research Prioritization Topic Brief: Comparative Effectiveness of Different Treatment Sequences for Castrate-Resistant Prostate Cancer

## Assessment of Prevention, Diagnosis and Treatment Options

**PCORI Scientific Program Area:**
Comparative Effectiveness Research

## Executive Summary

**Overall Comparative Research Question:** What is the comparative effectiveness of different sequences of treatments (abiraterone, enzalutamide, sipuleucel-T, docetaxel, cabazitaxel, radium-223) for improving survival and quality of life and relieving symptoms for metastatic castrate resistant prostate cancer?

**Brief Overview of the Topic.** Prostate cancer is the most frequent malignancy diagnosed in men in the United States. This brief focuses on a key group of patients with metastatic castrate resistant prostate cancer (mCRPC) who have clinical evidence of prostate cancer progression despite medical or surgical castration.[1] Over the past five years, clinical trials have shown that several new agents, in addition to standard chemotherapy with docetaxel, can improve survival and potentially also quality of life. These include the chemotherapeutic agent cabitaxel, the novel androgen receptor-targeted agents enzalutamide and abiraterone, the immunotherapy agent sipuleucel-T and the alpha emitter radium-223. However, no comparative effectiveness studies have compared these agents for first- or second-line therapy or evaluated treatment sequencing or combinations. Therefore, current treatment decisions are made based on patient preferences, prior treatment, symptoms, potential side effects, patient comorbidities, presence of visceral disease and cost and insurance considerations. Of note, newly-approved medications are extremely costly. Furthermore, the design and conduct of studies in men with mCRPC evaluating standard outcome measures (progression-free and overall survival and quality of life) is complicated by the Food and Drug Administration's recent approval of multiple agents that have been shown to affect these outcomes. This would ideally require studies with multiple arms and sequences to fully evaluate comparative effectiveness.

**Patient-Centeredness.** Improved knowledge of appropriate sequencing would help decrease the burden of less effective treatments and potentially improve both survival and quality of life. Different side effect profiles and burdens of treatments are also key considerations in the choice of treatments, which also often involves the challenging issue of weighing quality versus

quantity of life. Newer options are extremely costly, and patients often cannot afford them when copayments are required.

**Impact on Health and Populations.** Symptoms from metastatic disease are common, with bony disease in most patients and resulting pain, as well as serious complications of fractures and spinal cord compression and paralysis. As more therapeutic options have become available, the pattern of metastatic disease has changed, including more liver metastases. All treatments for prostate cancer have significant morbidity and complications, including marked fatigue, decrease in muscle mass with loss of strength, osteopenia/osteoporosis with increased risk of pathological fractures, and sexual dysfunction. In addition, chemotherapeutic agents and radium-223 cause bone marrow suppression and increase the risk of infection. Both metastatic prostate cancer and its treatments also significantly affect patients' psychosocial, financial and caregiving needs.

**Assessment of Current Options.** Current clinical practice guidelines based on systematic reviews of the literature recommend enzalutamide, abiraterone, cabazitaxel, and sipuleucel-T for selected patients and radium-223 for certain patients with bone metastases with the highest level of evidence rating, based on Phase III clinical trials. These reviews identified no completed comparative studies of these agents for first- or second-line therapy, combinations of these agents or sequencing, or use of biomarkers to select initial therapy.

**Likelihood of Implementation of Research Results in Practice.** Given the lack of high-quality evidence on sequencing, relatively small survival benefits from individual treatment options, and increased availability and use of novel treatments, there is a high likelihood that new research results will be implemented in practice. Challenges include the need for multi-arm, long-term studies to provide information needed for treatment sequencing and the high cost of new therapies.

**Durability of Information.** New treatments are increasingly being tested to treat mCRPC, and new drugs with novel mechanisms of action and novel combinations of existing agents are in active development. As the treatment armamentarium for this prevalent disease expands, it is likely that new models will become available. However, the treatments currently available will still be key, and the information derived from comparative effectiveness research with these agents will likely represent the background and potentially the basis for future developments.

# Topic 3: Comparative effectiveness of different treatment sequences for castrate resistant prostate cancer

## Overall comparative research question:

What is the comparative effectiveness of different sequences of treatments proven to impact survival (abiraterone, enzalutamide, sipuleucel-T, docetaxel, cabazitaxel, radium-223) for improving survival and quality of life and relieving symptoms for metastatic castrate resistant prostate cancer?

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## 2. Introduction:

Prostate cancer is the most frequent malignancy diagnosed in men in the United States. Although most cases are diagnosed and treated for localized disease, some patients are diagnosed with or develop disseminated disease. Since prostate cancer is an androgen-dependent cancer, a key treatment for disseminated disease is surgical castration or medical androgen ablation, also known as medical castration or androgen deprivation therapy (ADT).[2] However, many patients eventually develop resistance and are then classified as having castrate resistant prostate cancer, defined by the American Urological Association (AUA) as "a rising prostate specific antigen level and/or radiographic evidence of prostate cancer progression despite medical or surgical castration."[3] The key clinical trials demonstrating the effectiveness of anticancer agents have all been conducted in patients with evidence of progressive disseminated (i.e., metastatic) disease, rather than those with rising prostate specific antigen (PSA) alone. This topic brief therefore focuses on patients with disseminated disease.

Until recently, the standard treatment for metastatic castrate resistant prostate cancer (mCRPC) was chemotherapy with docetaxel, but over the past few years, a number of new therapies have been approved, with significant improvements in patient survival.[3] The current treatments for castrate-resistant prostate cancer that have been shown to extend survival in randomized clinical trials are addressed in this topic brief, including:

- Novel drugs targeting the androgen receptor pathway: abiraterone and enzalutamide
- Immunotherapy: sipuleucel-T
- Chemotherapy: taxane chemotherapy (docetaxel, cabazitaxel)
- Radium-223, an alpha emitter, for patients with bony metastases (which are present in >90% of patients with mCRPC)

For mCRPC, treatment sequencing is of particular interest because there are no randomized controlled trials comparing these agents and no data or predictive models on the best sequence for them. Current decisions on which agents to select for first- and second-line therapy are generally based on patient preferences, prior treatment, symptoms, potential side effects, presence of visceral disease, and cost and insurance considerations (since newly-approved medications are extremely costly).

The use of some agents may potentially affect responses to subsequent treatment. For example, development of resistance to abiraterone or enzalutamide might affect the ability to subsequently use other androgen-targeted agents, although trials of biomarkers and sequencing are ongoing. In addition, a new biomarker, androgen-receptor splice variant 7 messenger ribonucleic acid (AR-V7), has been shown in an initial study to predict response to both enzalutamide and abiraterone in patients with castrate resistant prostate cancer and may help to personalize treatment sequencing regimens.[4]

## 3. Patient-Centeredness:

Treatment choice and sequencing have multiple implications for patient centeredness in prostate cancer. Improved knowledge of appropriate sequencing would help decrease the burden of less-effective treatments and potentially improve both survival and quality of life. Different side effect profiles and burdens of treatments are key considerations in the choice of treatments, and it may be challenging to weigh quality versus quantity of life. Newer options are extremely costly, and patients often cannot afford them when copayments are required.

For example, in one recent evaluation of pharmacy costs, the monthly total cost was approximately $6000 for abiraterone and $7000 for enzalutamide, or approximately $60,000 for a full eight-month course.[5] The cost of a complete course of sipuleucel-T is currently more than $100,000.[6]

## 4. Impact/Burden of the Condition:

In 2012, 177,489 men in the United States were diagnosed with prostate cancer and 27,244 died.[7] A systematic review of studies of the prevalence of castrate resistance (albeit with limitations, including studies from the 2000s and some not using current definitions of mCRPC) estimated that 10%-20% of patients develop mCRPC within five years of medical or surgical castration, and 84% of these have metastatic disease.[8] Symptoms from metastatic disease are common, with bony disease in most patients and resulting pain, as well as pathological fractures, spinal cord compression and paralysis.

Treatments for prostate cancer also have significant morbidity and complications. All treatments frequently cause fatigue. Androgen deprivation therapy causes loss of lean body mass and strength, sexual dysfunction, and gynecomastia. Both chemotherapeutic agents and radium-223 cause bone marrow suppression and increase the risk of infection. Common side effects of chemotherapy include nausea and vomiting as well as neuropathy. The most common side effects of sipuleucel-T include nausea, fever and pain.

## 5. Evidence Gaps:

For patients with metastatic disease, the 2016 National Comprehensive Cancer Network (NCCN) guidelines[9] currently include the following recommendations:

- Docetaxel remains a category 1 recommended option for first-line therapy.
- Sipuleucel-T is a category 1 recommended option for first-line therapy for patients who are asymptomatic or minimally symptomatic and have good performance status, an estimated prognosis of more than six months and no liver metastases, based on Phase III randomized trials. In these trials, only 18.2% of patients had received prior chemotherapy due to inclusion criteria; in a subset analysis, both those who did and who did not receive prior chemotherapy had improved survival with sipuleucel-T.
- Enzalutamide and abiraterone acetate are also now category 1 recommended options for first-line therapy. These are also now recommended as the new standard of care after failure of docetaxel chemotherapy (category 1).Radium-223, an alpha emitter, is a recommended option for patients with symptomatic bony metastases without visceral disease or bulky lymphadenopathy (category 1).

- Cabazitaxel is recommended as a category 1 second-line therapy option for symptomatic patients based on phase III RCT data, but survival benefits are limited and there are significant side effects.
- Docetaxel rechallenge may be useful in some patients (category 2a).
- Some patients unsuitable for taxane chemotherapy can be considered for a second-line hormonal agent (traditional antiandrogens or ketoconazole) or mitoxantrone. These agents have not been adequately evaluated in randomized trials to determine their impact on survival.

The American Urological Association (AUA) updated its systematic review and guidelines through February 2015[10] based on new data, and released an amendment in October 2015[11] for castrate-resistant prostate cancer. This added 10 additional studies since 2014, focusing on enzalutamide. In general, recommendations are similar to those of the NCCN, except that the AUA recommends giving the least toxic agent first, although other considerations may apply.

The most recent American Society of Clinical Oncology/Cancer Care Ontario Guideline was published in 2014[12] and classifies treatments by survival, quality-of-life benefit, or both. Therapies with a survival and and an unclear quality-of-life benefit (with recommendation strength noted) include abiraterone (strong), enzalutamide (strong), radium-223 for bone metastases (strong) and docetaxel (moderate). Therapies with survival benefit and unclear quality-of-life benefit include sipuleucel-T for asymptomatic/minimally-symptomatic patients (weak) and cabazitaxel after progression with docetaxel (moderate). The only therapy determined to have a quality-of-life benefit but no demonstrated survival benefit was mitoxantrone (weak).

Key evidence gaps in completed research include:

- No completed studies have compared the use of these agents to each other for first- or second-line therapy.[10,12]
- No completed studies have evaluated optimal sequencing of currently approved treatments,[10,12] addressing survival, quality of life, symptoms, and costs. In particular, optimal sequencing of sipuleucel-T is unknown.
- No completed studies have evaluated combinations of treatments.[10,12]
- Few studies have adequately addressed patients with diminished performance status, since Phase III studies generally exclude these patients.[12]

- Few completed studies have evaluated clinical parameters and validated predictive biomarkers to better personalize therapy.[10] Emerging evidence demonstrates potential for this approach to

mCRPC, with new evidence showing that androgen deprivation therapy resistance can be predicted using AR-V7.[4] In addition, a Phase II study demonstrated that deletions, deleterious mutations or both in DNA-repair genes predicted response to the poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitor olaparib as third-line therapy.[13]

## 6. Ongoing Research:

The pace of relevant research is rapid. The AUA 2015 update had 10 new studies in one year, resulting in updated information on two therapies. Most ongoing studies of the agents of interest are either comparative studies or studies of combinations of treatment. There is only one ongoing Phase III or IV study on sequencing. This study is evaluating two different androgen deprivation therapy agents in sequence. A few Phase II studies are evaluating sequencing of other agents, but none are evaluating sipuleucel-T or radium-223.

Ongoing relevant comparative Phase III and IV studies of the agents of interest include:

- Comparing chemotherapeutic agents: A Phase III study comparing cabazitaxel to docetaxel, which includes assessment of patient preferences regarding which treatment they prefer (NCT02044354) (the estimated completion date is February 2016)
- Comparing chemotherapy to novel anti-androgen agents: A Phase IV study of cabazitaxel versus enzalutamide or abiraterone in patients previously treated with docetaxel and who rapidly failed a prior androgen receptor-targeted agent (NCT02485691)
- Combining agents: A Phase III study of enzalutamine with or without abiraterone and prednisone (NCT01949337)
- Treatment sequencing: A Phase IV study of enzalutamide after abiraterone (NCT02116582)

Relevant ongoing Phase II studies include:

- Comparing chemotherapy to novel anti-androgen agents:
  - An open-label, randomized study of cabazitaxel versus abiraterone or enzalutamine in poor-prognosis patients (NCT02254785)
  - A study of cabazitaxel versus the switch to alternative enzalutamide or abiraterone in patients with primary resistance to abiraterone or enzalutamide (NCT02379390)

- Combining existing agents:

- Radium-223 and one of the following agents: abiraterone (NCT02097303); abiraterone or enzalutamide (NCT02034552); enzalutamide (NCT02507570, NCT02199197, NCT02225704); sipuleucel-T (NCT02463799)
- A study of enzalutamide with cabazitaxel (NCT02522715)
- Two studies of enzalutamine with abiraterone (NCT01650194)

- Sequencing agents:
- A study of cabazitaxel versus the switch to alternative enzalutamide or abiraterone in primary resistant patients to abiraterone or enzalutamide (NCT02379390)
- A study of cabazitaxel after docetaxel for AR-V7 positive patients (NCT02621190)
- A study of sequencing abiraterone and enzalutamide (NCT02125357) (with outcomes of PSA, biomarkers)
- A study evaluating a potential role of biomarkers in circulating tumor cells to determine and monitor the efficacy of taxane-based chemotherapy (NCT01718353).

## 7. Likelihood of Implementation of Research Results in Practice:

Given that high-quality evidence is lacking, survival benefits from individual treatment options are relatively small, and treatments are increasingly being offered and requested by providers and patients, it is highly likely that research results would be implemented into practice. Challenges include the high cost of new therapies and the need for complex long-term studies to guide sequencing.

## 8. Durability of Information:

New treatments are increasingly being tested for mCRPC. New drugs with novel mechanisms of action and novel combinations of existing agents are in active development. It is likely that additional new treatments will be approved in the next few years . However, the currently available treatments will still be key to treatment, and the information derived from comparative effectiveness research with these agents will likely represent the background and potentially the basis for future developments.

## 9. Potential Research Questions:

- What is the optimal sequence for immunotherapy, chemotherapy and androgen receptor targeted treatments, particularly the comparative effectiveness of sipuleucel-T before versus after chemotherapy, for maximizing patient survival and quality of life?

Currently, sipuleucel-T is approved only for patients who have not yet received chemotherapy. Earlier treatment might sensitize cells to later therapies. (No ongoing studies are evaluating sequencing of sipuleucel-T).

- What is the comparative effectiveness of radium-223 in chemotherapy naïve versus chemotherapy-treated patients with mCRPC? (Current trials are only evaluating radium-223 as combination therapy including chemotherapy, androgen receptor targeted drugs and immunotherapy).
- What is the comparative effectiveness of treatment options (immunotherapy, chemotherapy or androgen receptor targeted treatments) for patients who have received chemotherapy for prostate cancer prior to developing mCRPC?
- What is the comparative effectiveness of sequencing of novel ADTs for mCRPC: enzalutamide followed by abiraterone or the reverse sequence, informed by biomarkers and with biomarker evaluation for prediction of response to therapy? (A currrent Phase IV trial is only evaluating one of these sequences).

## 10. Conclusion:

Given the impact of metastatic castrate resistant prostate cancer on patients' survival and quality of life, the rapid increase in effective treatment options, and the lack of comparative effectiveness research studies, further research in this area is key to improving outcomes for patients with this disease. Important comparative effectiveness research questions include choice of effective therapies for first- and second-line treatment and appropriate sequencing, including the use of biomarkers. Facilitators include the many stakeholders providing care for these patients and a relatively small number of providers who would make use of new effectiveness research. Barriers include the complexity and costs of these studies, including the high costs of the new medications, and challenges associated with conducting relevant long-term studies with patient-reported outcomes in an area where many efficacy studies of new and existing drugs are ongoing.

**APPENDIX**

**Methods**

Literature search:

Since there have been multiple recent systematic reviews and guidelines on this rapidly changing literature, we focused our search on the three major organizations producing systematic reviews and guidelines on this topic in the US: the National Comprehensive Cancer Network, American Urological Association, and American Society of Clinical Oncology. All three organizations recently (2014-2015) summarized and updated the evidence.

Clinical trials:

We conducted two searches (search date December 16, 2015) on clinicaltrials.gov for open clinical trials related to the topic. We searched clinicaltrials.gov for “prostate cancer” and Phase III and IV trials. We also searched clinicaltrials.gov for the key agents of interest and “castration resistant” or “castrate resistant” and “prostate cancer” for Phase II studies.

**References for topic: Comparative effectiveness of different treatment sequences for castrate resistant prostate cancer**


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