



**Second-Line Hormonal Therapy for Men With
Chemotherapy-Naïve, Castration-Resistant Prostate Cancer:
American Society of Clinical Oncology Provisional
Clinical Opinion**

Introduction

- The PCO is intended to offer timely clinical direction to ASCO oncologists after publication or presentation of potentially practice-changing data from major studies.
- This PCO addresses the use of second-line hormonal therapy for chemotherapy-naïve men with castration-resistant prostate cancer (CRPC) who range from being asymptomatic with only biochemical evidence of CRPC to having documented metastases but minimal symptoms.

PCO Methodology

An ASCO provisional clinical opinion (PCO) offers timely clinical direction to oncologists following publication or presentation of potentially practice-changing data from major studies.

The full ASCO PCO methodology supplement can be found at:
www.asco.org/genitourinary-cancer-guidelines

Statement of the Clinical Issue

- Goals of treatment in men with CRPC include chemotherapy deferral and palliation, that is, symptom relief with extension of life while maximizing quality of life for as long as possible or as a preemptive intervention against symptoms.
- Treatment patterns for CRPC vary considerably, likely as a result of the paucity of high-quality data on the topic, the relative efficacy and nonspecific mechanisms of action of available treatment approaches, and uncertainty among clinicians about optimal treatment.
- In light of these issues, ASCO convened an Expert Panel to provide focused PCOs about second-line hormonal therapy options for chemotherapy-naïve men with CRPC.
- The PCOs refer to the management of adenocarcinoma of the prostate.

Target Population and Audience

Target Population

Chemotherapy-naïve men with CRPC maintained in a continuous or intermittent castrate state through orchiectomy or pharmacologic castration. The primary target population is asymptomatic men but also includes those with minimal symptoms.

Target Audience

Urologists, radiation, and medical oncologists.

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RESEARCH QUESTION 1

Should a castrate state be maintained in patients who develop CRPC?

PCO 1.

For men who develop CRPC despite castrate levels of testosterone:

- Patients should be maintained in a castrate state indefinitely. This PCO is based on indirect scientific evidence and current understandings of disease progression mechanisms in prostate cancer. A discussion with patients about the limited nature of available scientific evidence and the balance among potential harms, benefits, costs, and patient preferences is essential when planning treatment.
- A castrate state should be maintained through orchiectomy or pharmacologic castration (e.g., luteinizing hormone–releasing hormone [LHRH] agonists/antagonists, antiandrogens).

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RESEARCH QUESTION 2

In chemotherapy-naïve patients who develop CRPC but have no radiographic evidence of metastases (M0 CRPC), should second-line hormonal therapies be used? If so, what agents or specific sequence of agents should be offered?

PCO 2.

- For chemotherapy-naïve patients believed to be at low risk for metastases (low PSA and slow PSA doubling time),^{1,2} second-line hormonal therapies are not suggested.
- For chemotherapy-naïve patients at high risk of developing metastases (rapid PSA doubling time or velocity), second-line hormonal therapies that lower PSA values or slow the rate of PSA rise may be offered (preferably in a clinical trial setting where available) after discussion with the patient about limited scientific evidence, potential harms, benefits, costs, and patient preferences.

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- Alternative treatment options include observation (with maintenance of a castrate state) or participation in a clinical trial.
- Chemotherapy or immunotherapy is not suggested except in a clinical trial.
- No evidence provides guidance about the optimal order of hormonal therapies after second-line hormonal therapy for high-risk chemotherapy-naïve patients with M0 CRPC. The panel was unable to come to consensus about sequencing.

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RESEARCH QUESTION 3

In chemotherapy-naïve patients who develop CRPC and have radiographic evidence of metastases but minimal symptoms (M1a/M1s CRPC), should second-line hormonal therapies be used? If so, what agents are recommended?

PCO 3. After first-line hormonal treatment failure and a discussion with chemotherapy-naïve patients about potential harms, benefits, costs, and patient preferences,

- Abiraterone acetate plus prednisone should be offered because they significantly improved rPFS and OS as well as secondary end points, including median time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression (v prednisone alone). The drugs are also well tolerated.

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- Enzalutamide should be offered because it significantly improves rPFS and OS. Secondary end points are also improved, including time to initiation of cytotoxic chemotherapy, risk of a first skeletal-related event, complete or partial soft tissue response, time to PSA progression, time to deterioration in quality of life, and decline in PSA of $\geq 50\%$ from baseline (v placebo). The drug is also well tolerated.
- Alternative treatment options include immunotherapy (sipuleucel-T),³ chemotherapy (docetaxel and prednisone),⁴ and radium-223.
- If none of these therapies can be obtained or tolerated by the patient, other antiandrogens, prednisone, and ketoconazole/hydrocortisone may be offered because they provide modest clinical benefits in this population, but no survival benefits have been established.
- Other alternative treatment options include enrollment in a clinical trial and observation.

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- No evidence provides guidance about the optimal order of hormonal therapies after second-line hormonal therapy for patients with M1 CRPC. The panel was unable to come to a consensus about sequencing.
- Other second-line hormonal therapy options where results from phase III trials are pending are not suggested.
- Palliative care should be offered to all chemotherapy-naïve men with M1 CRPC, particularly to those who exhibit symptoms or decreased quality of life.⁵

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RESEARCH QUESTION 4

How often should patients with CRPC undergo PSA monitoring?

PCO 4. No evidence provides guidance about the optimal frequency of PSA monitoring before starting second-line hormonal therapy or after treatment has begun.

- For patients with no radiographic evidence of metastases and a slow PSA doubling time^{1,2} or velocity, a PSA evaluation every 4 to 6 months is reasonable. If PSA levels rise, checking serum testosterone levels should be considered.
- For patients with a rapid PSA doubling time, velocity, or radiographic evidence of metastases, a PSA evaluation every 3 months is reasonable.

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RESEARCH QUESTION 5

What imaging modalities are appropriate for patients with CRPC?

PCO 5.

- When imaging is considered for patients both before and while receiving treatment, a bone scan and either computed tomography or magnetic resonance imaging of the abdomen and pelvis are reasonable.
- Imaging with ^{18}F -labeled positron emission tomography (^{18}F PET) generally is not recommended because it is currently only approved in the United States for the diagnosis of recurrent prostate cancer among men with elevated PSA after treatment. The use of this technique is otherwise limited to patients who participate in clinical trials and prospective registries.

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RESEARCH QUESTION 6

How often should patients with CRPC undergo radiographic imaging or routine radiographic restaging?

PCO 6.

- Radiographic imaging is not indicated for men with rising PSA unless treatment selection would be altered on the basis of radiographic findings or if symptoms potentially attributed to prostate cancer develop or worsen (e.g., bone pain).
- Routine radiographic restaging generally is not recommended, except among patients in whom PSA is not a reliable marker of disease.

Cost Implications

- Few studies examined cost-effectiveness or the budgetary impact associated with second-line hormonal therapies for CRPC.
- The only study that directly examined cost-effectiveness for the asymptomatic, chemotherapy-naïve population found that neither abiraterone nor sipuleucel-T were cost-effective compared with prednisone on the basis of a willingness-to-pay threshold of \$150,000 per quality-adjusted life-year.⁶
- Few patients fully understand the likely out-of-pocket (OOP) costs in advance of the treatment decision.⁷
- OOP costs, the potential adverse effects of OOP costs (referred to as financial toxicity),⁸ and expected quality of life should be discussed with patients during the treatment decision-making process.
- Oncologists must continue to advocate for patient access to beneficial therapies while being responsible stewards of health care resources.

Limitations and Future Directions

- The primary limitation for almost all the research questions (except Research Question 3) that the Expert Panel addressed was lack of data from phase III RCTs to support evidence-based recommendations.
- The sequencing of hormonal therapies (third-line, fourth-line, etc) for patients who progress on abiraterone or enzalutamide was not addressed because of the lack of both evidence and Expert Panel consensus but should be addressed in future updates of the current PCO as evidence develops.
- Further studies of cost and quality-of-life implications of second-line, third-line, and so forth hormonal therapies are needed to aid oncologists in discussing treatment options with patients.

Additional Resources

More information, including a Data Supplement, Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/genitourinary-cancer-guidelines

Patient information is available at www.cancer.net

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