

# PROSTATE CANCER: NON-METASTATIC CASTRATE-RESISTANT PROSTATE CANCER (nmCRPC)

*Proper Treatment of non-metastatic Castrate-Resistant Prostate Cancer  
can delay metastasis and improve quality of life.*

## 10 QUESTIONS TO ASK YOUR DOCTOR ABOUT NON-METASTATIC CASTRATE-RESISTANT PROSTATE CANCER (nmCRPC)

- 1. What is Castrate-Resistant Prostate Cancer (CRPC)?**  
Castrate-Resistant Prostate Cancer is cancer that no longer responds to, or is resistant to, hormonal therapy (also called ADT, or Androgen Deprivation Therapy), which is used to lower testosterone to slow the progression of the cancer. CRPC is prostate cancer that is growing (usually evidenced by a climbing PSA) in the setting of low testosterone levels.
- 2. What is “non-metastatic” Castrate-Resistant Prostate Cancer?**  
Non-metastatic Castrate-Resistant Prostate Cancer (nmCRPC) means that the cancer has stopped responding to hormonal therapy as evidenced by a climbing PSA in the setting of low testosterone levels; but that it has not been found in other areas of the body with conventional imaging (such as bone scan, plus MRI or CT scan).
- 3. How is PSA Monitoring helpful in nmCRPC? What is PSA “doubling time” (PSADT) and how does it relate to nmCRPC?**  
PSA levels should be checked regularly in men with nmCRPC. Men with nmCRPC whose PSA is climbing rapidly are at higher risk of developing metastases seen on conventional imaging, and at higher risk for death from prostate cancer. An easy way to measure the PSA rate of climb is called PSA doubling time (PSADT). A very short PSADT (10 months or less) means the PSA is climbing rapidly (it takes less time to double), and identifies patients at risk for developing metastases.
- 4. What types of imaging are generally used to rule out metastatic disease in CRPC?**  
The most commonly used conventional imaging to rule out metastatic spread of prostate cancer is a bone scan, plus a scan that looks at nodes and soft tissue (either CT or MRI of abdomen and pelvis.)
- 5. Does functional imaging play a part in diagnosing nmCRPC?**  
Conventional imaging seeks to detect anatomic abnormalities, whereas functional imaging is much more sensitive and detects cells that have the biologic function of cancer. Functional imaging can pick up areas of cancer that conventional imaging might miss. The three types of functional imaging relevant to nmCRPC are PSMA PET, Choline PET, and Fluciclovine PET (Axumin). If metastatic disease is identified by functional imaging, THIS DOES NOT MEAN THAT THERE IS NOT A ROLE FOR SYSTEMIC THERAPY with one of the three agents approved for nmCRPC. The identification of a small number of metastases might also be an opportunity to use metastasis-directed therapy like focal radiation.
- 6. Should non-metastatic CRPC be treated systemically (affecting the whole body)?**  
Yes. In men at high risk for developing metastases, that is, with a PSADT of 10 months or less, systemic treatment has been shown to delay or prevent metastatic disease, delay time to symptoms of progression, including pain, delay the time to use of chemotherapy, and extend survival, thus improving quality of life.
- 7. What is the treatment for nmCRPC? Are androgen-receptor inhibitors (ARI's) helpful in nmCRPC?**  
Suppressing testosterone with ADT is continued in men with CRPC, since there are always some cancer cells that continue to be driven by testosterone. In men with nmCRPC and PSADT less than or equal to 10 months, there are 3 FDA-approved agents that have been shown to delay the time to metastases, and prolong life. All three are second-generation anti-androgens: **enzalutamide**, **apalutamide**, and **darolutamide**, all known as ARI's (Androgen Receptor Inhibitors).
- 8. Are there therapies to protect bone health and cardiovascular health in nmCRPC?**  
Most patients with nmCRPC are older and at risk for age-related bone loss; ADT increases that risk. For men at high risk of fracture, denosumab can be prescribed (if contraindicated, zoledronic acid is recommended). Since ADT and an ARI present risks for cardiovascular health, and many patients have cardiovascular risk factors or disease, it is important to be aware of these increased risks and ensure appropriate monitoring of cholesterol, blood sugar, blood pressure, and bone density.
- 9. What are the quality of life (QOL) issues that should be considered in nmCRPC?**  
ADT and ARI's do have the potential for adverse events, including mental impairment. However, the studies evaluating these agents found that overall, patient-reported quality of life did not decline with their use, and that the longer metastases are delayed, the better the QOL.
- 10. How will I know if my prostate cancer becomes metastatic (mCRPC)?**  
Sometimes prostate cancer stops responding to ARI's. Your doctor will continue to monitor your PSA, and will re-check your testosterone and do imaging studies if your PSA starts to climb (or you develop new symptoms). If metastatic spread is detected, your disease is now mCRPC. You and your doctor should discuss treatment options for this stage of prostate cancer.

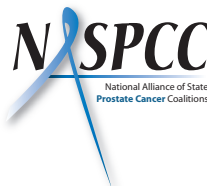
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# PROSTATE CANCER: NON-METASTATIC CASTRATE-RESISTANT PROSTATE CANCER (nmCRPC) FOR PHYSICIANS

nmCRPC is a  
distinct entity that  
requires systemic  
treatment to delay  
metastasis

## PLEASE REVIEW THE 10 PATIENT QUESTIONS AND ANSWERS ON THE REVERSE SIDE

1. Prostate cancer growth is dependent on testosterone, resulting in the common use of Androgen Deprivation Therapy (ADT), typically LHRH Agonists (leuprolide, goserelin) or GnRH Antagonists (degarelix, relugolix). Resistance to ADT, usually first identified by a climbing PSA in the setting of castrate levels of testosterone, is commonly referred to as Castrate-Resistant Prostate Cancer (CRPC).
2. **non-metastatic CRPC (nmCRPC)** is defined as CRPC in the setting of negative conventional imaging (bone scan plus cross-sectional imaging of the abdomen and pelvis, either MRI or CT scan). This definition was used as entry criteria for the pivotal trials of 3 approved agents in this setting.
3. **nmCRPC** is a heterogenous disease, with the risk of metastasis or death dependent on PSA kinetics. In particular, a PSA doubling time (PSADT) of 10 months or less is predictive of developing metastases or death. PSA levels should be checked regularly in nmCRPC patients - monthly in patients whose PSA is climbing rapidly, and every 3 to 6 months in patients with a longer PSADT. Memorial Sloan-Kettering Cancer Center has a valuable nomogram for calculating PSADT: [mskcc.org/nomograms/prostate/psa\\_doubling\\_time](http://mskcc.org/nomograms/prostate/psa_doubling_time).
4. While the current definition of "nmCRPC" is based on conventional imaging, it is important to remember that analysis of the pivotal trials that led to the approval of 3 agents for nmCRPC suggests most of those patients would have been found to have previously undetected metastases. One can think of this disease entity as "nmCRPC by conventional imaging", with therapeutic decisions made on that basis.
5. If functional imaging is used, the most important patients to identify might be those with a small number of metastases ("oligometastatic prostate cancer", defined as fewer than 3 or 5 metastases), for whom metastasis targeted therapy such as Intensity Modulated Radiotherapy (IMRT) appears useful. Although some of these lesions may be amenable to focal therapy, their discovery using ultra-sensitive imaging may result in a re-classification of **nmCRPC** to **mCRPC** but probably should not change systemic treatment options. [guconnect.info/wp-content/uploads/1.0-GU\\_CONNECT\\_Experts\\_Knowledge\\_Share\\_Feb\\_2021\\_Newsletter\\_Slide\\_Set.pdf](http://guconnect.info/wp-content/uploads/1.0-GU_CONNECT_Experts_Knowledge_Share_Feb_2021_Newsletter_Slide_Set.pdf)
6. Systemic treatment of high risk nmCRPC (nmCRPC with PSADT less than or equal to 10 months) has been shown to significantly delay the time to metastases; delay the time to development of symptoms due to metastases, including pain; delay the time to use of chemotherapy; and prolong overall survival.
7. The systemic therapy used in this setting is the addition of a next-generation anti-androgen, **enzalutamide** (PROSPER Trial); **apalutamide** (SPARTAN Trial) or **darolutamide** (ARAMIS Trial), all FDA-approved following Phase 3 trials demonstrating improved metastasis-free survival (MFS) and overall survival (OS) compared to placebo, to continuing ADT. These trials demonstrated a delay in time to metastasis from 22 to 24 months, but comparison is not possible, since no trial compared one agent to another. The most important result from these trials was that in patients with high risk nmCRPC it was far preferable to initiate therapy early, than to wait to use these or other agents once metastases had developed.
8. Most nmCRPC patients are older and at higher risk of fracture and age-related bone loss, a risk increased by ADT. Regular assessment of bone density is warranted. ASCO Guidelines suggest denosumab, unless contraindicated, in which case a bisphosphonate may be used. All patients should take Vitamin D and Calcium, and undertake weight-bearing exercises to maintain bone density. [ascopubs.org/doi/abs/10.1200/JCO.19.03148](http://ascopubs.org/doi/abs/10.1200/JCO.19.03148). They may also have significant cardiovascular (CV) comorbidities and risk factors. In addition to the pre-existent potential of increased cardiovascular morbidity associated with ADT, these agents may modestly increase this risk. Additionally, drug-drug interactions are especially important to check with next-generation anti-androgens. [sciencedirect.com/science/article/pii/S1078143920303707](http://sciencedirect.com/science/article/pii/S1078143920303707)
9. Side effects of these agents are relatively minor. Patient-reported Quality of Life (QOL) while on these agents showed no decline while on therapy, and in fact an overall improvement compared to placebo patients, because of the decline in QOL that occurred once metastases developed.
10. In addition to undergoing periodic PSA testing, nmCRPC patients under treatment should have a re-check of testosterone, and re-staging scans (bone scan and cross-sectional imaging) in the event of climbing PSA or development of new symptoms. The optimal therapy for nmCRPC that develops resistance to a next-generation anti-androgen is not well-defined.

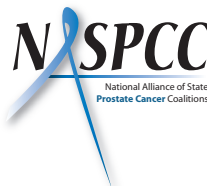
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