Initial Management of Noncastrate Advanced, Recurrent or Metastatic Prostate Cancer: ASCO Guideline Update

Virgo et al.
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Background & Methodology
Introduction

• ASCO published two earlier versions of a clinical practice guideline on the initial hormonal management of androgen-sensitive (noncastrate), advanced, recurrent, or metastatic prostate cancer\textsuperscript{1,2} and one on standard initial treatment options for metastatic prostate cancer.\textsuperscript{3}

• This current guideline updates and replaces all three prior guidelines.

• Existing ASCO guidelines already address several aspects of prostate cancer care complementary to this guideline, including:
  ▪ Optimum Imaging Strategies for Advanced Prostate Cancer,\textsuperscript{4}
  ▪ Molecular Biomarkers in Localized Prostate Cancer,\textsuperscript{5} and
  ▪ Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a CCO Guideline.\textsuperscript{6}

• Thus, none of these topics will be addressed in the current guideline as they are considered out of scope. Discussion of ADT, radical prostatectomy (RP), or radiotherapy (RT) as treatment for localized prostate cancer is also out of scope for the current guideline.
ASCO Guideline Development Methodology

• The ASCO Clinical Practice Guidelines Committee guideline process includes:
  ▪ a systematic literature review by ASCO guidelines staff
  ▪ an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  ▪ final guideline approval by ASCO CPGC

• The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses four clinical questions:

1. What are the standard initial treatment options for metastatic noncastrate prostate cancer?

2. Are combination therapies such as combined androgen blockade (castration plus a nonsteroidal antiandrogen) better than castration alone for men with noncastrate locally advanced non-metastatic prostate cancer?

3. Does early (immediate) androgen deprivation therapy improve outcomes over deferred therapy for men with noncastrate locally advanced non-metastatic disease?

4. Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy for men with biochemically recurrent non-metastatic disease?
Target Population and Audience

Target Population

• Men with noncastrate advanced, recurrent, or metastatic prostate cancer.

Target Audience

• Medical oncologists, radiation oncologists, urologists, nurses, other health care practitioners, social workers, patients, and caregivers.
Summary of Recommendations
Summary of Recommendations

Clinical Question 1

• What are the standard initial treatment options for metastatic noncastrate prostate cancer?

Recommendation 1.0

• Docetaxel, abiraterone, enzalutamide, or apalutamide, each when administered with ADT, represent four separate standards of care (SOCs) for noncastrate metastatic prostate cancer. The use of any of these agents in any particular combination or in any particular series cannot yet be recommended.
Summary of Recommendations

Recommendation 1.1

• For men with metastatic noncastrate prostate cancer with high-volume disease (HVD) as defined per CHAARTED\textsuperscript{7} who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered.

 Recommendation 1.2

• For patients with low-volume metastatic disease (LVD) as defined per CHAARTED\textsuperscript{7} who are candidates for chemotherapy, docetaxel plus ADT should not be offered.
Summary of Recommendations

Recommendation 1.3

- The recommended regimen of docetaxel for men with metastatic noncastrate prostate cancer is six doses administered at 3 week intervals at 75 mg/m² either alone (per CHAARTED)⁷ or with prednisolone (per STAMPEDE)⁸

Qualifying Statements for ADT Plus Docetaxel

- The strongest evidence of benefit for docetaxel is for those men who were diagnosed with de novo metastatic disease or HVD (defined per CHAARTED⁷ as four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease). The criteria apply independent of the presence or absence of nodal disease.³
Summary of Recommendations

Qualifying Statements for ADT Plus Docetaxel (continued)

• Men with metastatic disease who do not fit into these categories should not be offered docetaxel. The strength of the evidence to support an OS benefit is not compelling for men who do not have de novo metastatic disease and/or who do not meet the HVD criteria. Long term survival data from CHAARTED and a post hoc aggregated analysis of CHAARTED and GETUG-AFU-15 data only showed an OS benefit for men with HVD and de novo metastases. There was no OS benefit for LVD, irrespective of whether the patients had metastases at diagnosis or after failure of prior local therapy. Clarke et al. reexamined OS by disease burden using STAMPEDE data with longer follow-up but the study was inadequately powered (<80%) to detect an OS difference by disease burden if in fact one existed.

• As a chemotherapy agent, docetaxel is associated with somewhat greater toxicity than androgen-targeted therapies, such as abiraterone, but the treatment course is relatively short and the costs associated with treatment are generally covered by insurance, hence reducing the financial burden to the patient.
Summary of Recommendations

Recommendation 1.4

• For men with high-risk de novo metastatic noncastrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE\textsuperscript{11}

Recommendation 1.5

• For men with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE\textsuperscript{12}
Summary of Recommendations

Recommendation 1.6

- The recommended regimen for men with metastatic noncastrate prostate cancer is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until progressive disease is documented.

Evidence-based benefits outweigh harms

Evidence Quality: High
Strength of Recommendation: Strong
Summary of Recommendations

Recommendation 1.7

• ADT plus enzalutamide should be offered to men with metastatic noncastrate prostate cancer including both those with de novo metastatic disease and those who have received prior therapies, such as radical prostatectomy or radiotherapy for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (PSA progression-free, clinical progression-free, and overall) when compared to ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET\textsuperscript{13}. 

Evidence-based benefits outweigh harms

Evidence Quality
High

Strength of Recommendation
Strong
Summary of Recommendations

Recommendation 1.8

- The recommended regimen for men with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT

Evidence-based benefits outweigh harms

Evidence Quality
High

Strength of Recommendation
Strong
for patients with LVD
Qualifying Statement for ADT Plus Enzalutamide

- Among the subgroup of men with metastatic noncastrate prostate cancer previously treated with docetaxel, it is currently unclear whether similar survival benefits accrue long term when compared to treatment with first-generation antiandrogens plus ADT, as the final trial results for ENZAMET\textsuperscript{13} and ARCHES\textsuperscript{14} are not yet available, though it is anticipated that the long-term results will confirm the early findings. Early results (14.4 months median follow-up) from the ARCHES trial show that the risk of radiographic disease progression or death was significantly reduced with ADT plus enzalutamide versus ADT plus placebo overall as well as for pre-specified subgroups, such as prior docetaxel versus no prior docetaxel and high-volume disease versus low-volume disease. In the ENZAMET trial at 34 months, none of the planned subgroup analyses for heterogeneity, such as among those receiving early docetaxel, were significant after adjusting for multiple comparisons. Enzalutamide was FDA approved for use in the metastatic noncastrate prostate cancer setting on December 16, 2019. Discussions with patients should include the lack of data regarding long-term benefits and the cost of enzalutamide treatment compared to other options such as abiraterone.
Summary of Recommendations

Recommendation 1.9

- ADT plus apalutamide should also be offered to men with metastatic noncastrate prostate cancer, including those with de novo metastatic disease or those who have received prior therapy, such as radical prostatectomy or radiotherapy for localized disease per TITAN\textsuperscript{15}

Recommendation 1.95

- The recommended regimen for men with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT
Summary of Recommendations

Qualifying Statement for ADT Plus Apalutamide

• Men with metastatic noncastrate prostate cancer previously treated with docetaxel appear to benefit with respect to radiographic progression-free survival, but the answer is not yet conclusive. At 22.7 months, ADT plus apalutamide was associated with significantly longer radiographic progression-free survival (rPFS) and OS compared to ADT plus placebo. The effect of ADT plus apalutamide on rPFS was consistently favorable and statistically significant for most subgroups, including disease volume, Gleason score and metastasis stage (M0/M1) at initial diagnosis, but not previous docetaxel use (favored ADT plus apalutamide but was not statistically significant). It is anticipated that the long-term results will confirm the early findings. Median OS among men previously treated with docetaxel could not yet be estimated. Longer follow-up is needed. Apalutamide was FDA approved for use in the metastatic noncastrate prostate cancer population as of September 17, 2019. Discussions with patients should include the lack of long-term benefit data for men previously treated with docetaxel and the cost of apalutamide treatment.
Summary of Recommendations

Clinical Question 2

• Are combination therapies such as combined androgen blockade (castration plus a nonsteroidal antiandrogen) better than castration alone for men with noncastrate locally advanced non-metastatic prostate cancer?
Summary of Recommendations

Recommendation 2.1

- ADT plus abiraterone and prednisolone should be considered for men with noncastrate locally advanced non-metastatic prostate cancer, rather than castration monotherapy, due to the failure-free survival benefit per STAMPEDE. Radiotherapy to the primary was mandated in STAMPEDE for patients with newly diagnosed node-negative, non-metastatic disease and encouraged in patients with newly diagnosed node-positive, non-metastatic disease. Failure-free survival (time to the earliest of biochemical failure, disease progression, or death), was significantly improved for patients with non-metastatic disease treated with ADT plus abiraterone and prednisolone compared to those treated with ADT alone, even though ADT plus abiraterone was administered for two or less years to men with non-metastatic disease.
Summary of Recommendations

Recommendation 2.2

• In resource-constrained settings where drugs such as abiraterone may not be available, combined androgen blockade using ADT plus a first-generation antiandrogen, such as flutamide, nilutamide, or bicalutamide, may be offered to men with locally advanced non-metastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses.
Summary of Recommendations

Qualifying Statement for Combination Therapies Such as Combined Androgen Blockade

• For men with high-risk non-metastatic prostate cancer progressing after radical prostatectomy or radiotherapy or both, it is currently unclear whether enzalutamide (160 mg) plus leuprolide, improves metastasis-free survival compared to enzalutamide monotherapy or placebo. Though recruitment is complete for the ongoing phase III EMBARK trial, which is designed to answer this question, results are not yet available. Thus, no recommendation can be made at this time.
Summary of Recommendations

Clinical Question 3

• Does early (immediate) androgen deprivation therapy improve outcomes over deferred therapy for men with noncastrate locally advanced non-metastatic disease?

Recommendation 3.1

• Early (immediate) ADT may be offered to men who initially present with noncastrate locally advanced non-metastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo radiotherapy based on evidence in one meta-analysis of a modest, but statistically significant benefit in terms of both overall survival and cancer-specific survival among the larger population of men with locally advanced non-metastatic disease.
Summary of Recommendations

Qualifying Statements for Early versus Deferred ADT

• Discussions with patients regarding early ADT should include the risk of short- and long-term side effects. Deferred ADT is often preferred by patients who desire to avoid, or at least delay, potential ADT side effects. Consideration should be given to restricting deferred ADT to those patients who are asymptomatic.

• No recommendation can be provided at this time for men with PSA relapse after local treatment. Though existing studies suggests a potential overall survival benefit, additional research is needed as such studies were underpowered.
Summary of Recommendations

Clinical Question 4

• Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy for men with biochemically recurrent non-metastatic disease?
Summary of Recommendations

Recommendation 4.1

• Intermittent therapy may be offered to men with high-risk biochemically recurrent non-metastatic prostate cancer after RP and/or RT based on evidence in meta-analyses of the non-inferiority of intermittent androgen deprivation therapy (IADT) when compared to continuous androgen deprivation therapy (CADT) with respect to overall survival. This is further supported by evidence from four meta-analyses testing superiority. Low-risk biochemical recurrence after radical prostatectomy is defined as a PSA doubling time > 1 year and pathologic Gleason score < 8. Low-risk biochemical recurrence after radiotherapy is defined as an interval to biochemical recurrence > 18 months and clinical Gleason score < 8. High-risk biochemical recurrence after radical prostatectomy is defined as a PSA doubling time < 1 year or a pathologic Gleason score of 8-10. High-risk biochemical recurrence after radiotherapy is defined as an interval to biochemical recurrence < 18 months or a clinical Gleason score of 8-10. Active surveillance may be offered to men with low-risk biochemically recurrent non-metastatic prostate cancer.
Summary of Recommendations

Qualifying Statements for IADT

• Although men with noncastrate de novo metastatic prostate cancer were included in the studies reviewed for this clinical question, alternative standard of care therapies with proven survival benefits now exist, as outlined in Recommendation 1 to include ADT plus docetaxel, ADT plus abiraterone, ADT plus enzalutamide or ADT plus apalutamide. Similar support for these existing standards of care does not universally exist for men with LVD or those who develop M1 disease after prior local therapy and further research is needed. No specific additional recommendation with respect to the use of IADT in the noncastrate metastatic prostate cancer population was possible at this time because IADT has not been studied in combination with additional cytotoxic or hormonal agents in this population.

• Patients considering IADT should be made aware of the potential benefits of IADT associated with the off-treatment intervals, such as reduced treatment side effects, quality-of-life benefits and lower cost. As patients on IADT require close follow-up, they must be motivated to adhere to frequent doctor visits for monitoring, even during off-treatment periods.
Discussion
Patient and Clinician Communication

- Patients should be counseled about the potential side effects associated with ADT such as depression, dementia, stroke, myocardial infarction, deep venous thrombosis, hot flush, fatigue and nausea.

- Shared decision making is very important. Discussions should clarify whether treatment options are palliative versus curative and the associated likelihood of progression associated with each option.

- Considering the patient’s level of anxiety regarding their condition is important in determining when to start ADT, immediately versus later in the disease process. Patients considering IADT should be aware of the potential benefits of IADT associated with the off-treatment intervals. As patients on IADT require close follow-up, they must be motivated to adhere to frequent monitoring, even during off-treatment periods.

- Survivorship care plans provide a road map for the patient’s care and reduce patient uncertainty regarding what lies ahead with respect to treatment. They also help patients plan for the future.
Cost Implications

- Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient’s disease and there are two or more treatment options that are comparable in terms of benefits and harms.

- The price of cancer treatments varies, depending on factors including the source of the drugs, availability and use of generic or biosimilar alternative drugs, supportive care agents, the legal structure of the dispensing clinic and patient characteristics, such as weight and estimated body surface area.
  - Table 4 in the full guideline displays various prices for these agents, by month or by cycle.

- Patient out of pocket costs may vary depending on insurance coverage. Patients should be aware that different products may be preferred or covered by their insurance plan. Price may vary between different pharmacies.

- When discussing financial issues and concerns, patients should be made aware of any financial counseling services available.24
Additional Resources

• More information, including a supplement and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines

• Patient information is available at www.cancer.net
# Guideline Panel Members

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<tr>
<th>Name</th>
<th>Affiliation/Institution</th>
<th>Role/Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katherine S. Virgo, PhD, MBA, FASCO (cochair)</td>
<td>Rollins School of Public Health, Department of Health Policy and Management, Emory University, Atlanta, GA</td>
<td>Health Services Research and Health Economics</td>
</tr>
<tr>
<td>James Talcott, MD, SM (cochair)</td>
<td>Nanhealth, Inc., Culver City, CA</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Prof. Ronald de Wit, MD, PhD</td>
<td>Lead, Experimental Systematic Therapy of Urogenital Cancers, Erasmus MC, Rotterdam, NL</td>
<td>Internal medicine, GU oncology</td>
</tr>
<tr>
<td>Thomas J. Smith, MD, FACP, FASCO, FAAHPM</td>
<td>Johns Hopkins Medicine, Baltimore, MD</td>
<td>Medical Oncology, Hospice and Palliative Medicine, Pain Management, Palliative Care</td>
</tr>
<tr>
<td>Mary-Ellen Taplin, MD</td>
<td>Dana-Farber Cancer Institute, Boston, MA</td>
<td>Hematology/Medical Oncology</td>
</tr>
<tr>
<td>James L. Wade III, MD, FASCO</td>
<td>CancerCare Specialists of Illinois, Decatur, Illinois</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Charles L. Bennett, MD, PhD</td>
<td>University of South Carolina College of Pharmacy, Columbia, SC</td>
<td>Hematology/Medical Oncology</td>
</tr>
<tr>
<td>Howard I. Scher, MD</td>
<td>Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Paul L. Nguyen, MD</td>
<td>Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Martin Gleave, MD</td>
<td>University of British Columbia, Vancouver, BC, Canada</td>
<td>Urology/Surgery</td>
</tr>
<tr>
<td>Scott C. Morgan, MD, MSc</td>
<td>The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Sean Sachdev, MD</td>
<td>Northwestern University, Chicago, IL</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Andrew Loblaw, MD, MSc</td>
<td>Sunnybrook Health Sciences Centre, Toronto, ON, Canada</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>David S. Mendelson, MD</td>
<td>Virginia G Piper Cancer Network, Scottsdale, AZ</td>
<td>Practice Guidelines Implementation Network (PGIN) representative</td>
</tr>
<tr>
<td>David L. Graham, MD, FACP, FASCO</td>
<td>Levine Cancer Institute, Charlotte, NC</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Neha Vapiwala, MD, FACR</td>
<td>University of Pennsylvania Perelman School of Medicine, Philadelphia, PA</td>
<td>Radiation Oncology</td>
</tr>
<tr>
<td>Amy M. Sion, PharmD, BCOP</td>
<td>Medical University of South Carolina, Charleston, SC</td>
<td>Oncology Pharmacy</td>
</tr>
<tr>
<td>Virgil H. Simons, MPA</td>
<td>The Prostate Net, Sanford, NC</td>
<td>Patient representative</td>
</tr>
<tr>
<td>R. Bryan Rumble, MSc</td>
<td>American Society of Clinical Oncology, Alexandria, VA</td>
<td>ASCO Practice Guidelines Staff (Health Research Methods)</td>
</tr>
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References

References

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