ASCO special articles

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

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abstract

PURPOSE Update all preceding ASCO guidelines on initial hormonal management of noncastrate advanced, recurrent, or metastatic prostate cancer.

METHODS The Expert Panel based recommendations on a systematic literature review. Recommendations were approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee.

RESULTS Four clinical practice guidelines, one clinical practice guidelines endorsement, 19 systematic reviews with or without meta-analyses, 47 phase III randomized controlled trials, nine cohort studies, and two review papers informed the guideline update.

RECOMMENDATIONS Docetaxel, abiraterone, enzalutamide, or apalutamide, each when administered with androgen deprivation therapy (ADT), represent four separate standards of care for noncastrate metastatic prostate cancer. Currently, the use of any of these agents in any particular combination or series cannot be recommended. ADT plus docetaxel, abiraterone, enzalutamide, or apalutamide should be offered to men with metastatic noncastrate prostate cancer, including those who received prior therapies, but have not yet progressed. The combination of ADT plus abiraterone and prednisolone should be considered for men with noncastrate locally advanced nonmetastatic prostate cancer who have undergone radiotherapy, rather than castration monotherapy. Immediate ADT may be offered to men who initially present with noncastrate locally advanced nonmetastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo radiotherapy. Intermittent ADT may be offered to men with high-risk biochemically recurrent nonmetastatic prostate cancer. Active surveillance may be offered to men with low-risk biochemically recurrent nonmetastatic prostate cancer. The panel does not support use of either micronized abiraterone acetate or the 250 mg dose of abiraterone with a low-fat breakfast in the noncastrate setting at this time.

Additional information is available at www.asco.org/genitourinary-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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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[1,2] and one on standard initial treatment options for metastatic prostate cancer.[3] As new information is now available, the current guideline updates and replaces all three prior guidelines.

Existing ASCO guidelines already address several aspects of prostate cancer care complementary to this guideline. These include Optimum Imaging Strategies for Advanced Prostate Cancer,[4] Molecular Biomarkers in Localized Prostate Cancer,[5] and Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a Cancer Care Ontario Guideline.[6] Thus, none of these topics will be addressed in the current guideline as they are considered out of scope. Discussion of androgen deprivation therapy (ADT), radical prostatectomy (RP), or radiotherapy (RT) as treatment for localized prostate cancer is also out of scope for the current guideline.

Guideline Questions

The current guideline addresses four clinical questions: (1) What are the standard initial treatment options for metastatic noncastrate prostate cancer? (2)

THE BOTTOM LINE

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

Guideline Question

What are the optimum evidence-based treatment modalities for men with noncastrate advanced, recurrent, or metastatic prostate cancer?

Target Population

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

Target Audience

Medical oncologists, radiation oncologists, urologists, nurses, other healthcare practitioners, social workers, patients, and caregivers.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

CLINICAL QUESTION 1

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

Recommendation 1

Recommendation 1.0. Docetaxel, abiraterone, enzalutamide, or apalutamide, each when administered with androgen deprivation therapy (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 (Type: evidence-based, benefits-harms ratio unknown; Evidence quality: no evidence available; Strength of recommendation: strong).

ADT Plus Docetaxel[3]

Recommendation 1.1. For men with metastatic noncastrate prostate cancer with high-volume disease (HVD) as defined per CHAARTED[7] who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with HVD).

Recommendation 1.2. For patients with low-volume metastatic disease (LVD) as defined per CHAARTED[7] who are candidates for chemotherapy, docetaxel plus ADT should not be offered (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with LVD).

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/m^2 either alone (per CHAARTED)[7] or with prednisolone (per Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE])[8] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).[3]

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 CHAARTED[7] 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]
- Men with metastatic disease who do not fit into these categories should not be offered docetaxel. The strength of the evidence to support an overall survival (OS) benefit is not compelling for men who do not have de novo metastatic disease and/or who do not meet the HVD criteria.[3] Long term survival data from CHAARTED[9] 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.[9] Clarke et al[10] re-examined 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.

ADT Plus Abiraterone[3]

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[11] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with high-risk disease as defined per LATITUDE).

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THE BOTTOM LINE (CONTINUED)

Recommendation 1.5. For men with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE[12] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with low-risk disease per STAMPEDE).

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 (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

ADT Plus Enzalutamide

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 (RP) or radiotherapy (RT) for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (prostate-specific antigen [PSA] progression-free, clinical progression-free, and overall) when compared with ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET[13] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.8. The recommended regimen for men with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 with treatment with first-generation antiandrogens plus ADT, as the final trial results for ENZAMET[13] and ARCHES[14] are not yet available, although 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 (DP) or death was significantly reduced with ADT plus enzalutamide versus ADT plus placebo overall as well as for prespecified subgroups, such as prior docetaxel versus no prior docetaxel and HVD versus LVD. 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 with other options such as abiraterone.

ADT Plus Apalutamide

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 RP or RT for localized disease per TITAN[15] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.95. The recommended regimen for men with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 (rPFS), but the answer is not yet conclusive. At 22.7 months, ADT plus apalutamide was associated with significantly longer rPFS and OS compared with 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.

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THE BOTTOM LINE (CONTINUED)

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 nonmetastatic prostate cancer?

Recommendation 2

Recommendation 2.1. ADT plus abiraterone and prednisolone should be considered for men with noncastrate locally advanced nonmetastatic prostate cancer, rather than castration monotherapy, because of the failure-free survival benefit per STAMPEDE.[12] RT to the primary was mandated in STAMPEDE for patients with newly diagnosed node-negative, nonmetastatic disease and encouraged in patients with newly diagnosed node-positive, nonmetastatic disease. Failure-free survival (time to the earliest of biochemical failure, DP, or death) was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone, although ADT plus abiraterone was administered for 2 or less years to men with nonmetastatic disease (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 nonmetastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses (Type: evidence-based; Evidence quality: high, benefits outweigh harms; Strength of recommendation: moderate).

Qualifying statement for combination therapies such as combined androgen blockade

- For men with high-risk nonmetastatic prostate cancer progressing after RP or RT or both, it is currently unclear whether enzalutamide (160 mg) plus leuprolide improves metastasis-free survival compared with enzalutamide monotherapy or placebo. Although 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.

CLINICAL QUESTION 3

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

Recommendation 3

Recommendation 3.1. Early (immediate) ADT may be offered to men who initially present with noncastrate locally advanced nonmetastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo RT based on evidence in one meta-analysis of a modest, but statistically significant benefit in terms of both OS and cancer-specific survival (CSS) among the larger population of men with locally advanced nonmetastatic disease (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

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. Although existing studies suggest a potential OS benefit, additional research is needed as such studies were underpowered.

CLINICAL QUESTION 4

Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy for men with biochemically recurrent nonmetastatic disease?

Recommendation 4

Recommendation 4.1. Intermittent therapy may be offered to men with high-risk biochemically recurrent nonmetastatic prostate cancer after RP and/or RT based on evidence in meta-analyses of the noninferiority of intermittent androgen deprivation therapy (IADT) when compared with continuous androgen deprivation therapy (CADT) with respect to OS.[16] This is further supported by evidence from four meta-analyses[17–20] testing superiority. Low-risk biochemical recurrence after RP is defined as a PSA doubling time $>$ 1 year and pathologic Gleason score $<$ 8. Low-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence $>$ 18 months and clinical Gleason score $<$ 8. High-risk biochemical recurrence after RP is defined as a PSA doubling time $<$ 1 year or a pathologic Gleason score of 8-10. High-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence $<$ 18 months or a clinical Gleason score of 8-10.[21] Active surveillance may be offered to men with low-risk biochemically recurrent nonmetastatic

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THE BOTTOM LINE (CONTINUED)

prostate cancer (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 SOCs 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.

See Figure 1. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer Algorithm for a visual aid to the recommendations.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Are combination therapies such as combined androgen blockade (castration plus a nonsteroidal antiandrogen) better than castration alone for men with noncastrate locally advanced nonmetastatic prostate cancer? (3) Does early (immediate) androgen deprivation therapy improve outcomes over deferred therapy for men with noncastrate locally advanced nonmetastatic disease? (4) Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy for men with biochemically recurrent nonmetastatic disease?

METHODS

Guideline Update Development Process

This systematic review-based guideline product was developed by a multidisciplinary expert panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The expert panel met via teleconference and/or webinar and corresponded through e-mail. Based on consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the expert panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the expert panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of rigorously conducted meta-analyses, phase III randomized clinical trials (RCTs), systematic reviews with or without meta-analyses, other relevant comparative study designs, and clinical experience. The PubMed database[22] was initially searched on August 9, 2018, for evidence published since the previous guideline was completed (January 2007 through to the end of July 2018) using the following criteria:

- Population: men with noncastrate advanced, recurrent, or metastatic prostate cancer
- Fully published or recent meeting presentations of English-language reports of rigorously conducted systematic reviews with or without meta-analysis, meta-analyses, phase III RCTs, or other relevant comparative study designs that reported on any of the following comparisons: orchiectomy versus placebo, estrogens versus placebo, antiandrogen versus orchiectomy or placebo; luteinizing hormone-releasing hormone (LHRH) agonists versus orchiectomy or placebo, LHRH

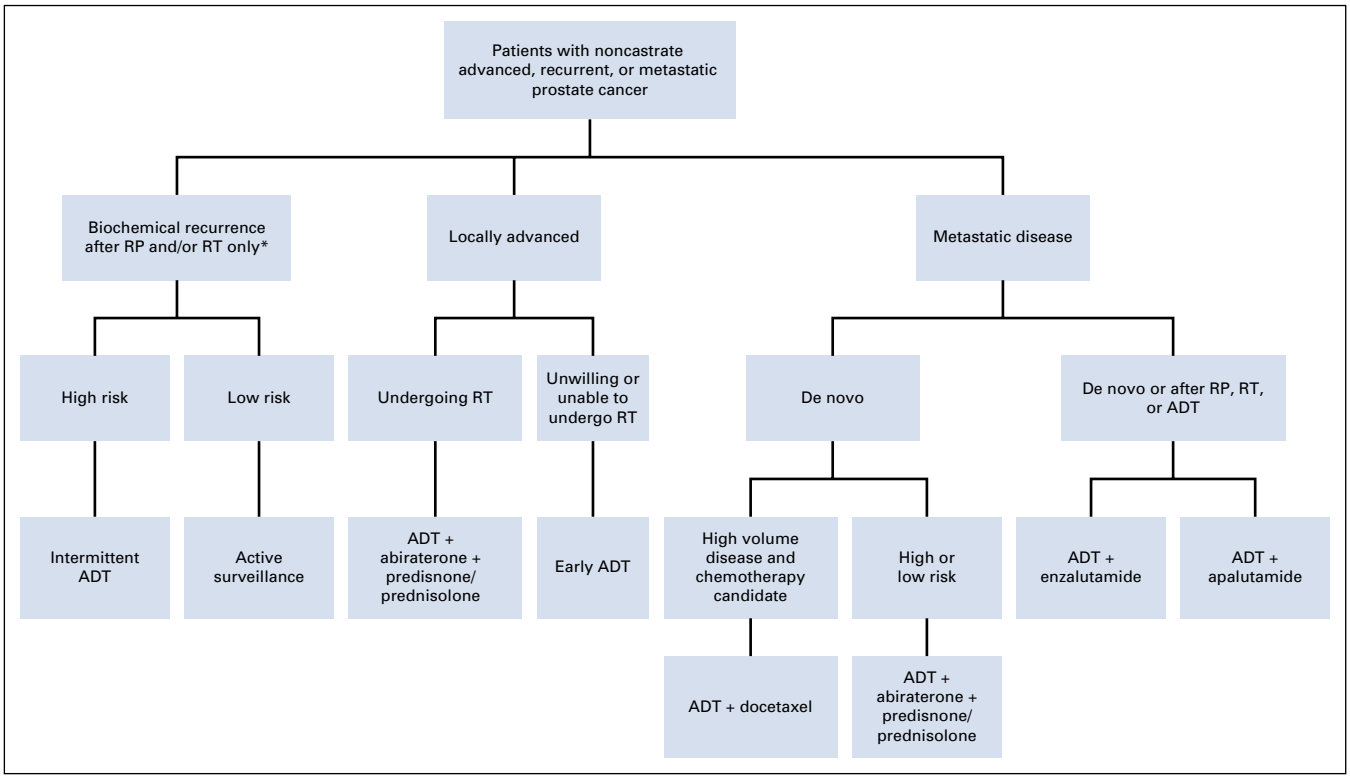

FIG 1. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer algorithm. ADT, androgen deprivation therapy; RP, radical prostatectomy; RT, radiotherapy. *Consult Lowrance et al[1] and Bekelman et al[2] for further information regarding salvage therapy options after failure of local therapy. [1]Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, Jarrard DF, Kibel AS, Morgan TM, Morgans AK, Oh WK. Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART I. *J Urol*. doi:10.1097/JU.0000000000001375. [2]Bekelman JE, Rumble RB, Chen RC, Pisansky TM, Finelli A, Feifer A, Nguyen PL, Loblaw DA, Tagawa ST, Gillessen S, Morgan TM. Clinically localized prostate cancer: ASCO clinical practice guideline endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology guideline. *J Clin Oncol* 36:3251-3258, 2018.

antagonists versus orchiectomy or placebo, early versus late therapy, intermittent versus continuous therapy.

There were 1,566 hits obtained in the initial PubMed search. After reviewing the title and abstract of these hits for relevance, 87 continued to full-text review. Of these 87 that went to full-text review, 25 were retained and an additional 12 papers were identified by panelists bringing the total to 37 included papers. The actual searches used and the included terms can be found in Data Supplement 3, online only. The literature searches were updated in June 2019 (through to the end of May 2019), bringing the total number of papers to 42; the final literature search was completed on July 21, 2020; additional papers were obtained as needed for context and interpretation.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, narrative reviews, and case reports; or (3) published in a non-English language. Also excluded were (1) studies for which results for advanced, recurrent, or metastatic prostate cancer were not reported separately from results for patients with localized disease and (2) severely underpowered studies providing inconclusive evidence for which higher quality evidence has subsequently become available. The guideline recommendations were crafted, in part, using the Guidelines into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[23] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on the formal review of the emerging literature, ASCO will determine the need for future updates to revise its recommendations on initial management of noncastrate advanced, recurrent, or metastatic prostate cancer. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional

information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

CLINICAL QUESTION 1

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

Recommendation 1

Recommendation 1.0. Docetaxel, abiraterone, enzalutamide, or apalutamide, each when administered with ADT, represent four separate 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 (Type: evidence-based, benefits-harms ratio unknown; Evidence quality: no evidence available; Strength of recommendation: strong).

ADT Plus Docetaxel[3]

Recommendation 1.1. For men with metastatic noncastrate prostate cancer with HVD as defined per CHAARTED[7] who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with HVD).

Recommendation 1.2. For patients with low-volume metastatic disease (LVD) as defined per CHAARTED[7] who are candidates for chemotherapy, docetaxel plus ADT should not be offered (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with LVD).

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/m^2 either alone (per CHAARTED)[7] or with prednisolone (per STAMPEDE)[8] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).[3]

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 CHAARTED[7] 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]
- 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.[3] Long-term survival data from CHAARTED[9] 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.[9] Clarke et al[10] re-examined 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.

ADT Plus Abiraterone[3]

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[11] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with high-risk disease per LATITUDE).

Recommendation 1.5. For men with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE[12] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with low-risk disease per STAMPEDE).

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 (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Currently, there are two FDA-approved formulations of abiraterone acetate. The original drug formulation is FDA-approved for use in conjunction with prednisone in men with high-risk metastatic noncastrate prostate cancer as well as those with metastatic castration-resistant prostate cancer. A generic version is also available. However, the drug's composition is poorly water-soluble, leading to variations in bioavailability if administered with food. The Sun Pharma Global micronized fine-particle formulation of abiraterone was designed to overcome the food-related effects and unpredictable pharmacodynamics of the original Janssen-Biotech formulation. Based on the results of the STAAR study,[24] the micronized version was approved for use in men with metastatic castration-resistant prostate cancer but is not yet FDA-approved for use in the noncastrate population (M0, M1). The two drugs are not interchangeable in terms of indications or dosing. The panel does not support the use of the micronized formulation in the noncastrate setting at this time.

Abiraterone 250 mg daily with a low-fat breakfast has been examined as an alternative to abiraterone 1,000 mg on an empty stomach for men with metastatic castration-resistant prostate cancer (CRPC) and was shown in a small phase II trial to be noninferior based on the PSA response rate over 12 weeks.[25] Although the results are promising, similar trials have not yet been conducted in the noncastrate space. In addition, PSA response at 12 weeks is not a validated surrogate for metastasis-free survival or OS. Thus, the utility of this approach over time is unknown. Also, the ability of men to understand and comply with a low-fat breakfast while on this regimen, particularly if outside a clinical trial, is unclear. The panel does not support the use of abiraterone with a low-fat breakfast for men with noncastrate metastatic prostate cancer at this time.

ADT Plus Enzalutamide

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 RP or RT for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (PSA progression-free, clinical progression-free, and overall) when compared with ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET[13] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.8. The recommended regimen for men with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 with treatment with ADT plus first-generation antiandrogens, as the final trial results for ENZAMET[13] and ARCHES[14] are not yet available, although 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 DP or death was significantly reduced with ADT plus enzalutamide versus ADT plus placebo overall as well as for prespecified subgroups, such as prior docetaxel versus no prior docetaxel and HVD versus LVD. 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 with other options such as abiraterone.

ADT Plus Apalutamide

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 RP or RT for localized disease per TITAN[15] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.95. The recommended regimen for men with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement for ADT plus apalutamide

- Men with metastatic noncastrate prostate cancer previously treated with docetaxel appear to benefit with respect to rPFS, but the answer is not yet conclusive. At 22.7 months, ADT plus apalutamide was associated with significantly longer rPFS and OS compared with 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.

Literature Review Update and Analysis

A companion guideline[3] previously addressed the use of abiraterone combined with docetaxel, docetaxel combined with ADT, and abiraterone combined with ADT for men with de novo metastatic noncastrate prostate cancer. The content of the guideline is now outdated and superseded by this guideline.

The current guideline also addresses the use of ADT plus enzalutamide and ADT plus apalutamide for men with de novo metastatic noncastrate prostate cancer, as well as treatment options for patients with metastatic noncastrate prostate cancer who may have had some form of prior treatment, such as docetaxel. The three phase III RCTs that provide data to inform recommendations are the TITAN trial,[15] the ARCHES trial,[14] and the ENZAMET trial.[13]

The multinational ARCHES trial[14] randomly assigned 1,150 men with newly diagnosed or relapsed metastatic noncastrate prostate cancer to ADT plus enzalutamide (160 mg per day) versus ADT plus placebo, stratified by disease volume (low *v* high) and prior docetaxel administration (none, 1-5 cycles, and 6 cycles). At baseline, approximately 60% of men in each arm had HVD (as defined in the CHAARTED trial,[7] 61.7% and 64.8%, respectively. Slightly $<16\%$ in each arm had prior docetaxel chemotherapy. Most patients had some prior ADT, the majority (72.1% and 68.4%, respectively) for 3 months or less (median 1.6 months). Approximately one-third had prior antiandrogen use (35.8% and 39.9%, respectively). Prior local therapy was balanced between arms (RT 12.7% and 12.5%, respectively; RP 12.5% and 15.5%, respectively). Treatment per the protocol ceased if the patient experienced unacceptable toxicity, radiographic progression, or was started on any new prostate cancer therapy, including investigational therapies. The primary study end point was radiographic progression-free survival (rPFS). The main secondary end points were time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, objective response rate, time to urinary symptom deterioration, and OS.

At the planned interim analysis (after 262 events) at a median follow-up of 14.4 months, the risk of radiographic DP or death was significantly reduced with ADT plus enzalutamide versus ADT plus placebo (HR = 0.39, 95% CI, 0.30 to 0.50, $P < .001$; rPFS median not reached *v* 19 months). The results were consistent across prespecified subgroups, such as prior docetaxel (HR = 0.52, 95% CI, 0.30 to 0.89) versus no prior docetaxel (HR = 0.37, 95% CI, 0.28 to 0.49) and HVD (HR = 0.43, 95% CI, 0.33 to 0.57) versus LVD (HR = 0.25, 95% CI, 0.14 to 0.46). Crossover to enzalutamide was then permitted for those in the placebo arm. Although it was too early to assess OS (planned for assessment at 342 deaths), death within 24 weeks of treatment discontinuation in the absence of radiographic progression was similar (2% in each arm).

Secondary end points also favored ADT plus enzalutamide, including time to first symptomatic skeletal event, time to castration resistance, and time to pain progression. Higher percentages of men achieved an undetectable PSA level and/or an objective response with ADT plus enzalutamide ($P < .001$). Compared with baseline, higher quality of life (QoL) was maintained over time by patients in both treatment arms. However, additional analyses were planned as part of long-term follow-up. In the preliminary safety analysis, the percentage of men with grade 3 or higher adverse events was similar between the treatment groups (24.3% *v* 25.6%, respectively) with no unexpected adverse events. Patients were to be followed until the earlier of death

or 24 weeks after study drug discontinuation. The planned completion date for the ongoing study is December 2023.

ENZAMET, an open-label multinational phase III RCT,[13] randomly assigned 1,125 men with metastatic noncastrate prostate cancer to ADT plus enzalutamide (160 mg per day) versus ADT plus bicalutamide, nilutamide, or flutamide. After 88 patients had already been accrued, early administration of docetaxel was permitted based on evidence published after the study had begun.[7] Stratification was conducted by disease volume (low *v* high), planned early docetaxel administration, planned use of bone antiresorptive therapy, Adult Comorbidity Evaluation 27 (ACE-27) score and trial site. At baseline, slightly more than 50% of men in each arm had HVD (as defined in the CHAARTED trial[7]). Approximately 16% in each arm had prior docetaxel chemotherapy, 75% had prior LHRH agonist or antagonist therapy, and over 50% of patients had prior nonsteroidal antiandrogen therapy within 12 weeks before random assignment. Prior local therapy was 42% in each arm. Bone antiresorptive therapy was 10% in each arm. Early use of docetaxel was planned for approximately 45% of men in each arm. Actual receipt of early docetaxel treatment was 27% among men with LVD and 61% among those with HVD. The primary end point was OS. The secondary end point was PSA progression-free survival (PFS).

At a median follow-up of 34 months, enzalutamide plus ADT was associated with significantly longer PSA progression-free (HR = 0.39, CI: 0.33 to 0.47, $P < .001$), clinical progression-free (HR = 0.40, CI: 0.33 to 0.49, $P < .001$), and overall (HR = 0.67, CI: 0.52 to 0.86, $P = .002$) survival. None of the planned subgroup analyses for heterogeneity, such as among those receiving early docetaxel, were significant after adjusting for multiple comparisons. Longer follow-up (beyond 3 years) is needed to ascertain the effects of early docetaxel therapy on OS. The estimated study completion date is September 2020.

The double-blind, multinational TITAN phase III RCT[15] trial conducted at 260 sites in 23 countries randomly assigned 1,052 men with newly diagnosed or relapsed metastatic noncastrate prostate cancer to continuous ADT plus apalutamide (240 mg) or continuous ADT plus placebo, stratified by the Gleason score at diagnosis, geographic region, and previous treatment with docetaxel. At baseline, approximately 67% of men had a Gleason score ≥ 7 at initial diagnosis and 62% and 64%, respectively, had HVD. Among the 10%-11% previously treated with docetaxel, 47% and 40%, respectively, were node stage N1 at diagnosis. Previous therapy for localized disease was received by 18% and 15% of men, respectively.

At the first planned interim analysis with a median follow-up of 22.7 months, ADT plus apalutamide was associated with significantly longer rPFS (HR = 0.48, CI: 0.39 to 0.60, $P < .001$) and OS (HR = 0.67, CI: 0.51 to 0.89, $P = .005$) compared with placebo plus ADT. The effect of ADT plus apalutamide on rPFS was consistently favorable and statistically significant for most of the subgroups, including disease volume, Gleason score, and metastasis stage (M0/M1) at initial diagnosis, but not for previous docetaxel use which favored ADT plus apalutamide, but was not statistically significant. Longer follow-up is needed. Median time to subsequent administration of cytotoxic chemotherapy was also significantly longer for apalutamide plus ADT (HR = 0.39, CI: 0.27 to 0.56, $P < .001$). The frequency of grade 3 or 4 events was similar between groups. Study crossover was permitted. The estimated study completion date is July 2021.

ADT plus enzalutamide should be offered to men with metastatic noncastrate prostate cancer, including those with de novo metastatic disease and those who have received prior local therapies, such as RP or RT for localized disease. Enzalutamide plus ADT has demonstrated survival benefits (PSA progression-free, clinical progression-free, and overall) when compared with ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET, including among men previously treated with docetaxel. It is currently unclear whether similar survival benefits accrue long term when compared with treatment with first-generation antiandrogens plus ADT as the final trial results for ENZAMET[13] and ARCHES[14] are not yet available. Discussions with patients should include the lack of data regarding long-term benefits and the cost of enzalutamide treatment compared with other second-generation antiandrogens, such as abiraterone.

Based on the results of the TITAN trial,[15] apalutamide plus ADT may also be offered to men with metastatic noncastrate prostate cancer, including both those with de novo metastatic disease and those who have received prior therapy, such as RP or RT for localized disease. Men previously treated with docetaxel appear to benefit, but the answer is not yet conclusive. Apalutamide was 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.

Clinical Interpretation

Most trials of men with new or recurrent metastatic noncastrate prostate cancer include patients who have had prior local therapy (RT or RP), prior use of LHRH agonists or antagonists, and/or prior antiandrogens as long as such use has ceased for a prespecified period of time before random assignment. Such trials generally exclude men with any previous chemotherapy use. Per the ongoing ARCHES trial,[14] there are significant benefits (reduced risk of progression or death) associated with the use of enzalutamide with ADT compared with placebo plus ADT, including for men with HVD versus LVD and those previously treated with docetaxel.

Per the ENZAMET trial,[13] in comparison to treatment with first-generation antiandrogens (bicalutamide, nilutamide, or flutamide) plus ADT, treatment with enzalutamide plus ADT provided significant benefits in terms of PSA PFS, clinical PFS, and OS. However, longer follow-up is needed to determine whether these benefits apply to the subgroup of men treated with early docetaxel.

Similarly, the TITAN trial,[15] which permitted crossover at the first interim analysis, showed both rPFS and OS benefits for apalutamide plus ADT compared with placebo plus ADT for the study population as a whole as well as for most subgroups, although longer follow-up is needed for those previously treated with docetaxel. However, apalutamide is now approved for use in the United States in the metastatic noncastrate prostate cancer population.

Furthermore, patients and their partners should understand the potential side effects of docetaxel, abiraterone, enzalutamide, and apalutamide, each when used with ADT. Underlying comorbidities should also be taken into consideration.

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 nonmetastatic prostate cancer?

Recommendation 2

Recommendation 2.1. ADT plus abiraterone and prednisolone should be considered for men with noncastrate locally advanced nonmetastatic prostate cancer, rather than castration monotherapy, because of the failure-free survival benefit per STAMPEDE.[12] RT to the primary was mandated in STAMPEDE for patients with newly diagnosed node-negative, nonmetastatic disease and encouraged in patients with newly diagnosed node-positive, nonmetastatic disease. Failure-free survival (time to the earliest of biochemical failure, DP or death) was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone, although ADT plus abiraterone was administered for 2 or less years to men with nonmetastatic disease (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 for men with locally advanced nonmetastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses (Type: evidence-based; Evidence quality: high, benefits outweigh harms; Strength of recommendation: moderate).

Qualifying statement for combination therapies such as combined androgen blockade

- For men with high-risk nonmetastatic prostate cancer progressing after RP or RT or both, it is currently unclear whether enzalutamide (160 mg) plus leuprolide improves metastasis-free survival compared with enzalutamide monotherapy or placebo. Although 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.

Literature Review Update and Analysis

Six papers were obtained that reported on combination therapies versus castration[12,26–30] comprising two meta-analyses,[26,27] two RCTs,[12,30] and two large retrospective studies.[28,29] Two meta-analyses reported on combined androgen blockade versus castration.[26,27] Yang et al[26] conducted a systematic review and meta-analysis of 16 randomized controlled trials published between 1990 and 2014. The efficacy and safety of combined androgen blockade (CAB) using an antiandrogen (steroidal antiandrogen [SAA] or nonsteroidal antiandrogen [NSAA]) was compared with castration monotherapy (LHRH agonist or orchiectomy) in 6,084 men with previously untreated locally advanced or metastatic prostate cancer. NSAAs included flutamide, nilutamide, and bicalutamide. SAAs included cyproterone acetate (CPA) and chlormadinone acetate. Compared with castration monotherapy, CAB using an antiandrogen (SAA or NSAA) was associated with significantly improved OS (n = 14 studies; HR: 0.90, 95% CI, 0.84 to 0.97, $P = .003$) and PFS (13 studies; HR: 0.89, 95% CI, 0.80 to 1.00, $P = .04$). CAB incorporating an NSAA was associated with significantly improved OS (10 studies; HR: 0.88, 95% CI, 0.82 to 0.95, $P = .0009$) and PFS (9 studies; HR: 0.85, 95% CI, 0.73 to 0.98, $P = .007$). Similar results were not found for CAB incorporating an SAA (four studies). Diarrhea and liver dysfunction or elevated liver enzymes were statistically significantly more likely among men treated with CAB incorporating an SAA. Adverse events and grade 3 or 4 events were otherwise similar when comparing CAB with monotherapy. CPA is not approved for use in the United States.

The Rashid et al[27] meta-analysis pooled data from five RCTs, published between 1990 and 1997, involving 1842 men with metastatic prostate cancer postorchiectomy. The study compared the use of nilutamide postorchiectomy (n = 907) versus placebo postorchiectomy (n = 935). For the following primary outcomes, nilutamide was favored over placebo in the fixed-effects analyses: disease control rate (four studies; risk ratio [RR]: 1.21, 95% CI, 1.12 to 1.31, $P < .0001$), DP (four studies, RR: 0.59; 95% CI, 0.47 to 0.73, $P < .0001$), objective response (four studies; RR: 1.68, 95% CI, 1.42 to 1.99, $P < .0001$), and complete response (three studies; RR: 2.03, 95% CI, 1.35 to 3.06,

$P = .0007$). With respect to stable disease, the placebo was preferred (four studies, RR: 0.79, 95% CI, 0.67 to 0.93, $P = .004$). Fixed-effects models were not presented for secondary outcomes, such as OS or PFS, likely because such analyses would be underpowered.

Over the period November 2011 through January 2014, the phase III open-label STAMPEDE RCT[12] randomly assigned 1917 patients to ADT either alone (considered standard of care) or in combination with abiraterone and prednisolone. At baseline, LHRH-based ADT was either planned or underway for 99% of patients and short-term antiandrogen use for flare protection was planned for approximately 93% of patients. For the 960 patients (M0 and M1) randomly assigned to combination therapy, treatment with abiraterone plus prednisolone started a median of 1.3 (0.7-2.6) weeks after random assignment and a median of 8 (5.0-10.9) weeks after starting ADT and lasted a median of 23.9 weeks (14.9-46.4). Among 915 patients with advanced prostate cancer (N0 or N1) and no metastases, 455 were randomly assigned to ADT alone and 460 to ADT plus abiraterone. RT was mandatory at 6-9 months after random assignment for patients with node negative, nonmetastatic disease and strongly encouraged for patients with newly diagnosed, node-positive, nonmetastatic disease. Treatment continued until progression for those with nonmetastatic disease for whom RT was not planned.

An intermediate outcome, failure-free survival (time to the earliest of biochemical failure, DP, or death), was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone (HR: 0.21, 95% CI, 0.15 to 0.31, $P < .05$, exact value not reported). Combined treatment was associated with a 79% relative improvement, although treatment duration was 2 years or less. Subgroup analysis of OS (primary outcome measure) among men with nonmetastatic disease was premature as few men (8.3%) had died by the study publication date (HR: 0.75, 95% CI, 0.48 to 1.18).

Interim results from one double-blind phase III RCT[30] were included in the most recent version of this guideline.[1] Updated survival data, subsequently reported at a median follow-up of 5.2 years,[30] inform the current guideline update (and were also included in the Yang et al[25] meta-analysis). In the original trial, 205 patients from 49 centers in Japan with previously untreated, advanced prostate cancer were randomly assigned to CAB (investigator's choice of LHRH agonist [goserelin 3.6 mg or leuprorelin 3.75 mg] plus bicalutamide 80 mg) versus the investigator's choice of the same two LHRH agonists plus placebo. In the original analysis at a median follow-up of 2.4 years,[30] CAB significantly ($P < .001$) prolonged both time to progression (TTP) and time to treatment failure. In the updated report,[30] Cox regression analysis of the new survival data indicated a significant OS advantage for CAB compared with LHRH-agonist monotherapy (HR 0.78, 95% CI, 0.60 to 0.99, $P = .0498$; log-rank test: $P = .0425$). Cause-specific survival did not differ between the two groups. A PSA nadir concentration ≤ 1 ng/mL was predictive of improved survival. A higher percentage of patients achieved PSA nadir concentrations ≤ 1 ng/mL with CAB versus with LHRH-A monotherapy (81.4% *v* 33.7%, $P < .001$).

Currently ongoing is the phase III EMBARK trial (ClinicalTrials.gov identifier: NCT02319837). The study compares enzalutamide (160 mg) plus leuprolide versus enzalutamide monotherapy versus placebo plus leuprolide in patients with high-risk nonmetastatic prostate cancer progressing after RP or RT or both. The primary outcome of interest is metastasis-free survival. Enrollment as of July 29, 2019, was 1,068 and the study is no longer recruiting. The final data collection date for the primary outcome measure is planned for July 7, 2020. The estimated completion date of the trial is July 31, 2023. No other data are currently available.

Two large retrospective cohort studies compared CAB versus castration.[28,29] Using data from a Japanese multi-institutional registry, Onozawa et al[28] retrospectively compared 8,379 men treated with CAB (ADT + an NSAA) versus 5,395 men treated with castration monotherapy (medical or surgical castration) to determine how different methods of first-line ADT affected time to castration-resistant prostate cancer. ADT start dates ranged from January 1, 2001, to December 31, 2003, and patients were followed for a median of 3.7 years. Patients treated with an NSAA other than bicalutamide or flutamide were excluded as were patients on NSAA monotherapy. Overall, 18.3% of men had clinical stage III and 31.6% had stage IV disease. Medical castration (leuprolide or goserelin) was the initial form of treatment in 91.4% of patients. The majority (86.0%) of patients treated with CAB received bicalutamide (80mg) as their first NSAA. As the treatment method was not randomly assigned, CAB was more frequently selected for younger patients and those with high-risk characteristics. Thus, propensity score matching (operationalized as the probability of CAB) was used to eliminate significant differences between the two treatment groups at baseline with respect to age and high risk. The final matched sample contained 4,413 patients in each arm (8,826 in total). After matching, the PFS rate was higher for men treated with CAB versus castration monotherapy (65.6% *v* 59.6% at 5 years). The median TTP was significantly longer for CAB versus castration monotherapy (11.6 *v* 7.1 years, respectively; HR 0.78, 95% CI, 0.72 to 0.84, $P < .001$). In subgroup analyses, the PFS rate was higher in the CAB group for all risk subgroups except the highest risk categories, such as high J-CAPRA risk (Japan Center of Prostate Risk Assessment) and age older than 80 years. According to Onozawa et al,[28] based on the recent published

research,[7,12] docetaxel or abiraterone plus ADT may be better therapeutic options for patients at highest risk.

In a single-facility retrospective study,[29] 300 men with advanced disease who received maximal androgen blockade (goserelin or orchiectomy plus either bicalutamide or flutamide) were compared with 308 men who received castration alone.[29] Over 80% of men in both treatment arms had orchiectomy as opposed to medical castration. In the castration-alone group, 39% of those who underwent orchiectomy were reclassified as castration-alone because they received NSAAs for < 3 months. After a median follow-up of 40 months, OS was similar (61 months) between the two groups (HR 0.957, 95% CI, 0.719 to 1.131, $P = .092$), but PFS favored CAB (49.39 ± 14.88 *v* 44.30 ± 13.41 months, HR not reported, $P = .037$). Among 248 men with metastatic disease, CAB was associated with a 6-month improvement (51.49 ± 16.83 *v* 45.26 ± 17.15) in OS (HR = 0.794, 95%CI 0.627 to 0.954, $P = .006$) and a 10-month improvement (44.49 ± 15.44 *v* 34.48 ± 14.95, HR not reported, $P = .014$) in PFS versus castration alone. In contrast, for 360 men with nonmetastatic disease, there was no benefit associated with CAB compared with castration alone in terms of either OS ($P = .143$) or PFS ($P = .096$). Among 144 men with metastatic disease treated with CAB, those receiving bicalutamide had a significantly longer PFS than men treated with flutamide (45.24 ± 15.69 *v* 38.85 ± 15.21 months; HR 0.873, 95% CI, 0.656 to 1.234, $P = .045$).

Clinical Interpretation

ADT plus abiraterone plus prednisolone should be considered for men with noncastrate advanced prostate cancer who have undergone RT, rather than castration monotherapy. The recommendation with respect to abiraterone, for M0 disease is based on data from STAMPEDE.[12] In this phase III RCT, an intermediate outcome, failure-free survival (time to the earliest of biochemical failure, DP, or death), was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone. Combined treatment was associated with a 79% relative improvement, although treatment duration was 2 years or less. A recommendation supporting abiraterone plus ADT for men with M1 disease was already made in the Morris et al[3] guideline per LATITUDE[11] and STAMPEDE.[12]

For first-generation antiandrogens, the recommendation for M0 disease is based on evidence from meta-analyses.[26] Compared with castration monotherapy, CAB plus an NSAA was associated with significantly improved OS and PFS.

Discussions with patients and their partners should include potential side effects and additional costs associated with combination therapies such as CAB. Underlying comorbidities should also be taken into consideration.

CLINICAL QUESTION 3

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

Recommendation 3

Recommendation 3.1. Early (immediate) ADT may be offered to men who initially present with noncastrate locally advanced nonmetastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo RT based on evidence in one meta-analysis of a modest, but statistically significant benefit in terms of both OS and CSS among the larger population of men with locally advanced nonmetastatic disease (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

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. Although existing studies suggest a potential OS benefit, additional research is needed as such studies were underpowered.

Literature Review Update and Analysis

Studies that reported on early ADT compared with late ADT included one meta-analysis[31] and two RCTs, the TROG 03.06/VCOG PR 01-03 (TOAD) trial[32] and the EORTC 30846 trial.[33,34] As part of a larger study with the goal of determining whether a possible interaction exists between local treatment and ADT, Verhagen et al[31] systematically reviewed five RCTs published between 1973 and 2008 (VACURG I,[35,36] MRC,[37] SAKK 08/88,[38] EORTC 30891,[39] and EORTC 30846,[33,34]) involving 3,299 men with locally advanced or metastatic disease as well as those with disease at any stage who were unfit for or unwilling to undergo curative treatment, excluding those treated with diethylstilbestrol or an antiandrogen. None of those included in the meta-analysis had undergone previous local treatment. The meta-analysis showed that, in the absence of local treatment, early versus deferred ADT provided a modest but statistically significant benefit in terms of both OS (10% ± 4 reduction in deaths; HR: 0.90, 95% CI, 0.83 to 0.97, $P < .01$) and CSS (21% ± 5 reduction in cancer-specific deaths, HR: 0.79, 95% CI, 0.71 to 0.89, $P < .0001$). Limitations of the analysis include the variation in populations included in the meta-analysis as well as the inclusion of pre-PSA era studies.

The TROG 03.06/VCOG PR 01-03 (TOAD) open-label RCT[32] involving 29 centers in 3 countries (Australia, New Zealand, and Canada) randomly assigned 293 men (261 with PSA relapse and 32 with de novo incurable disease) with localized or locally advanced prostate cancer in 2004-2012 to receive either delayed (n = 151) or immediate (n = 142) ADT. The selection of ADT method was at the physician's discretion. After a 5-year median follow-up period, OS in the delayed group was 86.4% (95% CI, 78.5 to 91.5) versus 91.2% (95% CI, 84.2 to 5.2) in the immediate group ($P = .047$). However, because of insufficient sample size as a result of slower than expected accrual, neither the unadjusted (HR 0.55, 95% CI, 0.30 to 1.00, $P = .050$) nor the adjusted analyses were statistically significant (HR: 0.54, 95% CI, 0.27 to 1.06, $P = .074$). Similarly, there was no significant difference in OS for the PSA-relapse subgroup alone (HR 0.58, 95% CI, 0.30 to 1.12, $P = .10$). There was also no significant difference in time to first complication. The authors indicated plans to combine data from the TOAD and ELAAT trials in an attempt to increase statistical power. At present, the results of the combined analyses have not been published. There was also no difference in a secondary end point of the trial, global health-related quality of life (HRQoL) at 2 years or in, for example, physical, role, or emotional functioning. Both early hot flushes (OR: 2.87 [1.96 to 4·21, $P < .0001$]) and breast-related symptoms (OR: 2.64 [1.61 to 4.34], $P = .00013$) were significantly more frequent among patients receiving immediate ADT.[32]

The EORTC 30846 trial[33,34] was designed as a noninferiority trial, randomly assigning 234 men with N1-3, M0 prostate cancer to receive either delayed (n = 115) or immediate (n = 119) ADT over the period 1986-1998. Treatment consisted of goserelin plus 1 month of CPA or orchiectomy. After a median follow-up period of 13 years, no difference in median OS was detected between the two groups (6.1 years, delayed ADT *v* 7.6 years immediate ADT; HR: 1.22, 95% CI, 0.92 to 1.62). Unfortunately, the trial was underpowered for noninferiority as the upper bound of the CI exceeded the 1.5 cutoff.

Clinical Interpretation

Early (immediate) ADT may be offered to men who initially present with locally advanced disease who are unwilling to undergo curative-intent treatment. For men with PSA relapse after local treatment, existing research in this area suggests a potential OS benefit, but additional research is needed as these studies were underpowered. 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. Discussions with patients and their partners should include the potential side effects of ADT. Consideration should be given to the patient's underlying comorbidities and their level of anxiety regarding their condition.

CLINICAL QUESTION 4

Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy for men with biochemically recurrent nonmetastatic disease?

Recommendation 4

Recommendation 4.1. Intermittent therapy may be offered to men with high-risk biochemically recurrent nonmetastatic prostate cancer after RP and/or RT based on evidence in meta-analyses of the noninferiority of IADT when compared with CADT with respect to OS.[16] This is further supported by evidence from four meta-analyses[17–20] testing superiority. Low-risk biochemical recurrence after RP is defined as a PSA doubling time > 1 year and pathologic Gleason score < 8. Low-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence > 18 months and clinical Gleason score < 8. High-risk biochemical recurrence after RP is defined as a PSA doubling time < 1 year or a pathologic Gleason score of 8-10. High-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence < 18 months or a clinical Gleason score of 8-10.[21] Active surveillance may be offered to men with low-risk biochemically recurrent nonmetastatic prostate cancer (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 SOC 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 also be motivated to adhere to frequent doctor visits for monitoring, even during off-treatment periods.

TABLE 1. IADT *v* CADT Clinical Trials Included in Each Systematic Review and/or Meta-Analysis[a]

	Combined Systematic Review and Meta-Analysis						Systematic Review Only		
Clinical Trials Reviewed	Magnan et al[16]	Dong et al[39]	Botrel et al[17]	Brungs et al[18]	Niraula et al[19]	Tsai et al[20]	Hussain et al[42]	Kratiras et al[40]	Sciarra et al[41]
Verhagen et al[52]	X		X (2008, 2013)[b]	X (2008)[b]					
Calais da Silva et al[43]	X		X				X		
Salonen et al[51,54,55]	X	X	X	X	X	X	X	X	X
Hussain et al[47]	X		X	X	X (2012)[b]	X	X	X	X
Langenhuisen et al[48]			X	X		X	X	X	X
Organ et al[89]	X								
Crook et al[46]	X		X	X	X	X	X	X	X
Mottet et al[49]	X	X (2009)[b]	X	X	X	X	X	X	X
Tunn et al[90]	X (2007)[b]		X	X	X (2007)[b]				
Langenhuisen et al[91] (neoadjuvant to RT)		X							
Calais da Silva et al[44]	X	X	X	X	X	X	X	X	X
Irani et al[92]	X		X	X		X			
Miller et al[93]	X		X	X	X				
Yamanaka et al[94]	X			X					
Schasfoort et al[95]	X				X				
De Laval et al[55]	X	X	X	X	X	X		X	X
Herring et al[96]			X	X			X		
Crook et al[65]		X							
Total studies reviewed	14	6	13	13	9	8	8	7	7

[a]Three trials were not included in any of the published systematic reviews or meta-analyses (Casas et al,[46] Schulman et al,[52] and Klotz et al[66]).
[b]Review or meta-analysis cited only an abstract of the trial rather than the final published results.

Literature Review Update and Analysis

A total of nine systematic reviews,[16–20,37,40–43] six with meta-analyses[16–20,37,40] and 3 without,[41–43] reported on intermittent versus continuous androgen deprivation. Results from ten RCTs[44–53] were also published during the time period of interest.

Nine systematic reviews were identified[16–20,37,40–43] that reported on intermittent versus continuous androgen deprivation (IADT *v* CADT), comprising six that also conducted a meta-analysis[16–20,37,40] and three[41–43] that did not. The six meta-analyses will be discussed first as they summarize quantitative data on measures such as OS, PFS, and CSS. Purely systematic reviews tend to focus on differences in trial or analytic methodology across the RCTs reviewed. Both analytic types provide important data to inform the guidelines presented herein. Table 1 depicts which clinical trials are included in each of the nine review articles. Table 2 summarizes the findings of all the phase III RCTs that were published since the last guideline update (2007) and which inform the current guideline.

Table 3 compares the results of the six meta-analyses. Only one of the six meta-analyses (Magnan et al)[16] was designed to test whether IADT was noninferior to CADT. The remaining five tested whether IADT was superior to CADT. All six meta-analyses included OS as a primary outcome. In four meta-analyses, OS was the sole primary outcome.[17,18,20,40] Although secondary outcomes varied widely, CSS was a secondary outcome in all except Dong et al[40] With the exception of Tsai et al,[20] all included some measure of progression (PFS, TTP, or DP) as a secondary outcome.

The Dong et al[40] meta-analysis was excluded from further discussion at this point because the patient populations included in their analysis were considered too different to be suitable for analysis in the same meta-analysis. For example, Dong et al[40] combined results from phase II and phase III studies and also combined results from studies of ADT for castration-resistant disease with studies of ADT for castration-sensitive disease. In addition, the method for selecting studies for inclusion in the meta-analysis did not appear to be either systematic or exhaustive. Other meta-analyses, such as those of Magnan et al[16] and Botrel et al,[17] covered basically the same time period and included more than double the number of phase III RCTs and focused on a more consistently defined population.

TABLE 2. Phase III Clinical Trials of IADT *v* CADT Grouped by Nonsteroidal *v* Steroidal Treatment and Sorted by Stage

Trial	Trial Characteristics	N	Stage	Hx	Stratification Criteria	Induction Prerandom Assignment (mos, drugs)	Tx Regimen	Median F/U	Primary End Points	Secondary End Points	Results
Trials using nonsteroidal treatments											
Casas et al[46]: GICOR	Open label, noninferiority, 11 Spanish hospitals, 2005-2009	77	T1c-T3b, M0	Biochemical failure (PSA nadir +2 ng/mL) after EBRT; No prior ADT or RP	Gleason score (good *v* poor prognosis)	NR	6 months IADT; drugs not specified	48 mo	Disease progression (PSA GE 4 ng/mL), QoL		Underpowered; prematurely closed; slow accrual
Schulman et al[52]: ICELAND	Open label, superiority, 102 European facilities, 2006-2013	701	T3-T4, M0	Nonmetastatic relapsing, locally advanced or PSA GE 5 ng/mL after RP or RT	NR	6 mos; leuprorelin acetate q3m plus bicalutamide daily for 1 month	Leuprorelin acetate q3m plus bicalutamide	NR	Time to PSA progression at 3 years	PSA PFS, OS, WHO/ ECOG PS, QoL	Median time to PSA progression not reached
Crook et al[47]: PR7	Noninferiority, 5 int'l ca coop groups, 1999-2005	1,386	M0	Localized disease with rising PSA after primary or salvage RT (with or without RP)	Prior RP and ADT, time since RT completion, baseline PSA	No induction period.	8 mo. tx cycles of LHRH agonist plus nonsteroidal antiandrogen	6.9 years	OS	Time to CRPC, QoL	Trial stopped early; IADT noninferiority presumed but actual CADT survival longer than prespecified (9.2 *v* 7 years)
Hussain et al[48]: SWOG 9346	Noninferiority, 5 int'l ca coop groups, 1995-2008	1,535	M1, hormone sensitive	Metastatic; prior ADT or finasteride allowed	PS, prior ADT or finasteride, extent of disease	7 months: LHRH agonist plus antiandrogen; goserelin plus bicalutamide in the United States	LHRH agonist plus antiandrogen; goserelin plus bicalutamide in the United States	9.8 years	OS, QoL	NR	Statistically inconclusive results
Mottet et al[50]: TAP22	Open label, superiority, 58 European facilities 1996-2005	169	M1, PSA > 20 ng/mL	Metastatic disease; no previous HT	NR	6 months; leuprorelin plus flutamide	Consecutive 3 months periods of leuprorelin plus flutamide	3.7 years	OS	PFS, QoL	Underpowered
Langenhuijsen et al[49]: TULP	Open label, 43 facilities in 12 countries, 1998-2001; assessing whether PSA predictive of progression	193	N1 M0 or M1	37 M0, 156 M1; prior RP or RT allowed	NR	6 months; buserelin plus nilutamide	Buserelin plus nilutamide	31 mo	Time to clinical progression (EORTC 1989 criteria)	OS, QoL, side effects	Underpowered
Trials using steroidal treatments[a]											
Verhagen et al[53]: NTR 99/130	Open label, superiority, 23 European facilities, 2000-2006	258	M1, PSA GE 20 and LE 1000	Bone metastatic; no previous endocrine or systemic tx	NR	3-6 months: CPA	CPA; LHRH agonist added at progression	3.3 yrs	Time to PSA progression	TTP (clinical) while on CPA, QoL, OS, PCSS	Underpowered, prematurely closed; slow accrual; high dropout rate
Calais da Silva et al[44]: SEUG 9901	Noninferiority, 31 European facilities, 2000-2007	918	cT3-cT4 M0-M1	Locally advanced or metastatic; no prior RP, RT, chemo, or ADT	NR	3 months: CPA for 2 wks followed by monthly CPA plus triptorelin	CPA	66 mo	OS	DSS, TTP, QoL	Noninferiority of IADT unclear for OS. Reported early at 5 years follow-up but required N of deaths not reached

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TABLE 2. Phase III Clinical Trials of IADT *v* CADT Grouped by Nonsteroidal *v* Steroidal Treatment and Sorted by Stage (continued)

Trial	Trial Characteristics	N	Stage	Hx	Stratification Criteria	Induction Prerandom Assignment (mos, drugs)	Tx Regimen	Median F/U	Primary End Points	Secondary End Points	Results
Salonen et al[51]: FinnProstate VII	Open label, superiority, 27 clinics in Finland, 1997-2003	554	M0 and PSA GE 60 ng/mL; T3-4 M0 and PSA GE 20 ng/mL; M1 and any PSA;	Locally advanced, recurrent, or metastatic disease, prior RP or RT allowed but no previous HT	NR	24 weeks; goserelin acetate plus at least 12.5 days of CPA for flare protection	24 weeks; goserelin acetate plus at least 12.5 days of CPA for flare protection	65 mo	TTP	OS, PCSS, TTF, QoL	Underpowered
Calais da Silva et al[45]: SEUG 9401	Superiority, 32 European facilities, years NR	626	cT3—cT4 M0, cT3—cT4 M1; PSA < 4 ng/mL	Locally advanced or metastatic disease; no previous HT or chemo; 425 M0 and 191 M1	NR	3 months; LHRH agonist plus CPA	LHRH agonist plus CPA	51 mo	TTP	OS, QoL	No significant differences in outcomes of interest.

Abbreviations: ADT, androgen deprivation therapy; CADT, continuous androgen deprivation therapy; CPA, cyproterone acetate; CRPC, castration-resistant prostate cancer; DSS, disease-specific survival; EBRT, electron beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GICOR, Grupo de Investigacion Clınica en Oncologıa Radioterapica; HT, hormone therapy; IADT, intermittent androgen deprivation therapy; ICELAND, Intermittent versus Continuous ELigard ANDrogen deprivation therapy; LHRH, luteinizing hormone-releasing hormone; N/A, not applicable; NR, not reported; NTR, Netherlands Trial Register; OS, overall survival; PCSS, prostate cancer-specific survival; PFS, progression-free survival; PS, performance status; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomized clinical trial; RP, radical prostatectomy; RT, radiotherapy; SEUG, South European Uroncological Group; TTF, time to failure; TTP, time to progression; TULP, Therapy Upgrading Life in Prostate cancer.

[a]All four RCTs testing use of a steroidal drug used CPA which is not approved for use in the United States but is approved for use in other countries.

TABLE 3. Published Meta-Analyses Comparing IADT With CADT (2013-2015)[a]

Published Meta-Analyses	Years	RCTs	Men	Primary Outcomes	Secondary Outcomes	Median Follow-Up	Analysis Type	OS Results	CSS Results	PFS Results	TTP Results	DP Results	QoL and AE Results
Magnan et al[16]	2000-2013	15	6,856	OS, QoL	PFS, TTP, CSS	23.2-117.6 months	Noninferiority, random effects	HR: 1.02, CI: 0.93 to 1.11, I^2 = 23%) (8 trials; 5,352 men)	HR: 1.02, CI: 0.87 to 1.19, I^2 = 14% (5 trials, 3,613 men)	HR: 0.94, CI: 0.84 to 1.05, I^2 = 0% (4 trials, 1774 men)	HR: 0.96, CI: 0.76 to 1.21, I^2 = 75% (5 trials, 3,523 men)	N/A	No meta-analysis; no quantitative data and disparity of instruments
Dong et al[39]	1999-2012	6	2,996	OS	DP, QoL, AE	Short (not quantified)	Superiority, fixed effects	OR: 1.0, CI: 0.86 to 1.17, I^2 = 0% (4 trials, 2,634 men)	N/A	N/A	N/A	OR: 1.16, CI: 0.86 to 1.57, I^2 = 67% (3 trials, 863 men)	No meta-analysis for QoL; ED—OR: 0.42, CI: 0.24 to 0.74; I^2 = 71.9%, P = .003 (2 trials, 437 men)
Botrel et al[17]	2000-2013	13	6,419	OS	CSS, TTP, AE	2.4-9.2 years	Superiority, fixed effects	HR: 1.02, CI: 0.95 to 1.09, I^2 = 27%, P = .21 (8 trials, 5,656 men); > 90% M1 population: HR: 1.10, CI: 0.98 to 1.24, I^2 = 0% (4 trials, 2009 men)	HR: 1.06, CI: 0.96 to 1.18, I^2 = 38%, P = .14 (7 trials, 3,724 men); after removing Salonen et al[51] trial (unbalanced baseline PSA levels): HR: 1.16, CI: 1.02 to 1.31, P = .02, I^2 = 0%, NNT = 6 (6 trials, N = 3,170) favoring CADT	N/A	HR: 1.04, CI: 0.96 to 1.14, I^2 = 41%, P = .09 (9 trials, 4,340 men)	N/A	Random effects analysis for hot flushes: RR = 0.65, CI: 0.45 to 0.95, P = .03, NNH = 10, favoring IADT (6 trials, 3,732 men)

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TABLE 3. Published Meta-Analyses Comparing IADT With CADT (2013-2015)[a] (continued)

Published Meta-Analyses	Years	RCTs	Men	Primary Outcomes	Secondary Outcomes	Median Follow-Up	Analysis Type	OS Results	CSS Results	PFS Results	TTP Results	DP Results	QoL and AE Results
Brungs et al[18]	2002-2013	8	4,668	OS	CSS, PFS, noncancer mortality, QoL, toxicity	29-118 months	Superiority, fixed effects	HR: 1.01, CI: 0.93 to 1.10, I^2 = 12% (6 trials, 4,399 men); M1: HR: 1.04, CI: 0.91 to 1.19, I^2 = 39% (3 trials, 1895 men); M0: HR: 1.06, CI: 0.91 to 1.23, I^2 = 0% (2 trials, 1811 men)	HR: 1.03, CI: 0.88 to 1.21, I^2 = 14% (4 trials, 2,695 men)	HR: 0.93, CI: 0.84 to 1.04; I^2 = 57%, P = .03 (7 trials, 3,133 men)	N/A	N/A	No meta-analysis; insufficient data for quantitative analysis
Niraula et al[19]	2002-2013	9	5,508	OS, TTP	CSS, QoL	57-100 months	Superiority, random effects	HR: 1.02, CI: 0.93 to 1.11, I^2 = 10%, P = .34 (4 trials, 4,101 men)	HR: 1.08, CI: 0.85 to 1.38, I^2 = 62%, P = .07 (3 trials, 2,566 men)	N/A	HR: 0.96, CI: 0.76 to 1.20, I^2 = 74%, P = .02 (3 trials, 2,596 men)	N/A	Insufficient data for quantitative analyses
Tsai et al[20]	2002-2013	8	4,664	OS	CSS, DP, AE	4.8 years	Superiority, random effects	RR: 1.03, CI: 0.96 to 1.11; I^2 = 37%, P = .15 (7 trials, 4,586 men); M1: RR = 1.00, CI: 0.87 to 1.17; I^2 = 76%, P = .01 (4 trials, 2,168 men)	RR: 1.15, CI: 0.97 to 1.36; I^2 = 56%, P = .05; RD: 0.04, CI: −0.01 to 0.08; I^2 = 57%, P = .04, favoring CADT (6 trials, 4,292 men)	N/A	N/A	RR: 0.97, CI: 0.86 to 1.10; I^2 = 65%, P = .02 (5 trials, 2,803 men)	Hot flushes: RR = 0.82, CI: 0.67 to 1.01; I^2 = 47%, P = .15; RD = -0.09, CI: −0.15 to −0.03; I^2 = 0%, P = .70, favoring IADT (3 trials, 954 men)

Abbreviations: AE, adverse events; CADT, continuous androgen deprivation therapy; CSS, cancer-specific survival; DP, disease progression; ED, erectile dysfunction; HR, hazard ratio; I2, heterogeneity test; IADT, intermittent androgen deprivation therapy; N/A, not applicable; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomized clinical trial; RD, risk difference (excess risk); RR, risk ratio; TTP, time to progression.

[a]All results refer to both M0 and M1 unless otherwise stated.

The five remaining meta-analyses[16–20,40] all analyzed RCTs published during the 12-year period 2002-2013. Two meta-analyses (Mangan et al[16] and Botrel et al[17]) also included RCTs published in the 2 years prior (2000-2001). As a result, these two meta-analyses included the largest number of RCTs 15 and 13, respectively. Thus, the total number of trial participants with data to inform the primary outcome of OS was also the largest (over 5,300 men in both meta-analyses).

With respect to OS, the Magnan et al[16] meta-analysis showed that IADT was not inferior to CADT for the combined population of men with M0 or M1 disease (HR = 1.02, 95% CI, 0.93 to 1.11, upper bound set at 1.15; eight trials, 5,352 men) (Table 3). These results provide solid evidence to support the use of IADT in addition to the potential cost savings to the healthcare system and to the patient. Among the other four meta-analyses (which tested superiority),[17–20,40] there was no difference in OS between IADT and CADT for the combined population of men with M0 or M1 disease. Similarly, three meta-analyses[17,18,20] showed no difference in OS between IADT and CADT for the M1 population. Although the Tsai et al[20] meta-analysis for the M1 population showed significant heterogeneity ($P = .01$), their OS estimates were otherwise consistent with those of Brungs et al[18] and Botrel et al.[17] Brungs et al[18] also showed no difference in OS for the M0 population (HR = 1.06, 95% CI, 0.91 to 1.23, two trials, 1811 men).

For CSS (a secondary outcome), the Botrel et al[17] meta-analysis identified a significant ($P = .02$) CSS benefit for CADT, after removing one trial[51,54] with unbalanced baseline PSA levels from the analysis (Table 3). Although the data were considered somewhat weak, the risk of death was higher in the IADT group (6 trials, 3,170 men, HR = 1.16, CI: 1.02 to 1.33, NNT = 6). None of the other four CSS meta-analyses[16,18–20] excluded the trial[51,54] with unbalanced baseline PSA levels from their analysis, which likely affected their results. No difference in CSS between IADT and CADT was identified by either the Magnan et al[16] meta-analysis (five trials, 3,613 men) or the Brungs et al[18] meta-analysis (four trials, 2,695 men). Both studies reported similar hazard ratios and confidence intervals with low heterogeneity. As was the case in their OS meta-analysis, the Tsai et al[20] CSS meta-analysis, which included six trials and 4,292 men, suffered from significant heterogeneity ($P = .05$), but did agree with the finding of no difference in CSS. The Niraula et al[19] CSS meta-analysis (three trials and 2,566 men) also had high heterogeneity (62%) and wider confidence intervals than the other meta-analyses, but again found no difference in CSS between IADT and CADT.

Three meta-analyses[16,17,19] examined time to DP (from either date of diagnosis or date treatment started) among men on ADT with castrate testosterone levels. Significant heterogeneity was present in all the meta-analyses except Botrel et al[17] The results of Niraula et al[19] and Magnan et al[16] were almost identical. Nevertheless, there was no significant difference in TTP between IADT and CADT in any of the three meta-analyses (Table 3).

Only two meta-analyses[16,18,43] examined PFS, defined as the length of time during and after cancer treatment that patients live with the disease without any worsening of the condition. Once again, despite the significant heterogeneity present in the Brungs et al[18] meta-analysis, both meta-analyses reported almost identical hazard ratios and confidence intervals, although neither identified a significant difference in PFS between IADT and CADT.

Finally, the Tsai et al[20] meta-analysis examined DP, defined as progression to an androgen-independent disease state. Once again, no significant difference was detected in the risk of DP between IADT and CADT (Table 3).

Noncancer mortality was examined in two meta-analyses.[17,18] In the Brungs et al[18] meta-analysis, the results (RR = 0.90, 95% CI, 0.80 to 1.01, five trials, 4,230 men), although not significant ($P = .07$), favored IADT. The authors suggest that this finding should give clinicians pause when considering CADT for patients with more advanced disease, as potentially higher noncancer mortality might offset any potential CSS gains. In an analysis of mortality secondary to cardiovascular events, Botrel et al[17] identified significantly ($P = .007$) lower mortality for IADT (RR = 0.80, 95% CI, 0.67 to 0.94, four trials, 3,483 men), although heterogeneity approached significance ($P = .08$).

For QoL and adverse effects, lack of quantitative data precluded a meta-analysis in most instances. However, in a planned random effects analysis, Botrel et al[17] showed that the risk of hot flushes was significantly lower among men treated with IADT (RR = 0.65, 95% CI, 0.45 to 0.95, $P = .03$, NNH = 10; six trials, 3,732 men).

The three purely systematic reviews[41–43] largely focused on highlighting differences in RCT methodology across trials and how such differences explain inconclusive or contradictory results across trials. For example, Hussein et al[43] identified statistical power issues related to the use of noninferiority trial designs, consistent with Burotto et al[67] Actual outcomes for the control arm (CADT) in the three reviewed noninferiority trials[44,47,48] exceeded prespecified median values. Without adjustment for either follow-up duration or study sample size, statistical power to detect a difference when one exists suffers. There were also unintended consequences for the noninferiority margins (NIM) (how much worse performance in the experimental arm could be with respect to the primary outcome and still be considered noninferior to the control arm). The example of the PR7 trial[47] is used here, although NIM issues were identified as problematic for all three noninferiority trials.[44,47,48] Actual OS in the control group (CADT) was substantially longer than the prespecified OS (9.1 *v* 7 years). Thus, the original NIM of 1.25, intended to define a maximum of 1.4 years shorter survival in the IADT arm as

noninferior to CADT, translated into an even larger permissible survival difference between arms of 1.8 years, a value that may no longer be considered clinically permissible.

Although the definition of progression varied among the trials Hussein et al[43] reviewed,[44,45,47–51,54] none classified DP while off treatment in the IADT arm as progression. Therefore, retreatment was permitted. Thus, PFS for patients in the IADT arm was artificially lengthened, biasing ascertainment in favor of the IADT arm. Hussain et al[43] recommended OS as the preferred end point in studies comparing IADT with CADT. Citing lack of clinical or biological justification, Hussain et al[43] also advised against using the same study design for men with locally advanced disease as used for men with metastatic disease, because of inherent differences in risk of progression and risk of prostate cancer–related death. Although six of the reviewed RCTs included a run-in period with CADT to ensure hormonal responsiveness, none of the studies were adequately powered to permit differentiating between men who were more or less likely to achieve benefit from IADT.

The Kratiras et al[41] systematic review addressed other types of differences across the seven trials they reviewed.[45,47–51,63] Highlighted was variation in trial inclusion criteria such as EOD (metastatic, nonmetastatic, or both) and in criteria for starting and stopping IADT (PSA cutpoints *v* whether symptomatic or not). Kratiras et al[41] suggest that IADT could replace CADT as standard treatment for patients with nonmetastatic advanced prostate cancer, but believe that the role of intermittent treatment in the metastatic setting remains less clear.

The Sciarra et al[42] systematic review identified other related issues in the same seven trials[45,47–51,63] reviewed by Kratiras et al[41] Such factors included wide variation in sample size, median follow-up, time off therapy in the IADT arm, and the rarity of biochemical recurrence as an inclusion criterion. Also discussed was variation in the definition of progression (PFS, progression after RT, risk of progression to CRPC, and TTP). Sciarra et al[42] recommended that future trials stratify by important prognostic parameters, such as disease extension and Gleason score, when reporting results and increase focus on QoL and long-term complications.

All attempts to combine data from a variety of different trials struggle with similar limitations. ADT varies widely as does the definition of DP. Bias affects all trials in many ways as it is difficult to sufficiently blind everyone involved from all potential sources of bias. However, all systematic reviews (with or without meta-analyses) were assessed for quality using the AMSTAR2 instrument.[68] Although there were deficits in reporting, all the included studies were of acceptable quality with no major flaws detected that would affect the interpretation of the results (see Data Supplement 2: Quality Assessment Tables for complete results).

Ten RCTs published between 2009 and 2017 compared IADT with CADT in men with prostate cancer[44–54] (Table 2). Patient accrual started as early as 1995 and ended as recently as 2013, but all would be considered PSA era (post 1994 FDA approval of PSA). Four trials[44,46–48] were designed to test for noninferiority of IADT to CADT, one merely assessed whether PSA was predictive of progression,[49] and the remainder tested for superiority of IADT over CADT.[45,50–53] TTP was the most common primary end point,[45,46,49,51–53] followed by OS.[44,45,48,50] Three trials focused exclusively on the M1 population.[48,50,53] and three focused on the M0 population.[46,47,52] The four remaining trials included both populations.[44,45,49,51] Four trials tested the use of the steroidal, CPA either alone[44,53] or in combination with an LHRH agonist.[45,51] CPA is not approved for use in the United States, but is approved for use elsewhere, such as in Europe.

Five trials were underpowered, often due to accrual issues, and were unable to draw any definitive conclusions.[46,49–51,53] In addition, the Schulman et al[52] (ICELAND) trial of men with M0 disease did not reach the planned median for TTP, the primary outcome of interest. Actual PSA progression in the CADT arm was much lower than anticipated when the study was designed. No significant differences were detected for any of the other outcomes of interest.

Two trials reported early.[44,47] The Calais da Silva et al[44] (SEUG 9901) trial reported early at the planned 5-year follow-up mark, but the required number of deaths (658) had not yet been reached (525 actual), as the death rate was much lower than expected in the CADT arm. An additional 2 years of follow-up would have been required to reach 658 deaths. Thus, noninferiority of IADT among men with M0 or M1 disease, although reported as proven (HR $<$ 1.21) by the authors (HR = 0.90, 95% CI, 0.76 to 1.07, P = .25), remains unclear for OS, the primary end point of interest.

No difference was detected in progression-free survival (HR = 1.01, 95% CI, 0.86 to 1.19, P = .89) or any of the other secondary outcomes. However, the adjusted competing risk model showed that men with M1 disease (HR = 3.29, 95% CI, 2.28 to 4.73) and men whose PSA ranged from $>$ 2 to 4 ng/mL (HR = 2.12, 95% CI, 1.50 to 2.99) were at higher risk for PCa-specific death. CADT was associated with significantly more frequent reporting of hot flushes and gynecomastia (P $<$ .0001) compared with IADT. Sexual activity reporting was significantly more frequent among those treated with IADT versus CADT (24.9% *v* 6.4% at 30 months after random assignment, P $<$ .0001).

The Crook et al[47] trial (PR 7) also stopped early as the preplanned interim analysis noninferiority criteria (true difference in OS between IADT and CADT $<$ 8 percentage

points) had been met. For men with M0 disease, median survival was 8.8 years for IADT compared with 9.1 years for CADT (HR = 1.03, 95% CI, 0.86 to 1.22). IADT was reported as noninferior to CADT (HR < 1.25; $P = .009$). However, Hussain et al[43] suggest that, because actual survival in the CADT arm was longer than prespecified when calculating the noninferiority margin (9.2 *v* 7 years), the maximum permissible shorter survival in the IADT arm of 1.4 years translates into 1.8 years (approximately 5 additional months), which may no longer be clinically permissible. Thus, once again, noninferiority of IADT for OS remains unclear.

Time to castration-resistant disease, a planned secondary end point, was biased by an unknown magnitude against the CADT arm because of a study design–related delay in declaring castration resistance in the IADT arm among men who were off treatment. After 5 years, no difference was detected in overall QoL or for the functional QoL domains. Although IADT was associated with significantly better outcomes for hot flushes ($P < .001$), sexual activity desire ($P < .001$), and urinary symptoms ($P = .006$), no differences appeared until the first patients were in the off-treatment cycle. Crook et al[47] suggest that QoL benefits may vary by treatment cycle, testosterone recovery status, and age.

The Hussain et al[48] noninferiority trial (SWOG9346), which only included men with metastatic disease, did not stop early but had inconclusive results with respect to OS, the primary outcome of interest. After a median follow-up of 9.8 years, median survival time for men with M1 disease was 5.1 years for IADT compared with 5.8 years for CADT (HR = 1.10, 90% CI: 0.99 to 1.23). The findings were inconclusive because the CI for survival exceeded the upper boundary for noninferiority (1.20). Therefore, a 20% greater risk of death associated with intermittent therapy could not be ruled out. In addition, since the CI included 1, it also could not be concluded that IADT was significantly inferior to CADT. Thus, the OS results were indeed inconclusive. Hussain et al[48] suggest that because almost the entire CI favors CADT, IADT may negatively affect survival. The results for QoL, also a primary end point, were also largely inconclusive. Although IADT was associated with better erectile function ($P < .001$) and mental health ($P = .003$) at 3 months, this difference was not consistently detected in subsequent assessments.

Finally, the Calais da Silva et al[45] (SEUG 9401) trial of men with M0 or M1 disease identified no significant difference in either TTP (primary end point) (HR = 0.81, 95% CI, 0.63 to 1.05, $P = .11$) or in the secondary end points of OS (HR = 0.99, 95% CI, 0.80 to 1.23; $P = .84$) and CSS (HR = 0.80, 95% CI, 0.60 to 1.06). However, as this 2009 study was only powered to detect a 30% or greater difference in TTP between IADT and CADT, the question remains whether a difference as large as 30% in TTP between IADT and CADT would currently be considered clinically equivalent.

As described above, the long-term nature of randomized trials in this space requires constant vigilance by data monitoring committees to ensure that changes in practice and their effect on patient outcomes over the trial's lifetime do not cause trials to come up short with respect to the required number of events or sample size in general to derive meaningful conclusions at study end. The original assumptions made during the study planning stage, with respect to the primary end point of interest, should be revisited early and often enough to facilitate, for example, increasing sample size or extending follow-up, both of which are likely to require additional funding. The shortcomings of these 10 RCTs also emphasize the importance of the meta-analyses discussed earlier.

Clinical Interpretation

Intermittent therapy may be offered to men with high-risk biochemically recurrent nonmetastatic prostate cancer. Men with low-risk biochemical recurrent nonmetastatic prostate cancer may be offered active surveillance. This recommendation is based on evidence of the noninferiority of IADT compared with CADT with respect to OS from the Magnan et al[16] meta-analysis. This is further supported by evidence from four meta-analyses which tested superiority[17–20,40] and found no difference in OS between IADT and CADT not only for the combined population of men with M0 or M1 disease, but also separately for the M0[18] and M1[17,18,20] populations separately. Particularly for men who experience adverse effects from CADT, IADT is a reasonable option, as intermittent therapy offers patients a break from treatment and time to recover somewhat from treatment side effects.

The recommendation to offer intermittent therapy is not without caveats. For the combined M0 and M1 population, the Botrel et al[17] meta-analysis suggests a significantly higher ($P = .02$) risk of death from cancer in the IADT group (six trials, 3,170 men, HR = 1.16, CI: 1.02 to 1.31, NNT = 6) based on somewhat weak data and a significantly lower ($P = .007$) risk of death from cardiovascular disease (four trials, N = 3,484 men, RR = 0.80, CI: 0.67 to 0.94, NNH = 33). Further study is needed.

With respect to the M1 population, it is true that other standard-of-care therapies with proven OS benefits exist, such as docetaxel with ADT or abiraterone plus prednisone with ADT as originally recommended by Morris et al[3] However, available OS data only support docetaxel with ADT for men with de novo metastatic HVD who are candidates for chemotherapy. Similar support does not exist for men with LVD or those who develop M1 disease after prior local therapy. Clarke et al[10] re-examined metastatic disease burden using STAMPEDE data,[8] retrospectively collecting bone scans for 76% of the M1 docetaxel comparison cohort with available scans. Although no heterogeneity was detected in the disease burden results, the Clarke et al[10] study was inadequately powered (66% for LVD, 77% for HVD) to

detect a difference in OS by metastatic disease burden if in fact one existed.

Similarly, as recommended herein, abiraterone plus prednisone with ADT is also standard of care for men with high-risk de novo metastatic disease based on OS benefit data, but, once again, not for men with low-risk disease or those who develop M1 disease after prior therapy.[3] A recent post hoc analysis of the STAMPEDE[12] and LATITUDE[11] data, using newer imaging techniques and separately applying both CHAARTED[7] and LATITUDE[11] volume criteria, suggests that an OS benefit at 3 years (HR: 0.66, 95% CI, 0.44 to 0.98) also exists for men with low-risk de novo metastatic disease.[69] This is encouraging, but as a post hoc analysis, RCTs are needed to confirm this finding. Hoyle et al[69] were unable to provide separate results for men who develop M1 disease after prior local therapy because of small sample size (N = 42).

Thus, the question of whether IADT provides an advantage compared with CADT is indeed still relevant for a large segment of the noncastrate advanced prostate cancer population, but especially for those with high-risk biochemically recurrent nonmetastatic prostate cancer. Ongoing trials in the M1 space for enzalutamide plus ADT (ARCHES[14] and ENZAMET[13]) and apalutamide plus ADT (TITAN[15]) are designed to examine HVD versus LVD. Trials in the M1 space have not yet studied IADT versus CADT both in combination with additional cytotoxic or hormonal agents for the population of men with noncastrate de novo metastatic prostate cancer. Until further evidence becomes available, this question remains open.

Discussions with patients should include the lack of evidence showing a clear OS benefit for IADT compared with CADT as well as the potential benefits of IADT associated with the off-treatment intervals, such as reduced side effects and lower cost. Furthermore, patients and their partners should understand the potential side effects of ADT, whether administered intermittently or continuously. Underlying comorbidities should also be taken into consideration. As IADT requires close follow-up, patients must be motivated to adhere to frequent doctor visits for monitoring, even during off-treatment periods.

DISCUSSION

The guideline document updates all earlier versions,[1–3] while maintaining the focus on men with advanced prostate cancer and noncastrate testosterone levels whose disease is not yet castration-resistant, including those with biochemical recurrence only. This document provides specific guidance with respect to (1) treatment options for men with metastatic noncastrate prostate cancer (including those who have LVD, are not candidates for chemotherapy, who are older (70+), or who developed M1 disease after undergoing prior therapy (eg, RP, RT, ADT); (2) combination therapies such as combined androgen blockade using a nonsteroidal antiandrogen versus castration monotherapy; (3) early versus deferred ADT; and (4) IADT versus CADT. With the advent of first-generation (bicalutamide, nilutamide, and flutamide) and then second-generation antiandrogens (abiraterone, enzalutamide, apalutamide, and darolutamide), methods of treating men with advanced prostate cancer have changed dramatically in the past 13 years. For example, standard of care now includes docetaxel plus ADT or abiraterone plus ADT for men with high volume de novo M1 disease.[3] This guideline adds to the discussion by providing recommendations for the use of enzalutamide and apalutamide among men with M1 disease who have had prior docetaxel.

As mentioned in the introduction, existing ASCO guidelines already address several aspects of prostate cancer care complementary to this guideline. These include Optimum Imaging Strategies for Advanced Prostate Cancer,[4] Molecular Biomarkers in Localized Prostate Cancer,[5] and Bone Health and Bone-Targeted Therapies for Prostate Cancer: ASCO Endorsement of a Cancer Care Ontario Guideline.[6] Thus, none of these topics were addressed in the current guideline as they were considered out of scope. That said, the committee felt it was important to remind readers that antiresorptive bone therapy has not shown a benefit in the setting of noncastrate bone metastases for skeletal-related event risk reduction.[6] Discussion of ADT, RP, and RT as treatment for localized prostate cancer was also out of scope for the current guideline.

Questions that require further study include whether there is any OS advantage associated with adding docetaxel to ADT for patients with LVD. To a somewhat lesser extent, the same could be said for adding abiraterone to ADT for patients with LVD. Gravis et al[70] question whether patients with LVD are biologically more like those with a rising PSA and negative scans and less like those with HVD and positive scans. Small sample size, insufficient power, and post hoc designs have precluded a definitive answer to these questions to date, but the results are promising.

One ongoing phase III RCT that will inform future guideline recommendations in the noncastrate M1 space is the ARASENS trial, designed to compare darolutamide plus standard ADT and docetaxel versus placebo plus ADT and docetaxel among 1,300 previously untreated men with noncastrate metastatic prostate cancer. Although the study met its recruitment goal, no preliminary results were available at the time this guideline was written. The primary outcome is OS. Secondary outcomes include time to CRPC, time to initiation of subsequent antineoplastic therapy, and symptomatic skeletal event-free survival. The expected study completion date is August 2022.

Three more recently added arms (K, L, and M) of STAMPEDE will also inform future versions of this guideline. Arm J of STAMPEDE[71] examines FFS and toxicity associated with the addition of enzalutamide to

abiraterone plus prednisone and ADT among men with high-risk, advanced prostate cancer, who have undergone prior local therapy. STAMPEDE arm K[72] examines the OS impact of adding metformin to ADT among men with high-risk advanced prostate cancer, who have undergone prior local therapy. STAMPEDE arm L[73] examines efficacy and toxicity associated with the use of a transdermal estradiol patch rather than an LHRH agonist among men with high-risk advanced prostate cancer, who have undergone prior local therapy, but have had no more than one 4-week LHRH injection and < 8 weeks of an antiandrogen. A meta-analysis planned for 2021 will combine results from STAMPEDE arm L[73] with results from the PATCH trial.[74,75] When completed, these and other trials will inform future versions of this guideline.

Other questions requiring further study include whether patients with adverse prognostic factors gain a true survival advantage with early ADT versus deferred ADT. Adequately powered phase III RCTs are needed in this area. DNA vaccines (such as pTVG-HP) are being tested either alone or in combination with, for example, programmed cell death protein 1 (PD-1) blockade, in clinical trials as an alternative to early ADT among men with biochemically recurrent nonmetastatic, noncastrate disease and rapid PSA doubling times.[76] The goal of the vaccines under development is to delay further progression (extend metastasis-free survival) and avoid the side effects associated with ADT. Trials in this area will also affect future versions of this guideline.

Longer follow-up time would have benefited many of the RCTs reviewed herein. However, issues such as funding constraints, slower than expected accrual, higher dropout rates, competition with other trials for patients, the availability of newer drugs with proven efficacy requiring premature crossover, and confounding effects not originally accounted for in the original study design all contribute to RCTs not having sufficient statistical power to address the original primary research question. In addition, lack of standardization because of various decisions being left to physician discretion in RCTs is problematic, although it is clear that each patient is unique and discretion is important for patient welfare. Innovative trial designs, such as the multiarm, multistage design used in the STAMPEDE trial,[8] are critical to accelerating research in prostate cancer as are meta-analyses combining data from existing RCT data, including trials that did not reach their accrual goals.

Approved uses for ADT have changed dramatically over time. ADT is now used much earlier in the disease process, such as neoadjuvant or adjuvant to local therapy as well as in combination with antiandrogens and chemotherapy agents for patients with noncastrate advanced prostate cancer. Drugs already approved for use in the nmCRPC space, such as darolutamide, may soon be approved for use in the noncastrate advanced prostate cancer space.

Similarly, next-generation imaging (NGI) technologies, such as prostate-specific membrane antigen–targeted imaging and 11C-choline or 18F-fluciclovine positron emission tomography/computed tomography (PET/CT), could substantially improve staging accuracy, compared with conventional imaging (CT, MRI) even among men with low tumor burden. Clinical trials are ongoing, but NGI technologies show great promise and could potentially revolutionize the care of men with prostate cancer with respect to diagnosis, treatment, and monitoring.[4] Although few NGIs are approved for use in the United States, the FDA has already approved 11C-choline or 18F-fluciclovine PET for men with a suspected prostate cancer recurrence based on an elevated PSA following prior treatment.

The future of noncastrate advanced prostate cancer care is predicted to include highly personalized treatment plans based on advanced genetic testing and the availability of highly predictive biomarkers. Better matching of patients to approved therapies and clinical trials is the goal while concurrently minimizing the cost to patients.

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 (eg, Bosco et al,[77] Scailteux et al,[78] Jin et al,[79] Nead et al,[80] Nead et al,[81] Baik et al,[82] Tsai et al,[83] and Hall et al[72]). Side effects vary by type of ADT as well as age and patient comorbidities.

Shared decision making between the patient and the physician is very important, yet is often complicated from the patient perspective because of the stress of a cancer diagnosis and the general lack of knowledge, at least at diagnosis, of the ever-changing treatment options and potential outcomes of choices that are made. Discussions should clarify whether treatment options are palliative versus curative and the associated likelihood of progression associated with each option presented. Balancing treatment costs and insurance coverage against survival benefits and QoL can be difficult. In the clinic, social workers generally assist patients with navigating cost and insurance coverage issues, thus helping to decrease patient stress, so that the patient can concentrate on the clinician's treatment recommendations and issues regarding sexual function, potential activity limitations, whether a return to work will be possible, and fear of recurrence and end of life.

The timing of ADT is also important. Considering the patient's level of anxiety regarding their condition is important in determining when to start ADT, either immediately versus later in the disease process. Similarly, 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 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.

Survivorship care plans provide a road map for the patient's care over time and reduce patient uncertainty regarding what lies ahead with respect to treatment.[85,86] They also help patients plan for the future.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline[87] (https://ascopubs.org/doi/pdf/10.1200/JCO.2017.75.2311).

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[88–91] Many patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and healthcare providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients in order to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

For patients with prostate cancer under age 65 years, the 10 most common comorbidities are (in descending order) hypertension, hyperlipidemia, diabetes, ischemic heart disease, anemia, arthritis, chronic kidney disease, depression, chronic obstructive pulmonary disease (COPD), and heart failure. For patients with prostate cancer older than age 65 years, the 10 most common comorbidities are (in descending order) hypertension, hyperlipidemia, ischemic heart disease, anemia, diabetes, arthritis, chronic kidney disease, cataract, heart failure, and COPD (see Data Supplement 6: MCC).

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC (see Data Supplement 6: MCC table for the complete listing).

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[92,93] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[94,95]

Discussion of cost can be an important part of shared decision making.[96] 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.[96]

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 such as antiemetics and hematopoietic growth factors, and the legal structure of the dispensing clinic and patient characteristics, such as weight and estimated body surface area. Table 4 displays various prices for these agents, by month or by cycle. When available, generic or biosimilar alternatives are displayed. Group Purchasing Organization (GPO) pricing refers to a rate negotiated through a pharmaceutical GPO which aggregates the purchasing power of hospitals, clinics, and other healthcare providers. The term 340b pricing refers to a federal program that requires drug manufacturers participating in the Medicaid drug rebate program to provide covered outpatient drugs at or below the statutorily defined ceiling price to specific enrolled covered entities, such as hospitals that treat large numbers of poor and underserved populations.

TABLE 4. GPO, 340B, and Medicare Costs for Hormone Therapy, Cytotoxic Chemotherapy, Bone Agents and Other Related Therapies as of June 2020

Agent	Dose	Schedule	Cost Per Month GPO[a] Pricing	Cost Per Month 340B Pricing	Cost Per Month Medicare[b]	6-Month Total Cost[b]
Hormone therapy						
Firmagon (degarelix)	240 mg	Loading Dose	$1,429.53	$518.92	$953.04	$2,541.44
	Then 80 mg	Monthly	$586.14	$458.12	$317.68	
Lupron depot (leuprolide)	7.5 mg	once every 4 weeks	$1,453.37	$103.17	$205.87	$1,235.22
	22.5 mg	once every 12 weeks	$1,453.36	$103.17	$617.61	$1,235.22
	30 mg	once every 16 weeks	$1,453.36	$104.10	$823.48	$1,235.22
	45 mg	once every 24 weeks	$1,453.38	$46.09	$1,235.22	$1,235.22
Eligard (leuprolide)	7.5 mg	once every 4 weeks	$92.85	$87.69	$205.87	$1,235.22
	22.5 mg	once every 12 weeks	$92.85	$87.69	$617.61	$1,235.22
	30 mg	once every 16 weeks	$92.85	$87.69	$823.48	$1,235.22
	45 mg	once every 24 weeks	$92.85	$69.40	$1,235.22	$1,235.22
Zoladex (goserelin)	3.6 mg	once every 4 weeks			$504.30	$3,025.80
	10.8 mg	once every 14 weeks	$635.25	$108.85	$1,512.90	$3,025.80
Trelstar mixject (triptorelin)	3.75 mg	once every 4 weeks	$610.19	$126.54	$282.64	$1,695.84
	11.25 mg	once every 12 weeks	$610.19	$126.54	$847.92	$1,695.84
	22.5 mg	once every 24 weeks	$610.19	$97.14	$1,695.84	$1,695.84
Vantas (histrelin acetate)	50 mg implant	Yearly			$4,350.02	$4,350.02 (annual implant)
Flutamide	250 mg (125 mg × 2)	TID	$97.64	$14.51	$117.50	$705
Bicalutamide	50 mg	Daily	$6.84	$0.28	$16.10	$96.60
Nilutamide	300 mg (150 mg × 2)	Daily x 1 month	$8,677.28	$5,389.22	$9,714.91	$34,003.46
	Then 150 mg	Daily	$4,338.64	$2,694.61	$4,857.71	
Erleada (apalutamide)	240 mg (60 mg × 4)	Daily	$11,673.48	$8,382.68	$12,858.26	$77,149.56
Xtandi (enzalutamide)	160 mg (40 mg × 4)	Daily	$11,548.60	$5,516.11	$12,514.57	$75,087.42
Nubeqa (darolutamide)	600 mg (300 mg × 2)	BID	$11,550.00	$5,222.59	$12,128.00	$72,768
Zytiga (abiraterone)	1,000 mg	Daily	$2,491.38	$1.13	$13,064.92	$78,389.52
Zytiga (abiraterone) with fatty meal	250 mg	Daily	$622.85	$0.23	$3,300.51	$19,803.06
Abiraterone generic	1,000 mg	Daily			$1,624.26	$9,745.56
Abiraterone generic with fatty meal	250 mg	Daily	$622.85	$0.23	$825.50	$4,953
Ketoconazole	400 mg (200 mg × 2)	TID	$122.24	$103.16	$198.50	$1,191
With hydrocortisone	40 mg (10 mg × 4)	Daily	$31.85	$10.70	$28.26	$169.56

(continued on following page)

TABLE 4. GPO, 340B, and Medicare Costs for Hormone Therapy, Cytotoxic Chemotherapy, Bone Agents and Other Related Therapies as of June 2020 (continued)

Agent	Dose	Schedule	Cost Per Month GPO[a] Pricing	Cost Per Month 340B Pricing	Cost Per Month Medicare[b]	6-Month Total Cost[b]
Cytotoxic chemotherapy						
Docetaxel	75 mg/m^2	once every 3 weeks	$815.98	$43.24	$111.10	$666.62 (6 cycles)
	BSA 1.7 m^2 = 128 mg (2 vials of 80 mg)					
Jevtana (cabazitaxel)	20 mg/m^2	once every 3 weeks	$10,293.70	$6,509.81	$10,888.38	$65,330.28 (6 cycles)
	BSA 1.7 = 34 mg (1 vial of 60 mg)					
Carboplatin	AUC 5	once every 3 weeks	$80.88	$33.12	$28	$168 (6 cycles)
	Dose based on male, SCr 1, 70 kg AUC5 = 489.6 mg (2 vials of 450 mg)					
Etoposide	80 mg/m^2 D1-3	once every 3 weeks	$9.88	$6.28	$24.56	$147.37 (6 cycles)
	BSA 1.7 = 136 mg (2 vials of 100 mg)					
Mitoxantrone	12-14 mg/m^2	once every 3 weeks	$103.06	$124.64	$148.75	$892.50 (6 cycles)
	BSA 1.7 = 20.4-23.8 mg (1 vial of 25 mg)					
Other						
Sipuleucel-T					$47,617.87	$142,853.61 (3 cycles)
Pembrolizumab (MSI-H)	200 mg	once every 3 weeks	$9,580.40	$7,059.84	$10,185.40	$81,483.20 (8 cycles)
Radium-223						$83,996 (6 cycles)
Bone agents						
Zoledronic acid	4 mg	once every 12 weeks	$44.55	$8.44	$34.18	$68.36
Xgeva	120 mg	once every 4 weeks	$2,141.92	$1,334.78	$2,388.12	$14,328.72
Neulasta	6 mg	Per cycle	—	$2,269.78	$3,807.30	$22,843.80 (6 cycles)
Biosimilar neulasta	6 mg	Per cycle	—	—	Udenyca: $3,621.58 Fulphila: $3,532.13 Ziextenzo: $3,807.40	Udenyca: $21,729.46 Fulphila: $21,192.77 Ziextenzo: $22,844.38 (all 6 cycles)

Abbreviation: BSA, body surface area.

[a]GPO, price from group purchasing organizations.

[b]Medicare: average sales price (ASP) for injectable Medicare Part B drugs; Medicare's Plan Finder for Medicare Part D oral drugs using the Humana Premier Rx Plan (PDP) plan for a beneficiary living within ZIP code 10065.

Medicare pricing refers to either injectable Part B drug pricing based on the Medicare average sales price (ASP) (CMS July 2020)[97] or oral Part D drug pricing identified in Medicare's Plan Finder (CMS 2020)[98] using a Humana Premier Rx Plan (PDP) plan for a beneficiary living within ZIP code 10065. Although LHRH agonists or antagonists are commonly used in combination with many of the treatments listed in Table 4 and costs vary, the table does not include

such costs in the cost of, for example, cytotoxic chemotherapy, bone agents, or items classified under other. Orchiectomy, a low-cost ADT treatment, does not accrue ongoing drug costs.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[96]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; and/or are industry-sponsored. No cost-effectiveness analyses were identified to inform the topic.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from May 22, 2020, through June 5, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with 16 responses received. Of the 15 recommendations, respondents to the open comment either agreed as written or agreed with suggested modifications with 12 of the recommendations (80% agreement). Because of feedback received, the draft recommendations were modified focusing on the three with disagreement.

The draft was also submitted to three external reviewers with content expertise (Dr Thomasz M. Beer, Dr Nicholas D. James, and Dr Kim N. Chi). While all three external reviewers agreed with the spirit and intent of the recommendations in general, all had concerns about the presentation of the updated results alongside the original guideline and the Morris et al[3] guideline and suggested integration and reformatting. This reformatting of the content was completed before the final CPGC presentation.

An internal peer review was also completed by three ASCO staff with expertise in systematic review methodology (Thomas K. Oliver, Christina Lacchetti, and Brittany E. Harvey). All comments were integrated into the final CPGC submission.

The expert panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before CPGC review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Optimizing Anticancer Therapy in Metastatic Noncastrate Prostate Cancer: ASCO Clinical Practice Guideline[3] (http://ascopubs.org/doi/full/10.1200/JCO.2018.78.0619)
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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at: www.asco.org/genitourinary-cancer-guidelines.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Employment: NantHealth
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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update Expert Panel Membership

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