Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Michael J. Morris, R. Bryan Rumble, Ethan Basch, Sebastien J. Hotte, Andrew Loblaw, Dana Rathkopf, Paul Celano, Rick Bangs, and Matthew I. Milowsky

A B S T R A C T

Purpose

This clinical practice guideline addresses abiraterone or docetaxel with androgen-deprivation therapy (ADT) for metastatic prostate cancer that has not been treated (or has been minimally treated) with testosterone-lowering agents.

Methods

Standard therapy for newly diagnosed metastatic prostate cancer has been ADT alone. Three studies have compared ADT alone with ADT and docetaxel, and two studies have compared ADT alone with ADT and abiraterone.

Results

Three prospective randomized studies (GETUG-AFU 15, STAMPEDE, and CHAARTED) examined overall survival (OS) with adding docetaxel to ADT. STAMPEDE and CHAARTED favored docetaxel (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; n = 2,962 and HR, 0.73; 95% CI, 0.59 to 0.89; n = 790, respectively). GETUG-AFU 15 was negative. LATITUDE and STAMPEDE examined the impact on OS of adding abiraterone (with prednisone or prednisolone) to ADT. LATITUDE and STAMPEDE favored abiraterone (HR, 0.62; 95% CI, 0.51 to 0.76; n = 1,199 and HR, 0.63; 95% CI, 0.52 to 0.76; n = 1,917, respectively).

Recommendations

ADT plus docetaxel or abiraterone in newly diagnosed metastatic non-castrate prostate cancer offers a survival benefit as compared with ADT alone. The strongest evidence of benefit with docetaxel is in men with de novo high-volume (CHAARTED criteria) metastatic disease. Similar survival benefits are seen using abiraterone acetate in high-risk patients (LATITUDE criteria) and in the metastatic population in STAMPEDE. ADT plus abiraterone and ADT plus docetaxel have not been compared, and it is not known if some men benefit more from one regimen as opposed to the other. Fitness for chemotherapy, patient comorbidities, toxicity profiles, quality of life, drug availability, and cost should be considered in this decision. Additional information is available at www.asco.org/genitourinary-cancer-guidelines.

J Clin Oncol 36:1521-1539. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men, representing 19% of all newly reported cases (estimated new cases in 2017, n = 161,360).[1] It is responsible for 8% of all deaths resulting from cancer in men (estimated deaths in 2017, n = 26,730).[1] Patients who have newly diagnosed radiographically evident metastatic disease, either as part of a de novo diagnosis of prostate cancer or as a manifestation of disease progression through earlier clinical disease states, are considered to have "clinical metastatic: non-castrate" disease by Prostate Cancer Working Groups 2 and 3,[2,3] provided that they have non-castrate testosterone levels (> 50 ng/dL). These patients may or may not have received limited courses of androgen-deprivation therapy (ADT) for earlier clinical states. Historically, standard treatment of metastatic non-castrate disease has been ADT until progression, at which time patients are described as having metastatic castration-resistant prostate cancer (mCRPC), and ADT is then continued with additional treatments offered.[4]

THE BOTTOM LINE

Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Guideline Question
Is there an overall survival (OS) advantage associated with the addition of docetaxel or abiraterone to androgen-deprivation therapy (ADT) in men with metastatic non-castrate prostate cancer? Other outcomes of interest include progression-free survival (PFS), failure-free survival (FFS), PSA response, overall response rate, and quality of life (QOL).

Target Population
Men with metastatic non-castrate prostate cancer being considered for treatment with ADT.

Target Audience
Urologists, radiation oncologists, medical oncologists, physician assistants, nurse practitioners, and other allied health professionals.

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

Key Recommendations
- Docetaxel and abiraterone are two separate standards of care (SOCs) for metastatic non-castrate prostate cancer. The use of both standards in combination or in series has not been assessed and therefore cannot be recommended (Type: evidence based, benefits/harms ratio unknown; Evidence quality: no evidence available; Strength of recommendation: strong).

ADT Plus Docetaxel
- For men with metastatic non-castrate prostate cancer with high-volume disease (HVD) per CHAARTED 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 as per CHAARTED).

- For patients with low-volume disease (LVD) per CHAARTED who are candidates for chemotherapy, docetaxel plus ADT may be offered (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with LVD as per CHAARTED).

- The appropriate regimen of docetaxel is six doses of docetaxel administered every 3 weeks at 75 mg/m^2 either alone (per CHAARTED) or with prednisolone (per STAMPEDE) (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

ADT Plus Abiraterone
- For men with high-risk de novo metastatic non-castrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with high-risk disease per LATITUDE).

- For men with lower-risk de novo metastatic non-castrate prostate cancer, abiraterone may be offered per STAMPEDE (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with lower-risk disease per STAMPEDE).

- The appropriate regimen is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until treatment(s) for mCRPC are initiated (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statements
- The strongest evidence of benefit for docetaxel is for those men who were diagnosed with de novo metastatic disease or HVD per CHAARTED (defined 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 are agnostic to the presence or absence of nodal disease.

- Men who do not fit into these categories may be offered docetaxel; however, the strength of the evidence to support an OS benefit is less compelling for men who do not have de novo metastatic disease and/or who do not meet the HVD criteria. A subset analysis of CHAARTED did not demonstrate a survival benefit for low-volume disease, and the GETUG-15 trial was negative.

- LATITUDE examined the benefits of abiraterone acetate in newly diagnosed men with metastatic non-castrate disease defined by high-risk factors associated with a poor prognosis including at least two of the following high-risk factors: a Gleason score ≥ 8, at least three bone lesions, and presence of measurable visceral disease. STAMPEDE did not include a high risk definition.

- The addition of either docetaxel or abiraterone to ADT in men with newly diagnosed metastatic prostate cancer offers a survival benefit as compared with the use of ADT alone. The strongest evidence of benefit with docetaxel is in men with de novo metastatic HVD, whereas the data in other patients with metastatic disease are less clear. LATITUDE and STAMPEDE are mutually supportive for treating high-risk disease with ADT and abiraterone, with only STAMPEDE furnishing evidence that includes men with lower-risk disease.

- In the absence of randomized data comparing the addition of docetaxel versus abiraterone to ADT in men with metastatic non-castrate disease, additional variables including patient comorbidities, toxicity, QOL considerations, drug availability, and cost will ultimately need to be taken into consideration.

  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 Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. Patient information is available at www.cancer.net.

Reports from three randomized controlled trials (RCTs), GETUG-AFU 15 (Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; herein, GETUG-15),[5,6] CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; ECOG [Eastern Co-operative Oncology Group] 3805),[7-10] and STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy),[11,12] have compared standard ADT with ADT plus concurrent docetaxel for men with metastatic non-castrate disease. More recently, another RCT, LATITUDE (A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy [ADT] Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer [mHNPC]),[13] and another arm of STAMPEDE[12] compared standard ADT with ADT plus concurrent abiraterone (with prednisone or prednisolone; herein, AAP) for men with metastatic non-castrate disease. There have been no studies comparing ADT plus docetaxel with AAP in this patient population. To evaluate the data that these studies have generated, the American Society of Clinical Oncology (ASCO) formed an Expert Panel (Appendix Table A1, online only) to assess the implications of the research and provide clinical recommendations.

GUIDELINE QUESTIONS

This clinical practice guideline addressed the following clinical question: Is there an overall survival (OS) advantage associated with the addition of docetaxel or abiraterone to ADT in men with metastatic non-castrate prostate cancer? Other outcomes of interest include progression-free survival (PFS), failure-free survival (FFS), prostate-specific antigen (PSA) response, objective response rate, and quality of life (QOL).

METHODS

Guideline 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 with health research methodology expertise. The Expert Panel met via teleconference and/or Webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *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 Guideline Committee prior to publication.

The Expert Panel developed the recommendations using a modified systematic review process that confirmed all available evidence (comprising only phase III RCTs and meta-analyses) had been obtained. Articles were selected for inclusion based on the following criteria:

- Population: Men with metastatic non-castrate prostate cancer being considered for treatment with docetaxel or abiraterone in addition to ADT

- Evidence: Fully published English-language reports of phase III RCTs published from 2015 through October 2017, rigorously conducted systematic reviews, or meta-analyses (see Data Supplement 2 for criteria)

Articles were excluded from the systematic review if they were: (1) editorials, commentaries, letters, news articles, case reports, or narrative reviews or (2) published in a non-English language. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[14] In addition, a guideline implementability review is 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 (Methodology Supplement 2).

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/genitourinary-cancer-guidelines, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to determine the need for updating based on formal review of the emerging literature. This process uses a signals[15] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. The Methodology Supplement (available at www.asco.org/genitourinary-cancer-guidelines) provides additional information about the signals approach.

This is the most recent information as of the publication date. All funding for the administration of the project was provided by ASCO.

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.

RESULTS

Reports from four RCTs, GETUG-15,[5,6] CHAARTED (ECOG 3805),[7-10] STAMPEDE,[11,12] and LATITUDE,[13] have compared standard ADT with ADT plus concurrent docetaxel or abiraterone for men with metastatic non-castrate disease. Two of these trials (LATITUDE[13] and STAMPEDE[12]) provided comparative data on ADT versus AAP, and three trials (GETUG- 15,[5,6] CHAARTED,[7-10] and STAMPEDE[11]) provided comparative data on ADT with or without docetaxel. The Data Supplement provides a description of each of the included trials, including information on disease and patient characteristics, previous treatments, comparisons, and planned accruals.

Trial Overviews

ADT with or without abiraterone. Reports from two trials (LATITUDE[13] and STAMPEDE[12]) that provided comparative data on ADT versus ADT with AAP in patients with metastatic non-castrate prostate cancer were obtained.

The LATITUDE trial reported by Fizazi et al[13] included 1,199 M1 patients. Inclusion criteria for this trial included newly diagnosed ($\leq$ 3 months before random assignment), high-risk disease. High risk was defined as having at least two of the following three factors: Gleason score $\geq$ 8, at least three bone lesions, and presence of measurable visceral metastasis. Patients had to have metastatic non-castrate prostate cancer, confirmed by a positive bone scan or metastatic lesions by either computed tomography or magnetic resonance imaging. Patients were required to have ECOG performance status (PS) of 0 to 2. Exclusion criteria included previous chemotherapy, radiation therapy, or surgery for metastatic prostate cancer, although $\leq$ 3 months of ADT with luteinizing hormone-releasing hormone analogs or orchiectomy with or without androgen-receptor antagonists before trial intake or one course of palliative radiation or surgical therapy for symptoms associated with metastatic disease was allowed. The two primary outcomes of this trial were OS and radiographic PFS.

The STAMPEDE trial is a multiarm study comparing several regimens in combination with ADT versus ADT alone. The abiraterone data were reported by James et al[12]; in the study, 1,917 M0/M1 patients were randomly assigned to either ADT alone or with AAP. Inclusion criteria were newly diagnosed and metastatic, node-positive, or high-risk locally advanced disease or disease that had been previously treated with radical surgery or radiotherapy and was

relapsing with high-risk features. Patients with clinically significant cardiovascular disease were excluded. Of the 1,917 total patients, those with nonmetastatic disease were excluded from this guideline, because those patients are beyond its scope. The population for this guideline includes the 502 M1 patients allocated to the ADT alone arm and the 500 M1 patients allocated to the AAP arm. The primary outcome was OS, and the intermediate primary outcome was FFS, defined as the time to the following forms of treatment failure: biochemical (PSA) failure; progression of local, lymph node, or distant metastases; or death resulting from prostate cancer.

ADT with or without docetaxel. Reports from three trials (GETUG-15,[5,6] CHAARTED,[8-10] and STAMPEDE[11]) comparing ADT versus ADT plus docetaxel in patients with metastatic non-castrate prostate cancer were obtained, along with two meta-analyses[16,17] that included the data from these three trials.

The GETUG-15 trial reported by Gravis et al[5,6] included 385 M1 patients. Inclusion criteria for this trial included having metastatic prostate cancer (histologically confirmed adenocarcinoma and radiologically proven to be metastatic). Previous chemotherapy for metastatic disease was an exclusion criterion, but ADT for patients with metastatic disease was allowed if initiated no more than 2 months before entry. The primary outcome for the GETUG-15 trial was OS.

The CHAARTED trial reported by Sweeney et al[8-10] included a total of 790 M1 patients. Inclusion criteria for CHAARTED included a pathologic diagnosis of prostate cancer or a clinical presentation consistent with prostate cancer with an elevated PSA level, radiologic evidence of metastatic disease, and ECOG PS of 0 to 2. Prior adjuvant ADT was allowed if the duration of therapy was ≤ 24 months and progression had occurred more than 12 months after completion of therapy. Patients who received ADT for metastatic disease remained eligible if there was no evidence of progression and treatment had begun no more than 120 days before random assignment. The primary outcome for CHAARTED was OS.

The STAMPEDE trial, reported by James et al,[11] included a total of 2,962 patients overall, but only 1,776 were considered in this guideline (1,184 in the ADT alone arm and 592 in the ADT plus docetaxel arm). Approximately 39% of the total number of patients were M0 and were excluded from consideration within this guideline. Inclusion criteria for STAMPEDE were newly diagnosed metastatic, node-positive, or high-risk locally advanced (at least two of the following high-risk features: T3/4, Gleason score of 8 to 10, and PSA ≥ 40 ng/mL) prostate cancer or previous treatment with radical surgery, radiotherapy, or both and relapsing with high-risk features. All patients in STAMPEDE were to receive long-term ADT and remained eligible for trial entry as long as ADT began no more than 12 weeks before random assignment. The primary outcome for STAMPEDE was OS.

Demography and Prior Treatment

ADT with or without abiraterone. In both trials of ADT with or without abiraterone,[12,13] the median age was approximately 67 years. Both the LATITUDE[13] and STAMPEDE[12] trials included patients with predominantly good PS (LATITUDE, ECOG PS 0 to 2; STAMPEDE, WHO 0 to 1). In the LATITUDE trial,[13] the median time from gonadotropin-releasing hormone agonist/antagonist to first dose was 1.08 months, and the median time from the initiation of ADT to the initiation of abiraterone was 2 months in the STAMPEDE[12] trial.

ADT with or without docetaxel.

For the ADT with or without docetaxel trials, the median age was approximately 63 years in both the GETUG-15 and CHAARTED trials and 65 years in the STAMPEDE trial. All three trials included patients with predominantly good PS upon entry (GETUG-15,[5] ECOG PS of 0 to 2; CHAARTED,[10] ECOG PS of 0 to 1; STAMPEDE,[11] WHO 0 to 1). In the GETUG-15 trial, reported by Gravis et al,[5,6] approximately 50% of all patients started ADT 15 to 60 days before enrollment and the other half started within 15 days. CHAARTED[10] reported 24% of all patients having received prior radiation therapy, and 24% had undergone a prior prostatectomy. In the STAMPEDE trial,[11] approximately 3% of all patients reported previous treatment for M0 disease; no prior treatment was permitted for M1 disease. In the STAMPEDE trial,[11] patients started ADT at a median of approximately 40 days before random assignment.

Patient demographic characteristics and information on prior treatment are listed in Tables 1 and 2, respectively.

Risk of Bias

ADT with or without abiraterone. The LATITUDE[13] trial reported both industry funding and authorship but was otherwise a well-reported trial and was deemed to have a moderate risk of bias. STAMPEDE[12] was an open-label trial, performed using the intent-to-treat principle for all analyses, and was deemed to have a low risk of bias.

ADT with or without docetaxel. The risk-of-bias assessment found all three trials to have a low risk of bias. All were open-label trials, so allocation concealment and blinding were not performed. All of the trials comprised similar groups, used validated measures, and used intent-to-treat analyses.

Risk of bias is summarized in Table 3.

Outcomes

ADT with or without abiraterone. Primary outcomes of interest for the LATITUDE[13] trial were both OS and radiographic PFS, and secondary outcomes were as follows: time to next skeletal-related event (defined as a clinical or pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery on bone), time to PSA progression, time to next treatment for prostate cancer, time to start of chemotherapy, and time to pain progression (defined as an increase from baseline in the worst pain category on the Brief Pain Inventory–Short Form of at least 30% as observed at two consecutive evaluations performed at least 4 weeks apart). In the AAP cohort of the STAMPEDE trial,[12] the primary outcome of interest was OS, with FFS as an intermediate primary outcome. Both studies detected differences in OS between the AAP-treated patients and the patients treated with ADT alone. The LATITUDE trial reported a 38% reduction in the risk of death (hazard ratio [HR], 0.62; 95% CI, 0.51, 0.76; $P < .001$), with a median survival of 34.7 months in the ADT alone arm, whereas in the AAP arm, median survival was not yet reached. The STAMPEDE trial reported a reduction in the risk of death of 37% for the overall study population (HR, 0.63; 95% CI, 0.52 to 0.76; $P < .001$) and 39% in the M1 population (HR, 0.61; 95% CI, 0.49 to 0.75; $P < .05$). The LATITUDE trial detected a reduction in the risk for radiographic PFS of 53% (HR, 0.47; 95% CI, 0.39 to 0.55; $P < .001$) in favor of the abiraterone arm (14.8 months with ADT alone *v* 33 months with AAP), and the STAMPEDE trial detected a reduction in the risk of FFS of 69%

Table 1. Study Characteristics

Source	Arms	No. of Patients (%)	Median Age (years)	Performance Status (scale)	Prior Therapy — Type	%	Treatment Interval
ADT ± abiraterone							
Fizazi et al, 2017[13], LATITUDE 2013-2014	ADT alone	602	67 (range, 33-92)	ECOG 0: NR, 1: NR, 2: NR	Radiotherapy / Hormonal* / GnRH agonists/antagonists* / Orchiectomy* / First-generation androgen receptor Agonists* / Other	4 / 83 / 75 / 12 / 62 / 2	Median: 33 days from GnRH agonist/antagonist to first dose
	ADT + abiraterone	597	68 (range, 38-89)	ECOG 0: NR, 1: NR, 2: NR	Radiotherapy / Hormonal* / GnRH agonists/antagonists* / Orchiectomy* / First-generation androgen receptor Agonists* / Other	3 / 84 / 75 / 12 / 62 / 2	Median: 33 days from GnRH agonist/antagonist to first dose
James et al, 2017[12], STAMPEDE 2011-2014	ADT alone	957 total 502 M1	67 (IQR, 62-72)	WHO 0: 744, 1+: 213	Previously treated M0† / Previously treated M1†	1 / 3	Median: 45 days to start of ADT from random assignment
	ADT + abiraterone	960 total 500 M1	67 (IQR, 63-72)	WHO 0: 745, 1+: 215	Previously treated M0† / Previously treated M1†	3 / 4	Median: 44 days to start of ADT from random assignment
ADT ± docetaxel							
James et al, 2016[11], STAMPEDE 2005-2013	ADT alone	1,184	65 (range, 60-70)	WHO 0: 922, 1+: 262	Previously treated M0† / Previously treated M1†	3 / 3	Median: 41 days from start of ADT to random assignment
	ADT + docetaxel	592	65 (range, 61-71)	WHO 0: 461, 1+: 131	Previously treated M0† / Previously treated M1†	2 / 3	Median: 43 days from start of ADT to random assignment
Sweeney et al, 2015[9,10], CHAARTED 2006-2012	ADT alone	393, LVD: 143 (36.4), HVD: 250 (63.6)	63 (range, 39 to 91)	ECOG 0: 69.2%, 1: 29.3%, 2: 1.5%	No local treatment / Primary radiation therapy / Prostatectomy	72.8 / 8.4 / 18.6	1.3 months (range, .03 to 3.9) from start of ADT to random assignment
	ADT + docetaxel	397, LVD: 134 (33.8), HVD: 263 (66)	64 (range, 36 to 88)	ECOG 0: 69.8%, 1: 28.7%, 2: 1.5%	No local treatment / Primary radiation therapy / Prostatectomy	72.8 / 6.8 / 20.4	1.2 (range, .03 to 3.9) from start of ADT to random assignment
Gravis et al, 2013[6], 2016[5], GETUG-15 2004-2008	ADT alone	193, LVD: 102 (53), HVD: 91 (47)	64 (range, 58-70)	ECOG 0: 96%, 1-2: 4%	NR		15-60 days before enrollment: 47%; Approximately 15 days before enrollment: 53%
	ADT + docetaxel	192, LVD: 100 (52), HVD: 92 (48)	63 (range, 57-68)	ECOG 0: 99%, 1-2: 1%	NR		15-60 days before enrollment: 53%; Approximately 15 days before enrollment: 47%

Abbreviations: ADT, androgen-deprivation therapy; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; ECOG, Eastern Cooperative Oncology Group; GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; GnRH, gonadotropin-releasing hormone; HVD, high-volume disease; IQR, interquartile range; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naïve Prostate Cancer (mHNPC); LVD, low-volume disease; NR, not reported; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

*Patients were excluded if they had received > 3 months of ADT or orchiectomy.

†Radical surgery, radiotherapy, or both.

Table 2. Postprotocol Treatments

Study	Arm	No. of Patients	Paclitaxel	Docetaxel	Cabazitaxel	Etoposide	Cyclophos-phamide	Vinorelbine	Mitoxantrone	Platinum-based chemotherapy	Anthracy-clines	Other therapies	Abiraterone (steroidal)	Ketoco-nazole	Orteronel (nonsteroidal)	Enzalutamide	Other antiandrogens
ADT ± abiraterone																	
Fizazi et al, 2017[13], LATITUDE 2013-2014	ADT alone	602	NR	40	6	NR	NR	NR	NR	NR	NR	NR	11	NR	NR	16	NR
	ADT + abiraterone	597	NR	34	4	NR	NR	NR	NR	NR	NR	NR	3	NR	NR	10	NR
James et al, 2017[12], STAMPEDE 2011-2014	ADT alone	957 total 502 M1	NR	37	5	NR	NR	NR	NR	NR	NR	2	22	NR	NR	26	72
	ADT + abiraterone	960 total 500 M1	NR	46	6	NR	NR	NR	NR	NR	NR	4	3	NR	NR	10	33
ADT ± docetaxel																	
James et al, 2016[11], STAMPEDE	ADT alone	761*	NR	41	3	NR	NR	NR	NR	NR	NR	3	23	NR	NR	9	67
	ADT + docetaxel	315*	NR	14	7	NR	NR	NR	NR	NR	NR	7	28	NR	NR	8	57
Sweeney et al, 2015[9,10], CHAARTED	ADT alone	393	NR	39.9	9.4	NR	NR	NR	NR	6.9	NR	NR	26.5†	23.2‡	NR	26.5†	23.2‡
	ADT + Docetaxel	397	NR	13.6	14.4	NR	NR	NR	NR	7.3	NR	NR	26.4†	20‡	NR	26.4†	20‡
Gravis et al, 2013[6], 2016[5], GETUG-15 2004-2008	ADT alone	193	3	62	1	13	5	6	NR	11	18	< 1§ 11‖	11	NR	< 1	4	NR
	ADT + docetaxel	192	2	28	2	13	4	5	NR	11	12	1§ 7‖	10	NR	1	5	NR

(continued on following page)

Table 2. Postprotocol Treatments (continued)

%

Study	Arm	Radiotherapy			Bisphosphonates		Steroids		Nonsteroidal Estrogen	NSAIDs	Immunotherapy
		Strontium	Radium-223	Other radiotherapy	Zoledronic acid	Other bisphosphonates	Dexamethasone	Prednisolone	Diethylstilbestrol	Cox-2 inhibition	Sipuleucel T
ADT ± abiraterone											
Fizazi et al, 2017[3], LATITUDE 2013-2014	ADT alone	NR	6	NR	NR	NR	NR	NR	NR	NR	NR
	ADT + abiraterone	NR	4	NR	NR	NR	NR	NR	NR	NR	NR
James et al, 2017[12], STAMPEDE 2011-2014	ADT alone	NR	4	NR	15	2	21	16	NR	0	NR
	ADT + abiraterone	NR	8	NR	16	2	21	13	NR	< 1	NR
ADT ± docetaxel											
James et al, 2016[11], STAMPEDE	ADT alone	2	1	NR	17	3	14	9	11	0	NR
	ADT + docetaxel	1	2	NR	11	3	12	9	12	0	NR
Sweeney et al, 2015[9,10], CHAARTED	ADT alone	NR	NR	20.1	NR	NR	NR	NR	NR	NR	4.8
	ADT + Docetaxel	NR	NR	17.4	NR	NR	NR	NR	NR	NR	5.5
Gravis et al, 2013[6], 2016[5], GETUG-15 2004-2008	ADT alone	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADT + docetaxel	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: ADT, androgen-deprivation therapy; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naïve Prostate Cancer (mHNPC); NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.
*Patients with progressive disease only.
†Abiraterone and/or enzalutamide.
‡Antiandrogen and/or ketoconazole.
§Fluoropyrimidine.
‖Patients received efavirenz, BIBF 1120, enzastaurine, sagopilone, DTS-201, CNTO 328, or masitinib or were included in randomized studies testing ipilimumab, dasatinib, zibotentan, sunitinib, vandetanib, or aflibercept versus placebo.

	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	Intention-to-Treat Analysis	Insignificant COIs	Overall Potential Risk of Bias
Table 3. Quality Assessment										
Source										
ADT ± abiraterone										
Fizazi et al, 2017[13]; LATITUDE 2013-2014	+	+	+	+	+	+	+	NR	—	Moderate
James et al, 2017[12]; STAMPEDE 2011-2014	+	—	+	+	—	+	+	+	+	Low
ADT ± docetaxel										
James et al, 2016[11]; STAMPEDE	+	—	+	+	—	+	+	+	+	Low
Sweeney et al, 2015,[10] 2016[9]; CHAARTED	+	—	+	+	—	+	+	+	+	Low
Gravis et al, 2013,[6] 2016[5]; GETUG-15	+	—	+	+	—	+	+	+	+	Low

NOTE. +, criterion met; —, criterion not met.
Abbreviations: CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; COI, conflict of interest; GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC); NR, not reported; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

(HR, 0.31; 95% CI, 0.26 to 0.37; $P < .05$) in the M1 population (median, 30 months with ADT alone v 43.9 months with AAP). The LATITUDE trial also demonstrated superiority of AAP over ADT alone for all secondary end points.

ADT with or without docetaxel. Two[9-11] of the included trials detected differences in OS. The GETUG-15 trial[5] did not detect a survival difference at a median of 83.9 months of follow-up (for all patients; HR, 0.88; 95% CI, 0.68 to 1.14; $P = .3$; median OS, 48.6 months with ADT alone v 62.1 months with ADT plus docetaxel).

In the 2015 publication on the CHAARTED trial reported by Sweeney et al,[10] a benefit in favor of ADT in combination with docetaxel was detected (HR, 0.61; 95% CI, 0.47 to 0.80; median survival, 44 v 57.6 months; $P < .001$) after 28.9 months median follow-up. In a planned subgroup analysis, chemotherapy prolonged survival in men with high-volume disease (HVD; HR, 0.60; 95% CI, 0.45 to 0.81; 32.2 v 49.2 months; $P < .001$). Such a treatment effect was not seen in men with low-volume disease (LVD), where an HR of 0.60 (95% CI, 0.32 to 1.13; median OS, not reached in either arm; $P = .11$) was observed between the patients who received docetaxel and those who did not.[10] In 2016, an updated report of the CHAARTED trial[9] was presented. The addition of docetaxel to ADT continued to have a significant benefit in median survival compared with ADT alone after 53.7 months median follow-up (HR, 0.73; 95% CI, 0.59 to 0.89; median survival, 47.2 months with ADT alone; 95% CI, 41.8 to 52.8 v 57.6 months with ADT plus docetaxel; 95% CI, 52 to 63.9; $P = .0018$). This benefit was also detected in a comparison of patients with HVD (HR, 0.63; 95% CI, 0.50 to 0.79; $P < .0001$; median survival, 34.4 months [95% CI, 30.1 to 42.1] with ADT alone v 51.2 months [95% CI, 45.2 to 58.1] with ADT plus docetaxel). No OS benefit was found in patients with LVD (HR, 1.04; 95% CI, 0.70 to 1.55; $P = .86$; median survival, not reached [95% CI, 59.8 to not reached] with ADT alone v 63.5 months [95% CI, 58.3 to 78.5] with ADT plus docetaxel).

Subgroups in GETUG-15 according to the CHAARTED criteria (HVD, n = 183; LVD, n = 202) trended in favor of an OS advantage in the HVD group with docetaxel, but ultimately, these subgroups were too small for a conclusive comparative analysis.

The STAMPEDE trial detected a median survival benefit in favor of the addition of docetaxel to ADT compared with ADT alone (median, 81 v 71 months).[11] This was true for the overall study population that received docetaxel (HR, 0.78; 95% CI, 0.66 to 0.93; median survival, 81 months; $P = .006$) and specifically those patients with metastatic disease who received ADT plus docetaxel (HR, 0.76; 95% CI, 0.62 to 0.92; median survival, 60 months; $P = .033$).

For biochemical PFS, both trials[5,10] detected a significant improvement in the docetaxel arms (GETUG-15: HR, 0.67; $P < .001$; 12.9 months ADT alone v 22.9 months ADT plus docetaxel and the 2015 publication of the CHAARTED trial[10]: HR, 0.61; 95% CI, 0.51 to 0.72; $P < .001$; 11.7 months ADT alone v 20.2 months ADT plus docetaxel). In the CHAARTED trial, Sweeney et al[10] detected a higher likelihood of achieving a PSA level of less than 0.2 ng per milliliter at 12 months for men treated with the combination arm (16.8% ADT alone v 27.7% ADT plus docetaxel; $P < .001$). For FFS, which was defined as a composite end point including biochemical and radiographic measures and death, the STAMPEDE trial[11] detected an improvement with docetaxel (HR, 0.61; 95% CI, 0.53 to 0.70; $P < .001$; 20 months ADT alone v 37 months ADT plus docetaxel).

Outcomes are summarized in Table 4.

Adverse Events (grade ≥ 3)

ADT with or without abiraterone. In the LATITUDE trial, serious adverse event rates were similar between the two arms. Adverse effects that resulted in treatment discontinuation were 10% in the ADT alone arm versus 12% in the AAP arm, and adverse events that resulted in a dose modification or interruption were 17% in the ADT alone arm versus 32% in the AAP arm. Hypertension and hypokalemia occurred at a higher frequency in the abiraterone group. For the entire population in the STAMPEDE trial, the percentage of grade ≥ 3 adverse events was similar in both arms (ADT alone, 11% v AAP, 15%). Hypertension, increases in aminotransferase levels, and respiratory disorders were associated with AAP.

Table 4. Efficacy Outcomes

Source	Intervention/Comparisons	No. of Patients Evaluated	Median Follow-Up (months)	Median OS (months)	HR (95% CI; P)	Survival bPFS (months)	Survival HR (95% CI; P)	Other Survival (months)	HR for FFS (95% CI; P)
ADT ± abiraterone									
Fizazi et al, 2017[13], LATITUDE 2013-2014	ADT alone	602	30.4	34.7	1	NR	NR	Radiographic: 14.8	1
	ADT + abiraterone	597	30.4	Not reached	0.62 (0.51 to 0.76; < .001)	NR	NR	Radiographic: 33.0	0.47 (0.39 to 0.55; < .001)
James et al, 2017[12], STAMPEDE 2011-2014	ADT alone	957 total 502 M1	40	NR	1	NR	NR	FFS (mean): 30.0	1
	ADT + abiraterone	960 total / 500 M1	40	Not reached	0.63 (0.52 to 0.76; < .001 all patients); 0.61 (0.49 to 0.75; < .05 M1 patients)	NR	NR	FFS (mean): 43.9	0.29 (0.25 to 0.34; < .001); 0.31 (0.26 to 0.37; < .05 M1 patients)
ADT ± docetaxel									
James et al, 2016[11], STAMPEDE	ADT alone	1,184	43 (IQR, 30-60)	71 (IQR, 32 to not reached)	1	NR	NR	FFS: 20	1
	ADT + docetaxel Median time to start docetaxel after starting hormone therapy: 8.6 weeks (range, 5.6-11.9)	592	43 (IQR, 30-60)	81 (IQR, 41 to not reached; ADT alone v ADT + docetaxel)	0.78 (0.66 to 0.93; .006)	NR	NR	FFS: 37 (ADT alone v ADT + docetaxel)	0.61 (0.53 to 0.70; < .0001)
Sweeney et al, 2015[9,10], CHAARTED	ADT alone	393	53.7	All: 47.2 (range, 41.8-52.8)	1	NR	NR	NR	NR
	2016 report[9]	LVD: 143		LVD: not reached (95% CI, 59.8 to not reached); HVD: 34.4 (95% CI, 30.1 to 42.1)					
		HVD: 250							
	ADT + docetaxel	397	53.7	All: 57.6 (range, 52-63.9)	ADT alone v ADT + docetaxel (all patients) 0.73 (0.59 to 0.89; < .0018)	NR	NR	NR	NR
	2016 report[9]	LVD: 134		LVD: 63.5 (95% CI, 58.3 to 78.5); HVD: 51.2 (95% CI, 45.2 to 58.1)	ADT alone v ADT + docetaxel (HVD) 0.63 (0.50 to 0.79; < .0001); ADT alone v ADT + docetaxel (LVD) 1.04 (0.70 to 1.55; .86)				
		HVD: 263							
	ADT alone 2015 report[10]	393	28.9	44	1	11.7	1	Biochemical, symptomatic, or radiographic progression: 11.7	NR
	ADT + docetaxel 2015 report[10]	397	28.9	57.6	0.61 (0.47 to 0.80; < .001)	20.2	0.61 (0.51 to 0.72; < .001)	20.2 ADT alone v ADT + docetaxel (all patients)	0.61 (0.51 to 0.72; < .001)

(continued on following page)

Table 4. Efficacy Outcomes (continued)

Source	Intervention/ Comparisons	No. of Patients Evaluated	Median Follow-Up (months)	Median OS (months)	HR (95% CI; *P*)	Survival — bPFS (months)	Survival — HR (95% CI; *P*)	Survival — Other Survival (months)	Survival — HR for FFS (95% CI; *P*)
Gravis et al, 2013,[6] 2016[5] GETUG-15	ADT alone	193	83.9	All: 48.6 (range, 40.9-60.6) HVD: 35.1 (range, 29.9-43.6) LVD: 83.4 (range, 61.8 to not reached)	1	All: 12.9 (range, 11.9-17.7) HVD: 9.2 (range, 8.3-12.2) LVD: 22.4 (range, 16.8-35.5)	1	NR	NR
	ADT + docetaxel	192	83.9	All: 62.1 (range, 49.5-73.7) HVD: 39.8 (range, 28-53.4) LVD: not reached (range, 69.5-not reached)		All: 22.9* (range, 19.5-28.4) HVD: 15.2 (range, 12-21.2) LVD: 40.9 (range 28.4-65.2)		NR	NR
				ADT alone *v* ADT + docetaxel (all patients)	0.88 (0.68 to 1.14; .3)		ADT alone *v* ADT + docetaxel (all patients) 0.67 (0.54 to 0.84; < .001)		
				ADT alone *v* ADT + docetaxel (HVD)	0.78 (0.56 to 1.09; .14)		ADT alone *v* ADT + docetaxel (HVD) 0.58 (0.42 to 0.79; < .001)		
				ADT alone *v* ADT + docetaxel (LVD)	1.02 (0.67 to 1.55; .9)		ADT alone *v* ADT + docetaxel (HVD) 0.79 (0.57 to 1.10; .16)		

Abbreviations: ADT, androgen-deprivation therapy; bPFS, biochemical progression-free survival; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; FFS, failure-free survival; GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital-Association Française d'Urologie; HR, hazard ratio; HVD, high-volume disease; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC); LVD, low-volume disease; NR, not reached; OS, overall survival; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.
*Intermediate- and low-prognosis patients experienced a bPFS benefit from the addition of docetaxel to ADT.

ADT with or without docetaxel. For hematologic toxicity, the neutropenia rates in the docetaxel arms of GETUG-15,[6] CHAARTED,[9,10] and STAMPEDE[11] were 32%, 3.1%, and 12%, respectively, which may be related to actual differences in rates of neutropenia or reflect variable rates at which patients had their counts checked between trials. For febrile neutropenia, GETUG-15[6] reported 7%, CHAARTED[10] reported 3.8%, and STAMPEDE[11] reported 15% (docetaxel arm). Only the GETUG-15 trial[6] reported any incidences of grade 3 or 4 thrombocytopenia, with < 1% being observed in the docetaxel arm. GETUG-15[6] and STAMPEDE[11] reported on neurologic outcomes, with 2% of patients reporting sensory neuropathy associated with docetaxel versus none in the ADT arm (GETUG-15) and 3% of patients reporting nervous system effects (including peripheral neuropathy) in the docetaxel arm versus 2% in the ADT alone arm (STAMPEDE). For fatigue, GETUG-15[6] reported 7% in the docetaxel arm versus none in the ADT arm, and CHAARTED[10] reported 4.1% in the docetaxel arm versus none in the ADT arm. Additionally, Sweeney et al[10] reported treatment-related mortality (TRM) of one of 397 in the ADT plus docetaxel arm versus none (of 393) in the ADT alone arm, Gravis et al[6] reported possible TRM of four of 192 in the ADT plus docetaxel arm versus none (of 193) in the ADT alone arm, and STAMPEDE reported TRM of one of 592 in the ADT plus docetaxel arm (resulting from neutropenic sepsis) versus none (of 1,184) in the ADT alone arm.

Adverse events grade ≥ 3 are listed in Table 5.

QOL

ADT with or without abiraterone. In LATITUDE, patients were assessed by a variety of instruments, including the Brief Fatigue Inventory, the Functional Assessment of Cancer Therapy–Prostate (version 4; FACT-P), and the EQ-5D-5L.[19] There was an advantage to treatment with AAP for pain control (37% risk reduction for worst pain progression; HR, 0.63; 95% CI, 0.52 to 0.77; $P < .0001$) and pain interference progression (33% risk reduction; HR, 0.67; 95% CI, 0.56 to 0.80; $P < .0001$). In addition, AAP conferred an improvement in fatigue progression (35% risk reduction; HR, 0.65; 95% CI, 0.53 to 0.81; $P = .0001$) and fatigue interference progression (41% risk reduction; HR, 0.59; 95% CI, 0.47 to 0.75; $P < .0001$). AAP reduced the risk of health-related QOL degradation by 15% (HR, 0.85; 95% CI, 0.74 to 0.99; $P = .0322$; HR, 0.85; 95% CI, 0.74 to 0.99; $P = .0322$ per FACT-P). Health status and health utility scores (EurQoL five-dimension five-level questionnaire Visual Analog Scale) were also statistically significantly improved. Reports for QOL data from STAMPEDE are pending.

ADT with or without docetaxel. For QOL outcomes, both Patrick-Miller et al[7] and Sweeney et al[9] reported on the CHAARTED trial using the FACT-P. Patients allocated to the docetaxel arm reported a decline in scores at 3 months ($P = .003$), but no differences were found between baseline and 12 months.[7] Scores differed between arms at 3 months ($P = .02$) and 12 months ($P = .04$), with the docetaxel arm being lower than baseline at 3 months. However, at 12 months, patients who had received docetaxel were found to have significantly higher scores than those who had not, raising the possibility that not only is there no durable negative impact on QOL with the addition of docetaxel, but perhaps there is a benefit.[7] Gravis et al[6] reported on QOL outcomes in the GETUG-15 trial using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 instrument. In this trial, QOL measures were not different at baseline, but significant differences in favor of the ADT alone arms were detected at 3 months, although when assessed at 1 year, these differences were absent.

QOL information is listed in Table 6.

Systematic Review With Meta-Analysis

ADT with or without docetaxel. Two systematic reviews[16,17] with meta-analyses were also obtained. The first, reported by Vale et al,[17] pooled data from 2,992 men with metastatic disease from the STAMPEDE, CHAARTED, and GETUG-15 trials. The findings were that the addition of docetaxel to standard of care (SOC) improved survival (SOC, 61% [656 deaths in 1,676] v SOC plus docetaxel, 70% [403 deaths in 1,316]; HR, 0.77; 95% CI, 0.68 to 0.87; $P < .0001$), resulting in an absolute 4-year survival improvement of 9% (95% CI, 5 to 14 years) compared with SOC. Adding docetaxel to SOC also improved FFS (SOC, 61.4% [1,029 failures in 1,676] v SOC plus docetaxel, 49.7% [650 failures in 1,316]; HR, 0.64; 95% CI, 0.58 to 0.70; $P < .0001$), resulting in a reduction in absolute 4-year failure rates of 16% (95% CI, 12% to 19%) compared with SOC.

The second, reported by Tucci et al,[16] pooled data from the same three trials and also found that the addition of docetaxel to SOC improved survival in patients with metastatic disease (HR, 0.73; 95% CI, 0.60 to 0.90; $P = .002$), with nonsignificant heterogeneity ($P = .15$; $I^2 = 48\%$). This same analysis found a significant PFS benefit with the addition of docetaxel to SOC (HR, 0.63; 95% CI, 0.57 to 0.70; $P < .001$), without significant heterogeneity among the three trials ($P = .7$; $I^2 = 0\%$).

ADT with or without abiraterone. A systematic review and meta-analysis reported by Rydzewska et al[20] using the novel Framework for Adaptive Meta-Analyses (FAME) pooled data from 2,201 men with metastatic disease from the STAMPEDE and LATITUDE trials. The findings were that the addition of abiraterone to ADT reduced the risk of death by 38% (HR, 0.62; 95% CI, 0.53 to 0.71; $P = 0.55 \times 10^{-10}$), resulting in a 14% absolute improvement in 3-year survival. Although PFS was defined differently in the two trials, the analysis combined the outcome demonstrating that the addition of abiraterone to ADT reduced the risk of radiographic or clinical progression by 55% (HR, 0.45; 95% CI, 0.40 to 0.51; $P = 0.67 \times 10^{-36}$), resulting in a 28% absolute improvement at 3 years. More grade 3 to 4 acute cardiac, vascular, and hepatic toxicities were seen; however, there was no statistically significant excess of deaths with the addition of abiraterone.

RECOMMENDATIONS

CLINICAL QUESTION 1

Is there an OS advantage associated with the addition of docetaxel or abiraterone to ADT in men with metastatic non-castrate prostate cancer?

Table 5. Acute Adverse Events

Source	Intervention/Comparison	No. of Patients Evaluated	No. of Deaths (%)	Grade ≥ 3 (%)														
				Neutropenia	Febrile Neutropenia	Infections With Neutropenia	Anemia	Thrombocytopenia	Fatigue	GI	Alopecia	Sensory Neuropathy/Motor Neuropathy	Peripheral Edema	Dyspnea	Hot Flushes	Erectile Dysfunction	Decreased Libido	Liver
ADT ± abiraterone																		
Fizazi et al, 2017[13], LATITUDE 2013-2014	ADT alone	602	24 (4)*	NR	NR	NR	5†	NR	2	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADT + abiraterone	597	28 (5)*	NR	NR	NR	3	NR	2	NR	NR	NR	NR	NR	NR	NR	NR	NR
James et al, 2017[12], STAMPEDE 2011-2014	ADT alone	960 total	3 (< 1)*	NR	NR	NR	NR	NR	2	4	NR	NR	NR	1	NR	NR	NR	NR
	ADT + abiraterone	948 total	9 (1)*	NR	NR	NR	NR	NR	2	5	NR	NR	NR	2	NR	NR	NR	NR
ADT ± docetaxel																		
James et al, 2016[11], STAMPEDE	ADT alone	1184	0	0	1	NR	NR	NR	4	3	NR	2	NR	NR	NR	NR	NR	NR
	ADT + docetaxel	592	1 (< 1)	12	15	NR	NR	NR	7	8	NR	3	NR	NR	NR	NR	NR	NR
Sweeney et al, 2015[10], CHAARTED	ADT alone	393	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ADT + docetaxel	397	1 (< 1)	3.1	3.8	1.3	NR	0	4.1	1	NR	1	NR	NR	NR	NR	NR	NR
Gravis et al, 2013[6], GETUG-15	ADT alone	186	0	0	NR	NR	NR	NR	NR	0	0	0	0	0	2	8	5	< 1
	ADT + docetaxel	189	4 (2)	32	7	2†	2	< 1	7	< 1	3	2	1	2	4	8	6	2

Abbreviations: ADT, androgen-deprivation therapy; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC); NR, not reached; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

*Treatment-related mortality and/or grade 5 adverse event.

†Approximate value.

Table 6. QOL

Source	Intervention/Comparison	No. of Patients Evaluated	QOL Instrument	Baseline	At Month 3	At Month 12
ADT ± abiraterone						
Fizazi et al, 2017[13]; LATITUDE 2013-2014	ADT alone	570	BPI-SF	1.5 (2.0)*	—	—
		578	BFI	2.2 (2.5)*	—	—
		579	FACT-P (v4)	113.2 (20.0)*	—	—
		578	EQ-5D-5L	0.8 (0.2)*	—	—
	ADT + abiraterone	579	BPI-SF	1.5 (2.0)*	37% risk reduction HR, 0.63; 95% CI, 0.52 to 0.47; $P < .001$	
		568	BFI	2.2 (2.6)*	53% risk reduction HR, 0.65; 95% CI, 0.53 to 0.81; $P = .0001$	
		568	FACT-P (v4)	112.4 (20.0)*	15% risk reduction HR, 0.85; 95% CI, 0.74 to 0.99; $P = .0322$	
		570	EQ-5D-5L	0.8 (0.2)*	HR, NR; $P < .05$	
ADT ± docetaxel						
Sweeney al, 2016[9]; CHAARTED	ADT alone	LVD: 143	FACT-P	LVD: 133	LVD: 120.3	LVD: 120
		HVD: 250		HVD: 116.1	HVD: 117	HVD:113.7
		Total: 393		Total: 249.1	Total: 237.3	Total: 233.7
	ADT + docetaxel	LVD: 134		LVD: 121.6	LVD: 117	LVD: 121
		HVD: 263		HVD: 118.2	HVD: 116.3	HVD:118
		Total: 397		Total: 239.8	Total: 233.3	Total: 239
					$P = .02$†	$P = .04$†
Gravis et al, 2013[6]; GETUG-15	ADT alone	193	EORTC QLQ-C30	65.4	70.96	66.36
	ADT + docetaxel	192		67.4	63.95	67.62
				$P = .41$	$P < .005$	$P = .7$

Abbreviations: ADT, androgen-deprivation therapy; BFI, Brief Fatigue Inventory; BPI-SF, Brief Pain Inventory–Short Form; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D-5L, EurQoL five-dimension five-level questionnaire Visual Analog Scale; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FACT-P (v4), Functional Assessment of Cancer Therapy–Prostate (version 4); GETUG-15, Groupe d'Etude des Tumeurs Uro-Genital–Association Française d'Urologie; HR, hazard ratio; HVD, high-volume disease; LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC); LVD, low-volume disease; QOL, quality of life.
*Reported as mean (standard deviation).
†Compared using paired t test.

Recommendations

For subsets of men with newly diagnosed metastatic non-castrate disease, treatment with abiraterone or docetaxel in combination with ADT should be offered on the basis of prolonging life relative to ADT alone. For docetaxel, the data are most compelling for men with de novo high-volume metastatic non-castrate prostate cancer (defined 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) who are chemotherapy candidates. The appropriate regimen of docetaxel is six doses of docetaxel administered every 3 weeks at 75 mg/m^2 either alone (per CHAARTED) or with prednisolone (per STAMPEDE) (Type: evidence based, benefits outweigh harms; Evidence quality: strong; Strength of recommendation: high).

Data to support the use of chemotherapy in men without HVD is less robust; an unqualified recommendation for chemotherapy in such men cannot be made without additional data and analysis.

Men with de novo metastatic non-castrate high-risk disease per LATITUDE (two or more of the factors of Gleason score ≥ 8, ≥ three bone metastases, and measurable visceral disease) who are fit for treatment with abiraterone should receive ADT and AAP. Men at lower risk may also be offered ADT and AAP (per STAMPEDE). The appropriate regimen is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily. (Type:

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

There are insufficient data to recommend which patients should receive abiraterone and which should receive docetaxel. There are no data by which to recommend both abiraterone and docetaxel for metastatic non-castrate disease, either combined or sequentially.

Literature review and analysis. Both abiraterone trials (LATITUDE and STAMPEDE) suggest that abiraterone should be administered at 1,000 mg with either prednisolone or prednisone 5 mg once daily. Two (CHAARTED and STAMPEDE) of the three trials obtained and both meta-analyses suggest that six doses of docetaxel administered every 3 weeks at or near the start of ADT confers a survival benefit to at least some of these patients.

Clinical interpretation. The addition of either docetaxel or abiraterone to ADT in men with newly diagnosed metastatic prostate cancer offers a survival benefit as compared with the use of ADT alone. The strongest evidence for benefit with docetaxel is in men with de novo extensive metastatic disease, whereas the data in other patients with metastatic disease are less clear. The benefit with the addition of abiraterone was seen in patients with lower-risk disease. In the absence of randomized data comparing the addition of docetaxel versus abiraterone to ADT in men with metastatic non-castrate disease, additional variables including patient comorbidities, toxicity, QOL considerations, and cost will ultimately need to be taken into consideration.

Since the discovery that testosterone-lowering maneuvers favorably affect the natural history of prostate cancer,[21-23] ADT has been a mainstay of therapy for men with metastatic non-castrate disease. Until recently, no interventions other than ADT had significantly altered OS in this group of patients, although numerous new treatments have improved outcomes for men with mCRPC. The first agent to demonstrate an OS benefit for men with mCRPC was docetaxel, which demonstrated modest gains and was approved for mCRPC in 2004.[25,26] That approval was based on data demonstrating that docetaxel and prednisone improved OS with an HR of 0.76, yielding a median OS survival advantage of 2 to 3 months relative to mitoxantrone and prednisone.[26,27]

More contemporarily, in 2011, AAP was approved for men with mCRPC who had received docetaxel on the basis of reducing the risk of death by 24% and improving median OS by 3.9 months (14.8 v 10.9 months; HR, 0.65; 95% CI, 0.54 to 0.77; $P < .001$) compared with men who were treated with prednisone alone.[28] In 2014, approval was extended to men with mCRPC who were docetaxel naïve on the basis of reducing the risk of radiographic PFS by 57% (HR, 0.43; 95% CI, 0.35 to 0.52; $P < .0001$).[29] Survival in this study was significantly longer in the AAP group than in the placebo group (34.7 months; 95% CI, 32.7 to 36.8 v 30.3 months; 95% CI, 28.7 to 33.3; HR, 0.81; 95% CI, 0.70 to 0.93; $P = .0033$).[30]

The GETUG-15,[5,6] CHAARTED,[10] and STAMPEDE[11] studies tested the hypothesis that docetaxel would prolong survival if applied earlier in the natural history of the disease than mCRPC. Two of these trials, STAMPEDE and CHAARTED, were positive in favor of using six cycles of docetaxel (with or without prednisolone). STAMPEDE yielded an HR of 0.78 (95% CI, 0.66 to 0.93; $P = .006$) for its overall study population in favor of treatment with docetaxel and prednisolone, with an absolute difference in median survival of 10 months between the ADT alone and ADT plus docetaxel groups. The survival advantage was maintained in favor of docetaxel when only those patients with metastatic disease were specifically examined. CHAARTED yielded an HR of 0.73 (95% CI, 0.59 to 0.89; $P = .0018$), with an absolute difference in OS of 10.4 months. In addition, these trials suggested that use of docetaxel in this setting is well tolerated and, according to the CHAARTED study, may have a durably favorable impact on QOL. The GETUG-15 trial, involving 385 patients who were randomly assigned to nine cycles of docetaxel or not, showed no survival advantage. The cause of the conflicting outcomes of the GETUG-15 trial from the other studies has been the subject of speculation and deliberation. Proposed factors have included imbalances in exposures to postprotocol therapies, different risks represented by the patient populations, different sizes of the trials, and other factors. Ultimately, the reasons for the negative findings of the GETUG-15 trial in contradistinction to the other studies are presently not known.

Two[16,17] meta-analyses examined the aggregate of the three trials, and each of those yielded a result in favor of the use of docetaxel. In one meta-analysis,[17] treatment of patients with metastatic non-castrate disease yielded an HR of 0.77 (95% CI, 0.68 to 0.87; $P < .0001$) in favor of treatment. In the other,[16] the addition of docetaxel yielded an HR of 0.73 (95% CI, 0.60 to 0.90; $P = .002$), with nonsignificant heterogeneity among the three trials.

STAMPEDE and LATITUDE examined the role of AAP in the treatment of metastatic non-castrate disease. Both were positive in favor of treatment with AAP in men with metastatic non-castrate prostate cancer. As with docetaxel, the STAMPEDE trial examined a wide range of men, from those with metastatic disease to those with nonmetastatic disease. In the broader population, treatment with AAP prolonged OS benefit. The risk of death was reduced by 37% for the overall study population (HR, 0.63; 95% CI, 0.52 to 0.76; $P < .001$) and by 39% in the M1 population (HR, 0.61; 95% CI, 0.49 to 0.75; $P < .05$), and the risk of FFS was reduced by 69% (HR, 0.31; 95% CI, 0.26 to 0.37; $P < .05$) in the M1 population (median, 30 months with ADT alone v 43.9 months with AAP). The LATITUDE study focused specifically on newly diagnosed patients with de novo metastatic disease with high-risk features defined by having any two of the features of Gleason grade 8 to 10 disease, at least three bone lesions, and any measurable visceral disease. Here, AAP reduced the risk of death by 38% (HR, 0.62; 95% CI, 0.51 to 0.76; $P < .001$) and the risk of radiographic PFS by 53% (HR, 0.47; 95% CI, 0.39 to 0.55; $P < .001$). As noted earlier, the superiority of AAP was also demonstrated for all the secondary end points in LATITUDE.

Understanding the differences between these trials, the nuances of their data, and the appreciation of the wide spectrum of risks that patients with prostate cancer face are key to the judicious application of docetaxel or AAP for prostate cancer. Prostate cancer is a heterogeneous disease with a high prevalence in elderly men, representing a wide spectrum of risk. It often manifests in patients with competing risks of disease and disability. The need to avert the dual harms of overtreatment and undertreatment is particularly acute in this disease, which has a long history of overly broad applications of treatment, screening, and diagnostic strategies.[31-33] Several factors seem to merit consideration:

1. Disease distribution: Rarely do SOCs alter via a single clinical trial. For men with high-risk disease (for AAP) or HVD (for docetaxel), a change in SOC is clearly warranted by virtue of two randomized prospective studies for each therapy, with mutually supportive results in favor of treatment either with AAP or docetaxel. Disease distribution was key to defining these groups, with number of bone metastases and visceral disease comprising key criteria in both CHAARTED and LATITUDE.

The issue of disease distribution is particularly vexing in deciding which patients should receive docetaxel. The CHAARTED population with LVD did not seem to enjoy a survival advantage by receiving chemotherapy. Docetaxel yielded an HR of 0.63 ($P < .0001$) in patients with HVD and an HR of 1.04 ($P = .86$) in patients with LVD. No doubt, subgroup analyses do not have the power to be conclusive and should be interpreted with appropriate circumspection and care; nonetheless, the lack of evident benefit in LVD is buttressed by the retrospective analysis of the GETUG-15 trial, and the data have similar, although not statistically significant, trends, where the patients with HVD were conferred an HR of 0.78 ($P = .14$), whereas the patients with LVD had an HR of 1.02 ($P = .9$).

As a result, the clinical recommendation in support of administering chemotherapy is high for HVD, and if one is going to use chemotherapy rather than AAP, it should be offered to men

with HVD. Chemotherapy for LVD at present is not necessarily an SOC. The data for the specific population of patients with LVD are not known from STAMPEDE. Administering chemotherapy to patients with LVD is not outside the SOC, given that CHAARTED and STAMPEDE were powered to examine the entire treatment population and that subpopulations, even if identified prospectively, need to be interpreted with caution.

For AAP, the issue of disease distribution is also pertinent. As with docetaxel, the data are most compelling for patients with higher volumes of bone disease (at least three lesions) and/or with visceral disease, given that LATITUDE studied these patients specifically, with the additional element of high Gleason score as a qualifying criterion for eligibility. For these patients, LATITUDE and STAMPEDE are mutually reinforcing that they should receive abiraterone in addition to ADT, if they are candidates for abiraterone. Unlike the circumstance with docetaxel, there are, at present, no negative studies to call into question the use of AAP in specific populations of men with metastatic non-castrate disease, nor subanalyses that would suggest that some men should specifically not receive such therapy. Therefore, ASCO recommends that men with high-risk disease receive AAP in addition to ADT. Only STAMPEDE addresses men with metastatic disease who do not have high-risk features as well. Although there are no data to refute that these men may benefit, there is no confirmatory trial, and therefore, the recommendation is that these patients might receive AAP.

The imaging data from these trials should be pooled and freshly modeled to identify the patient population that most benefits from chemotherapy or AAP. Not only do visceral and bone diseases have different prognoses, but even within visceral disease, the specific organs involved have individual prognostic value.[34] Furthermore, newer methods of assessing bone disease burden that are more quantitative and automated may offer more refined methods of correlating osseous disease burden with outcome compared with lesion counting.

2. Patient clinical course: According to 2017 estimates, only approximately 4% of patients with prostate cancer present with de novo metastatic disease in the United States.[1] However, many patients develop metastatic disease after primary treatment and an often prolonged period of biochemical relapse. In the GETUG-15 trial, 67% of patients in the ADT plus docetaxel group had metastatic disease at diagnosis compared with 75% of patients in the ADT alone arm; in the CHAARTED study, 73% of patients had received no prior local therapy; and in STAMPEDE, approximately 60% of patients were characterized as having newly diagnosed M1 disease in the docetaxel comparison along with approximately 50% in the abiraterone comparison. The LATITUDE study was specifically limited to patients with de novo metastatic disease. Hence, these trials speak primarily to those patients who present with metastatic disease rather than who develop metastases over a long period of biochemical relapse after definitive local therapy.

3. Early versus late treatment: Although the putative assumption of these trials was that early treatment might amplify the modest effects of treatment observed in mCRPC, none of these trials formally tested the hypothesis that docetaxel or

abiraterone delivered to patients with non-castrate disease is superior to chemotherapy administered for mCRPC, although analysis of postprotocol exposures might indirectly address this question.

Both AAP and docetaxel for metastatic non-castrate prostate cancer are SOCs, although the strength of evidence of benefit is not equivalent across the spectrum of risk or disease burden of that disease state; both drugs also remain an SOC for mCRPC. Because contemporary treatment paradigms for mCRPC are evolving rapidly, and the place for docetaxel and AAP for mCRPC is changing, the very meaning of the question of early versus late treatment also continues to change.

4. Docetaxel or abiraterone: Docetaxel and abiraterone should be considered as two separate SOCs for metastatic non-castrate prostate cancer, with the caveats and qualifications described above. These two standards have not been compared head to head, and at face value, their benefits seem to be quite similar. The HRs of the abiraterone arm of STAMPEDE, LATITUDE, and the patients with HVD in CHAARTED were 0.62, 0.63, and 0.63 respectively, with LATITUDE and CHAARTED having similar control arms comprised of their respective patients with high-risk disease/HVD, with median OS times of 34.7 and 34.4 months, respectively. It is not known which patient subgroups might do better with one standard as opposed to the other. Practical factors that should be considered, however, are patient fitness for one drug or the other, drug availability in various health care systems, affordability, QOL during and after treatment, and limited versus continuous duration of therapy. To date, there have not been assessments of cost effectiveness of each of these standards. The use of both standards in combination or in series for metastatic non-castrate disease has not been assessed, and treatment of patients with both at this juncture has unproven benefits. Because the use of both standards in patients has the potential to incur personal and social costs in terms of treatment and financial burden, ASCO encourages participation in clinical trials to address such important questions.

Therefore, continuous AAP or six doses of docetaxel administered every 3 weeks at 75 mg/m^2 with ADT with or without prednisolone should be considered two SOCs for many men with metastatic non-castrate disease who are candidates for each respective therapy. The strongest evidence of benefit is for those men who are diagnosed with de novo metastatic disease and who meet criteria for high-risk disease or HVD per LATITUDE and CHAARTED, respectively. These men should be offered either docetaxel or AAP if they are otherwise appropriate candidates. Men who do not fit into these categories may also be considered for treatment. However, the strength of the evidence to support an OS benefit is lower for men who do not meet the HVD criteria for chemotherapy, because only one study demonstrated a survival benefit in such men, and there are data that may suggest that men with LVD do not benefit from chemotherapy. Men with low-risk disease may benefit from AAP, but there is also only one trial that has demonstrated this benefit. There are no data at this time to suggest that men with lower-risk disease will not benefit from treatment with AAP, in contradistinction to men with LVD receiving chemotherapy. Additional explorations of pooled data to

better define the optimal features of patients who will benefit from either treatment are necessary and are either planned or under way.

PATIENT AND CLINICIAN COMMUNICATION

In panel discussions, three main topics were identified that should be raised between the clinician and the patient in the shared decision-making process. When deciding whether to administer a hormonal agent or chemotherapy, it should be acknowledged that chemotherapy can have greater adverse effects that negatively affect patient QOL compared with the lesser adverse effects associated with hormonal treatment. However, with the recommended chemotherapy regimen, the time on treatment is relatively short, and the evidence demonstrates that QOL is restored afterward. Also, although treatment with abiraterone is well tolerated, in some health care systems it is expensive or not available to all, and treatment must be administered for the full duration of castration sensitivity. Finally, which of the two options is preferable may depend on patient preference based on the balance of priorities in terms of the pros and cons listed above, the local health care system, and finances. Because prostate cancer treatment is a rapidly evolving field of study, patients should consider, and clinicians should encourage, enrollment in suitable and appropriate trials.

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/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.[35-38] Many other 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 health care 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 (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of 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, the study selection criteria of which may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. 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.

Because many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs, highlighting 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 younger than 65 years of age, 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, and heart failure. For patients with prostate cancer older than 65 years of age, the 10 most common comorbidities are (in descending order) hypertension, hyperlipidemia, ischemic heart disease, anemia, diabetes, arthritis, chronic kidney disease, cataract, heart failure, and chronic obstructive pulmonary disease.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with these MCCs, 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.

EXTERNAL REVIEW

An earlier draft of this guideline was submitted to four external reviewers with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Review comments such as updating the evidence to include more recent publications and interpretation of the evidence and what it means for various patient subgroups were reviewed by the Expert Panel and integrated into the final manuscript before approval by the Clinical Practice Guideline Committee.

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 the need 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 Web site and most often published in *JCO* and *Journal of Oncology Practice*.

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.

Related ASCO Guidelines

- Prostate Cancer Survivorship Care Guideline Endorsement[39] (http://ascopubs.org/doi/full/10.1200/JCO.2014.60.2557)

- Systemic Therapy in Men With Metastatic Castration-Resistant Prostate Cancer[4] (http://ascopubs.org/doi/full/10.1200/JCO.2013.54.8404)

- Integration of Palliative Care Into Standard Oncology Practice[40] (http://ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)

- Antiemetics[41] (http://ascopubs.org/doi/full/10.1200/JCO.2017.74.4789)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Administrative support: R. Bryan Rumble
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer Statistics, 2017. CA Cancer J Clin 67:7-30, 2017

2. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008

3. Scher HI, Morris MJ, Stadler WM, et al: Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34:1402-1418, 2016

4. Basch E, Loblaw DA, Oliver TK, et al: Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol 32:3436-3448, 2014

5. Gravis G, Boher JM, Joly F, et al: Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: Impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 70:256-262, 2016

6. Gravis G, Fizazi K, Joly F, et al: Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomised, open-label, phase 3 trial. Lancet Oncol 14:149-158, 2013

7. Patrick-Miller LJ, Chen Y-H, Carducci MA, et al: Quality of life (QOL) analysis from E3805, chemohormonal androgen ablation randomized trial (CHAARTED) in prostate cancer (PrCa). J Clin Oncol 34, 2016 (suppl; abstr 286)

8. Sweeney C, Chen YH, Carducci MA, et al: Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. J Clin Oncol 32, 2014 (suppl; abstr LBA2)

9. Sweeney C, Chen Y-H, Liu G, et al: Long term efficacy and QOL data of chemohormonal therapy (C-HT) in low and high volume hormone naïve metastatic prostate cancer (PrCa): E3805 CHAARTED trial. Ann Oncol 27:vi243-vi265, 2016

10. Sweeney CJ, Chen YH, Carducci M, et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373:737-746, 2015

11. James ND, Sydes MR, Clarke NW, et al: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 387:1163-1177, 2016

12. James ND, de Bono JS, Spears MR, et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 377: 338-351, 2017

13. Fizazi K, Tran N, Fein L, et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 377: 352-360, 2017

14. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012

15. Shojania KG, Sampson M, Ansari MT, et al: How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 147:224-233, 2007

16. Tucci M, Bertaglia V, Vignani F, et al: Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: A systematic review and meta-analysis. Eur Urol 69:563-573, 2016

17. Vale CL, Burdett S, Rydzewska LHM, et al: Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data. Lancet Oncol 17: 243-256, 2016

18. Reference deleted.

19. Chi KN, Protheroe A, Rodriguez-Antolin A, et al: Benefits of abiraterone acetate plus prednisone (AA+P) when added to androgen deprivation therapy (ADT) in LATITUDE on patient (Pt) reported outcomes (PRO). Presented at the European Society for Medical Oncology 2017 Congress, Madrid, Spain, September 8-12, 2017

20. Rydzewska LHM, Burdett S, Vale CL, et al: Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. Eur J Cancer 84:88-101, 2017

21. Huggins C, Bergenstal DM: Effect of bilateral adrenalectomy on certain human tumors. Proc Natl Acad Sci USA 38:73-76, 1952

22. Huggins C, Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 4: 293-297, 1941

23. Huggins C, Stevens R, Hodges CV: Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 43:209-223, 1941

24. Reference deleted.

25. Petrylak DP, Tangen CM, Hussain MH, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 351:1513-1520, 2004

26. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-1512, 2004

27. Berthold DR, Pond GR, Roessner M, et al: Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: Relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. Clin Cancer Res 14:2763-2767, 2008

28. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011

29. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013

30. Ryan CJ, Smith MR, Fizazi K, et al: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16:152-160, 2015

31. Cooperberg MR, Broering JM, Carroll PR: Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol 28: 1117-1123, 2010

32. Shahinian VB, Kuo YF, Freeman JL, et al: Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 103:1615-1624, 2005

33. Lin K, Croswell JM, Koenig H, et al: Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force. Rockville, MD, Agency for Healthcare Research and Quality, 2011

34. Halabi S, Kelly WK, Ma H, et al: Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol 34:1652-1659, 2016

35. Centers for Disease Control and Prevention: United States Cancer Statistics: 1999-2012 Incidence and Mortality Web-Based Report. https://nccd.cdc.gov/uscs/

36. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. http://seer.cancer.gov/csr/1975_2013/

37. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. Washington, DC, The Commonwealth Fund, 2008

38. American Cancer Society: Cancer Facts and Figures for African Americans 2016-2018. http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-047403.pdf

39. Resnick MJ, Lacchetti C, Bergman J, et al: Prostate cancer survivorship care guideline: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 33:1078-1085, 2015

40. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

41. Hesketh PJ, Kris MG, Basch E, et al: Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35: 3240-3261, 2017

Affiliations

Michael J. Morris and **Dana Rathkopf**, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY; **R. Bryan Rumble**, American Society of Clinical Oncology, Alexandria, VA; **Ethan Basch** and **Matthew I. Milowsky**, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; **Sebastien J. Hotte**, Juravinski Cancer Centre, Hamilton; **Andrew Loblaw**, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada; **Paul Celano**, Greater Baltimore Medical Center, Towson, MD; and **Rick Bangs**, patient representative.

Acknowledgment

Appendix

Member	Affiliation	Role/Area of Expertise
	Table A1. Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer Expert Panel	
Michael J. Morris, MD	Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY	Medical oncology, co-chair
Matthew I. Milowsky, MD	Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC	Medical oncology, co-chair
Ethan Basch, MD	Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC	Medical oncology
Sebastien J. Hotte, MD	Juravinski Cancer Centre, Hamilton, Ontario, Canada	Medical oncology
Andrew Loblaw, MD	Sunnybrook Health Sciences Center, Toronto, Ontario, Canada	Radiation oncology
Dana Rathkopf, MD	Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY	Medical oncology
Paul Celano, MD	Greater Baltimore Medical Center, Towson, MD	Medical oncology, Practice Guidelines Implementation Network representative
Rick Bangs, MBA		Patient representative
R. Bryan Rumble, MSc	American Society of Clinical Oncology, Alexandria, VA	Staff/health research methodologist