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

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Editor's note: Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, 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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A B S T R A C T

Purpose

ASCO provisional clinical opinions (PCOs) offer direction to the ASCO membership after publication or presentation of potential practice-changing data. This PCO addresses second-line hormonal therapy for chemotherapy-naïve men with castration-resistant prostate cancer (CRPC) who range from being asymptomatic with only biochemical evidence of CRPC to having documented metastases but minimal symptoms.

Clinical Context

The treatment goal for CRPC is palliation. Despite resistance to initial androgen deprivation therapy, most men respond to second-line hormonal therapies. However, guidelines have neither addressed second-line hormonal therapy for nonmetastatic CRPC nor provided specific guidance with regard to the chemotherapy-naïve population.

Recent Data

Six phase III randomized controlled trials and expert consensus opinion inform this PCO.

Provisional Clinical Opinion

For men with CRPC, a castrate state should be maintained indefinitely. Second-line hormonal therapy (eg, antiandrogens, CYP17 inhibitors) may be considered in patients with nonmetastatic CRPC at high risk for metastatic disease (rapid prostate-specific antigen doubling time or velocity) but otherwise is not suggested. In patients with radiographic evidence of metastases and minimal symptoms, enzalutamide or abiraterone plus prednisone should be offered after discussion with patients about potential harms, benefits, costs, and patient preferences. Radium-223 and sipuleucel-T also are options. No evidence provides guidance about the optimal order of hormonal therapies for CRPC beyond second-line treatment. Prostate-specific antigen testing every 4 to 6 months is reasonable for men without metastases. Routine radiographic restaging generally is not suggested but can be considered for patients at risk for metastases or who exhibit symptoms or other evidence of progression. Additional information is available at www.asco.org/genitourinary-cancer-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

ASCO has established a rigorous, evidence-based approach—the provisional clinical opinion (PCO)—to offer a rapid response to emerging data in clinical oncology. The PCO is intended to offer timely clinical direction to ASCO oncologists after publication or presentation of potentially practice-changing data from major studies.

This PCO addresses the use of second-line hormonal therapy for chemotherapy-naïve men with castration-resistant prostate cancer (CRPC) who range from being asymptomatic with only biochemical evidence of CRPC to having documented metastases but minimal symptoms. In 2016, an estimated 26,120 American men died as a result of prostate cancer.[1] First-line hormonal therapy (androgen deprivation therapy [ADT]) is commonly prescribed for men with recurrent, progressive, or metastatic prostate cancer that is

ASSOCIATED CONTENT

Appendix
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THE BOTTOM LINE

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

Research Question

Do second-line hormonal therapies play a role in the treatment of chemotherapy-naïve men with castration-resistant prostate cancer (CRPC)?

Target Population

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

Target Audience

Urologists, radiation, and medical oncologists.

Methods

Systematic review of the medical literature along with a formal consensus process (modified Delphi) performed using previously published ASCO methods.[17]

Key Points

Except where noted, the following provisional clinical opinions (PCOs) are based on formal consensus of Expert and Consensus Panel members:

- Men who develop CRPC despite castrate levels of testosterone should be maintained in a castrate state indefinitely.
- No data support the use of second-line hormonal therapies for chemotherapy-naïve men with M0 CRPC who are at low risk of developing metastases (low risk is defined as low prostate-specific antigen [PSA] and slow PSA doubling time).[18,19]
- For chemotherapy-naïve patients at high risk of developing metastases (rapid PSA doubling time or velocity), second-line hormonal therapies that lower PSA values or slow the rate of rise may be offered, preferably in a clinical trial setting where available, after a discussion with the patient about limited scientific evidence, potential harms, benefits, costs, and patient preferences.
- Abiraterone acetate plus prednisone or enzalutamide should be offered for second-line hormonal treatment after first-line hormonal treatment failure for chemotherapy-naïve men who develop CRPC and have radiographic evidence of metastases (M1a/M1s CRPC) because these agents have been shown to significantly increase radiographic progression-free survival and overall survival (PCO type: evidence based [three randomized controlled trials]; Strength of PCO: strong)
- A PSA evaluation every 4 to 6 months should be performed for men who develop CRPC and have no radiographic evidence of metastases (M0 CRPC) and a slow PSA doubling time or velocity. If PSA levels are rising, checking serum testosterone levels should be considered.
- A PSA evaluation every 3 months is recommended for men who develop CRPC with a rapid PSA doubling time, velocity, or radiographic evidence of metastases (M1 CRPC).
- When imaging is performed for men with CRPC, a bone scan and either computed tomography or magnetic resonance imaging of the abdomen and pelvis should be offered. Of note is that sodium fluoride positron emission tomography (^{18}F-labeled positron emission tomography) imaging is only approved in the United States for the diagnosis of recurrent prostate cancer among men with elevated PSA after treatment. The use of this technique is otherwise limited to patients who participate in clinical trials and prospective registries. Whole-body magnetic resonance imaging to detect oligometastatic disease and radiotracers and imaging agents such as c-11 choline, prostate-specific membrane antigen, and ^{18}F-flucicovine currently are considered investigational for chemotherapy-naïve patients with CRPC.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- Radiographic imaging is not indicated for men with CRPC and a rising PSA unless treatment selection would be altered on the basis of radiographic findings or if symptoms potentially attributable to prostate cancer develop or worsen (eg, bone pain). Routine surveillance radiographic restaging also is not indicated, with the exception of patients for whom PSA is not a reliable marker of disease.
- Palliative care should be offered to all chemotherapy-naïve men with M1 CRPC, particularly those who exhibit symptoms or decreased quality of life.[20]

The Literature Review and Analysis sections provide more detail about the PCOs.

Appendix Figure A1 shows an algorithm for second-line hormonal CRPC treatment.

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

Note: Opinions expressed in this article should not be interpreted as the official positions of any US or Canadian governmental agency, including the National Cancer Institute, National Institutes of Health, the Food and Drug Administration, or the US Department of Health and Human Services.

androgen sensitive.[2] Many men with androgen-sensitive disease who receive ADT will develop biochemical, radiographic, and/or symptomatic evidence of cancer progression despite castrate levels of testosterone ($<$ 50 ng/dL or $<$ 1.7 nmol/L).[3,4] This state is referred to as CRPC.[5] Conventionally, at least one adequate trial of an antiandrogen and subsequent withdrawal (AAWD) is used to define the CRPC state clinically.[6] Up to 20% of men with a biochemical relapse[7] and most with advanced disease will eventually develop castration resistance.[3,8] Patients are, therefore, generally divided into two groups: those with biochemical (serum prostate-specific antigen [PSA]) recurrence and no radiographic evidence of metastases (bCRPC, more commonly referred to as M0 CRPC) and those with radiographic or otherwise measurable/evaluable metastatic disease. The latter group often is differentiated into asymptomatic (M1a CRPC) and symptomatic (M1s CRPC) metastatic disease.

STATEMENT OF THE CLINICAL ISSUE

Goals of treatment in men with CRPC include chemotherapy deferral and palliation, that is, symptom relief with extension of life while maximizing quality of life for as long as possible or as a preemptive intervention against symptoms. Despite resistance to initial ADT (first-line hormonal therapy), most men respond to second-line hormonal therapies. However, the treatment of men with CRPC is now a rapidly evolving field. The past few years have seen an unprecedented number of systemic therapies that report improvements in patients pre- and postdocetaxel treatment, some of which, like enzalutamide and abiraterone acetate, are considered hormonal interventions. Abiraterone acetate has been approved for pre- and postdocetaxel treatment in patients with CRPC by the US Food and Drug Administration (FDA) and is approved for postdocetaxel use by Health Canada. Enzalutamide has been approved by the FDA for both pre- and postdocetaxel treatment. In addition, sipuleucel-T, a nonhormonal agent, has been approved for use in the prechemotherapy setting. A companion ASCO guideline addresses the use of systemic therapy agents, such as chemotherapy and radium-223, in men with radiographic or pathologic evidence of metastatic CRPC,[9] but it does not address second-line hormonal therapy management of nonmetastatic prostate cancer recurrence and does not directly address second-line hormonal therapy in the chemotherapy-naïve population.

Many challenges face clinicians when managing patients with CRPC, even before the emergence of these new data. Thus, treatment patterns for CRPC vary considerably, likely as a result of the paucity of high-quality data on the topic, the relative efficacy and nonspecific mechanisms of action of available treatment approaches, and uncertainty among clinicians about optimal treatment. The limited nature of evidence in this area and methodological challenges were highlighted at a 2011 meeting of the FDA Oncology Division Advisory Committee.[10]

In light of these issues, ASCO convened an Expert Panel to provide focused PCOs about second-line hormonal therapy options for chemotherapy-naïve men with CRPC (Appendix Table A1, online only). The target population under consideration is chemotherapy-naïve men who range from being asymptomatic with only biochemical evidence of CRPC (M0 CRPC) to having documented metastases but minimal symptoms (M1a CRPC).[11] The PCOs refer to the management of adenocarcinoma of the prostate.

Management of other histologies, such as small-cell, neuroendocrine, or intraductal prostate cancers, is beyond the scope of this guideline as is the use of immunotherapy and bone-targeted

agents and radionuclides. However, because these therapies have shown efficacy for men with M1a or M1s CRPC,[12-14] the Expert Panel endorses recommendations from the American Urological Association at this time.[15,16] The Data Supplement provides details on how the PCOs in this report fit in the greater context of care for men who develop CRPC. Use of palliative radiotherapy also is beyond the scope of this guideline.

RESEARCH QUESTIONS

This PCO addresses the following main research question: Do second-line hormonal therapies play a role in the treatment of chemotherapy-naïve men with CRPC? Subquestions are:

1. Should a castrate state be maintained in patients who develop CRPC?
2. In chemotherapy-naïve patients who develop CRPC but have no radiographic evidence of metastases (M0 CRPC), should second-line hormonal therapies be used? If so, which agents or specific sequence of agents are recommended?
3. In chemotherapy-naïve patients who develop CRPC and have radiographic evidence of metastases but minimal symptoms (M1a/M1s CRPC), should second-line hormonal therapies be used? If so, which agents are recommended?
4. How often should patients with CRPC undergo PSA monitoring?
5. What imaging modalities are appropriate for patients with CRPC?
6. How often should patients with CRPC undergo radiographic imaging or routine radiographic restaging?

METHODS

Expert Panel Composition

The ASCO Clinical Practice Guidelines Committee (CPGC) convened an Expert Panel that comprised prostate cancer experts with specific knowledge in and clinical experience with CRPC, including specialists from medical oncology, urologic oncology, radiation oncology, and guideline methodology. Academic and community practitioners were represented as were patients. The Expert Panel members are listed in Appendix Table A1.

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 therein 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" indicate 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.

PCO 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 www.asco.org/rwc). All members of the 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; speakers' 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 panel did not disclose relationships constituting a conflict under the Policy.

Consensus Panel Composition

In addition to the Expert Panel, the ASCO CPGC also convened a Consensus Panel, with similar representation to the Expert Panel, tasked with rating agreement with the drafted PCOs by using ASCO's formal consensus-based methodology.[17] This approach is based on the modified Delphi consensus development methodology for providing clinical guidance when available data do not support more traditional and definitive evidence-based recommendations. The Consensus Panel members are listed in Appendix Table A2 (online only).

PCO Development Process

This PCO was informed by a systematic review of the available evidence (search dates 1985 through October 2016), consensus opinion, and clinical experience. Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Chemotherapy-naïve men with nonmetastatic or metastatic CRPC who were being considered for second-line hormonal therapy
- Measured effect of continued hormonal interventions in patients with CRPC for at least one primary measure of therapeutic efficacy, such as radiographic progression-free survival (rPFS), overall survival (OS), time to PSA progression or time to progression in general, and median duration of response
- A minimum of 25 patients per trial arm

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, case reports, or narrative reviews; and (3) published in a non-English language. After review and approval by the Expert Panel, the penultimate draft was reviewed and approved by the ASCO guideline approval body, the CPGC. After CPGC approval, the PCOs are submitted to *Journal of Clinical Oncology*, and a summary of the main findings are submitted to *Journal of Oncology Practice* for consideration.

The ASCO panel and guidelines staff will work with co-chairs to keep abreast of substantive updates to the PCO. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

Table 1. Characteristics of Phase III Randomized Trials

First Author	No. of Patients	Treatment Arm (active agents only)	Initial Hormonal Therapy, %					Patient Status at Baseline, %	
					Single Method				
			Continuous Blockade*	CAB	LHRH	Anti-androgen	Orchi-ectomy	Measurable Metastases	Symptoms
Ryan[21,22]	542	Prednisone 5 mg twice a day, placebo	NR	NR	NR	NR	NR	40	33†
	546	Prednisone 5 mg twice a day, abiraterone acetate 1 g/d	NR	NR	NR	NR	NR	40	32†
Beer[23]	845	Placebo	NR	NR	NR	86.4	NR	NR	NR
	872	Enzalutamide 160 mg/d PO	NR	NR	NR	87.2	NR	NR	NR
Shamash[24]*	136	Dex 2 mg/d, DES 1 mg/d—immediate	NR	6	74‡	4	9	NR	65§
	133	Dex 2 mg/d, DES 1 mg/d—delayed	NR	8	71‡	6	8	NR	65§
Small[25]*	132	AAWD	87	60‖	NR¶	40	NR	31	30†
	128	AAWD/ketoconazole 400 mg three times a day	84	59‖	NR¶	41	NR	40	28†
Fossâ[26]*	101	Prednisone 5 mg four times a day	NR	0	NR¶	0	NR	100	100
	100	Flutamide 250 mg three times a day	NR	0	NR¶	0	NR	100	100
Dawson[27]*	73	Megestrol acetate 160 mg/d	NR	NR	40#	63	62	28	10§
	76	Megestrol acetate 640 mg/d	NR	NR	48#	55	55	31	8§

Abbreviations: AAWD, antiandrogen withdrawal; CAB, combined androgen blockade; DES, diethylstilbestrol; Dex, dexamethasone; LHRH, luteinizing hormone–releasing hormone; NR, not reported; PO, orally.
*Patients were enrolled before AAWD; in Dawson,[27] only 15 such patients were enrolled before protocol change.
†On the basis of reported use of opioid analgesics.
‡Patients were offered the choice of continuing with LHRH; approximately 47% continued.
§On the basis of reported European Cooperative Oncology Group performance status.
‖Patients who received CAB rather than intermittent androgen blockade.
¶Patients were required to continue use of initial LHRH.
#Continuation of initial LHRH NR.

Detailed information about the methods used to develop this PCO is available in the Methodology Supplement at www.asco.org/genitourinary-cancer-guidelines, which includes an overview (eg, panel composition, development process, revision dates), literature search and data extraction and accompanying consensus process, and quality assessment. This information is the most recent as of the publication date. For updates, the most recent information, and submission of new evidence, visit www.asco.org/genitourinary-cancer-guidelines and www.asco.org/guidelineswiki.

LITERATURE REVIEW AND ANALYSIS

Overview

As listed in Tables 1 and 2, six phase III randomized trials were identified in the systematic review of the evidence.[21-27] These trials spanned the years from 2000 to 2014 (a 14-year period), and none compared similar interventions. The primary outcome for all trials was therapeutic efficacy, although it was framed in a variety of ways, such as rPFS,[23] OS,[23] time to PSA progression,[24] time to progression in general,[25] and median duration of response.[25,27]

Upon review of the available evidence, the Expert Panel concluded that the majority of the evidence was insufficient to inform evidence-based recommendations and that formal expert consensus would be needed to help inform clinical opinions. Results of the consensus ratings can be found in the Data Supplement 8: Consensus Panel review results.

Quality Assessment of the Literature

The modest number of randomly assigned patients in the majority of the identified trials created obstacles with respect to determination of the true efficacy or generalizability of the findings. An additional challenge with the data identified by the systematic review was the lack of similar treatment arms; no two trials included the same comparisons. The largest trial included 1,717 participants.[28] However, most of the remaining trials included fewer than 140 patients per comparison arm.[24-27,29] The trial of abiraterone acetate in chemotherapy-naïve patients reported significant PFS results, which led to the trial being stopped early.[21] The enzalutamide trial in chemotherapy-naïve patients also reported a PFS advantage and was stopped early.[24] Patients were offered crossover in both studies.

PCO

Research Question 1

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

PCO 1. For men who develop CRPC despite castrate levels of testosterone:

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

Table 2. Results of Phase III Randomized Trials

First Author	No. of Patients	Treatment Arms (active agents)	Patient Outcomes					
				Objective Response, %			Median Survival, Months	
			PSA Decline ≥ 50%, %	CR	PR	SD	PFS	OS
Ryan[21,22]	542	Prednisone/placebo	24	16		69	8.3	30.3
	546	Prednisone/abiraterone acetate	62	36		61	16.5	34.7
			$P < .001$	$P < .001$			$P < .001$	$P < .01$
Beer[23]	845	Placebo	3	1	4	NR	3.9	30.2*
	872	Enzalutamide 160 mg/d PO	78	20	39	NR	Not reached (but at 12 months, 81% risk reduction)	32.4*
			$P < .001$	$P < .001$			$P < .001$	$P < .001$
Shamash[24]†	136	Dex/DES—immediate	68	NR	NR	NR	8.1	19.4
	133	Dex/DES—delayed	64	NR	NR	NR	8.1	18.8
Small[25]†	132	AAWD	11	2		NR	NR	16.7
	128	AAWD/ketoconazole	27	20		NR	NR	15.3
			$P = .002$	$P = .02$				
Fossâ[26]†	101	Prednisone	9	NR	NR	NR	3.4	10.6
	100	Flutamide	10	NR	NR	NR	2.3	11.2
Dawson[27]†	73	Megestrol acetate—low dose	14	NR	3	30	3.8	11.2
	76	Megestrol acetate—high dose	9	NR	1	37	4.3	12.1

Abbreviations: AAWD, antiandrogen withdrawal; CR, complete response; DES, diethylstilbestrol; Dex, dexamethasone; LHRH, luteinizing hormone–releasing hormone; NR, not reported; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; PSA, prostate-specific antigen; SD, stable disease.

*Including the 116 additional deaths after enzalutamide was offered to eligible patients receiving placebo, at 18 months, estimated median overall survival was 31 months (placebo) versus not yet reached (enzalutamide) (hazard ratio = 0.73; 95% CI, 0.63 to 0.85; $P < .001$), a 27% risk reduction following crossover.

†Patients were enrolled before AAWD; only 15 such patients were enrolled before protocol change.

Literature review and analysis. No randomized controlled trials (RCTs) met the sample size inclusion criteria. Within the supplementary literature, one small RCT suggested a cost and potential cause-specific survival advantage for intermittent versus continuous androgen blockade in men who develop CRPC (who have not had an orchiectomy), but the study was not adequately powered.[30] However, retrospective post hoc analyses of a prospective series reported that eugonadal or superphysiologic levels of testosterone are associated with a risk of progression and death in men with CRPC.[29] Multiple adverse effects and harms were reported with ADT, including hot flushes, fatigue, impotence, gynecomastia, loss of libido, osteoporosis, and a risk for metabolic syndrome.[31-33]

Clinical interpretation. Maintenance of a castrate state through orchiectomy or pharmacologic castration in patients who develop CRPC despite castrate levels of testosterone is suggested, which is supported by current understandings of disease progression mechanisms[34] and agrees with published guidelines.[35-37] RCTs are needed, such as the ongoing German SPARE trial of abiraterone acetate plus LHRH therapy versus abiraterone acetate–sparing LHRH therapy in chemotherapy-naïve patients with progressive CRPC, to measure the clinical benefit of continued ADT (LHRH therapy) during second-line hormonal therapy (ClinicalTrial.gov identifier NCT02077634).

Research Question 2

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

PCO 2.

- For chemotherapy-naïve patients believed to be at low risk for metastases (low PSA and slow PSA doubling time),[18,19] second-line hormonal therapies are not suggested.
- For chemotherapy-naïve patients at high risk of developing metastases (rapid PSA doubling time or velocity), second-line hormonal therapies that lower PSA values or slow the rate of PSA rise may be offered (preferably in a clinical trial setting where available) after discussion with the patient about limited scientific evidence, potential harms, benefits, costs, and patient preferences.
- Alternative treatment options include observation (with maintenance of a castrate state) or participation in a clinical trial.
- Chemotherapy or immunotherapy is not suggested except in a clinical trial.
- No evidence provides guidance about the optimal order of hormonal therapies after second-line hormonal therapy for high-risk chemotherapy-naïve patients with M0 CRPC. The panel was unable to come to consensus about sequencing.

Literature review and analysis. No phase III randomized trials have evaluated the association between second-line hormonal therapies and clinical outcomes in patients with CRPC and no radiographic evidence of metastases (M0 CRPC). However, evidence from supplementary literature has suggested associations between PSA absolute value and rate of rise with clinical outcomes in this population.[3] No evidence provides guidance about the optimal order of second-line hormonal therapies for patients with M0 CRPC.

In 201 patients with M0 CRPC, Smith et al[3] found that baseline PSA levels $>$ 10 ng/mL and higher PSA velocities were independently associated with shorter time to first bone metastasis, OS, and metastasis-free survival. A PSA doubling time of $<$ 6 months was associated with significantly ($P = .001$) shorter bone metastasis–free survival compared with doubling times of 6 to 19 months and $>$ 19 months. After multivariable adjustment, Gleason grade was not significantly associated with any of these outcomes. Second-line hormonal therapies that lower PSA values or slow the rate of rise may be reasonable for patients with castration-resistant disease and a baseline elevated PSA or a rapid PSA doubling time or velocity. (Online calculators for determining PSA doubling time or velocity can be found at nomograms.mskcc.org/prostate/psadoublingtime.aspx or www.asure.ca [PSA Calculator Tool tab].) Such men are at the greatest risk of developing metastatic disease and may, therefore, benefit from additional antitumor therapy, but this has not been prospectively demonstrated in studies to date. Age and life expectancy should be taken into consideration. Older patients with short life expectancies and a high risk of developing metastatic disease may not be optimal candidates for second-line hormonal therapies.

Within the supplemental literature was one related phase II trial (STRIVE) that compared enzalutamide (160 mg/day) to the antiandrogen bicalutamide (50 mg/day) for safety and efficacy among chemotherapy-naïve men with asymptomatic or mildly symptomatic disease (M0N0/1, n = 139; M1N1, n = 257) despite primary ADT.[38] For the M0 population, although PFS significantly favored enzalutamide (hazard ratio [HR], 0.24; 95% CI, 0.14 to 0.42), median PFS was not reached. PSA response, a secondary end point, was significantly greater ($P < .001$) for enzalutamide versus bicalutamide, irrespective of the definition of complete response (PSA decline $\geq$ 50% [or 90%] from baseline). (The M1 population will be discussed under Research Question 3.) Although an important phase II study, STRIVE was not designed to compare OS among patients with clinically defined CRPC. Phase III trials are needed.

With regard to the use of corticosteroid monotherapy for men with M0 CRPC, no phase III studies were identified. In the supplemental literature, one underpowered (n = 82) single-center phase II study compared PSA response rates among chemotherapy-naïve men with M0 disease randomly assigned to dexamethasone versus prednisolone,[39] but the results were inconclusive. Dexamethasone may be more active than prednisolone in M0 CRPC, but trials with larger sample sizes are needed.

Clinical interpretation. Clinicians face many challenges when treating patients with CRPC, particularly those who are chemotherapy-naïve with no evidence of radiographic metastases (M0 CRPC). The absence of clinical trial data on the topic leads to uncertainty among clinicians about optimal treatment and sequencing. Cost-effectiveness has not yet been demonstrated for second-line hormonal therapy in this population. Only for patients at high risk of developing metastases did the panel feel comfortable with providing guidance in the absence of high-quality data. Sequencing was particularly troublesome given the variety of agents fairly recently approved for use by the FDA in the chemotherapy-naïve population and patients still in clinical trials.[40]

Research Question 3

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

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

- Abiraterone acetate plus prednisone should be offered because they significantly improved rPFS and OS as well as secondary end points, including median time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression (*v* prednisone alone). The drugs are also well tolerated.
- Enzalutamide should be offered because it significantly improves rPFS and OS. Secondary end points are also improved, including time to initiation of cytotoxic chemotherapy, risk of a first skeletal-related event, complete or partial soft tissue response, time to PSA progression, time to deterioration in quality of life, and decline in PSA of ≥ 50% from baseline (*v* placebo). The drug is also well tolerated.
- Alternative treatment options include immunotherapy (sipuleucel-T),[11] chemotherapy (docetaxel and prednisone),[9] and radium-223.
- If none of these therapies can be obtained or tolerated by the patient, other antiandrogens, prednisone, and ketoconazole/hydrocortisone may be offered because they provide modest clinical benefits in this population, but no survival benefits have been established.
- Other alternative treatment options include enrollment in a clinical trial and observation.
- No evidence provides guidance about the optimal order of hormonal therapies after second-line hormonal therapy for patients with M1 CRPC. The panel was unable to come to a consensus about sequencing.
- Other second-line hormonal therapy options where results from phase III trials are pending are not suggested.
- Palliative care should be offered to all chemotherapy-naïve men with M1 CRPC, particularly to those who exhibit symptoms or decreased quality of life.[20]

Literature review and analysis. Three phase III RCTs identified in the systematic review provide the evidence base to inform this PCO.[21,23,25] An RCT (COU-AA-302) of abiraterone acetate plus prednisone administered in chemotherapy-naïve men with primarily asymptomatic metastatic CRPC resulted in a statistically significant rPFS benefit compared with placebo and prednisone (median rPFS, 16.5 *v* 8.3 months; HR, 0.53; 95% CI, 0.45 to 0.62; $P < .001$). Time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression also were significantly longer in the abiraterone acetate arm ($P < .01$).[21] After a median follow-up of 49.2 months, abiraterone acetate plus prednisone significantly prolonged OS (median, 34.7 *v* 30.3 months; HR, 0.81; 95% CI, 0.70 to 0.93; $P = .0033$) with an acceptable toxicity profile.[41] Similar OS and rPFS benefits for abiraterone acetate plus prednisone versus prednisone alone were seen among men age ≥ 75 years.[42]

An RCT[23] (PREVAIL) compared enzalutamide (160 mg oral) versus placebo administered in chemotherapy-naïve men with cytologically confirmed adenocarcinoma of the prostate with documented asymptomatic or mildly symptomatic metastases who had PSA progression, radiographic progression, or both in soft tissue or bone, despite receipt of LHRH analog therapy or orchiectomy. The trial was stopped early as a result of significantly improved survival results for patients administered enzalutamide, with an 81% reduction in the risk of radiographic progression or death at 12 months (HR, 0.19; 95% CI, 0.15 to 0.23; $P < .001$) and a 29% reduction in the risk of death at 18 months (HR, 0.71; 95% CI, 0.60 to 0.84; $P < .001$) as well as significantly improved time to initiation of chemotherapy, reduction in risk of first skeletal event, time to PSA progression, and response rate combined with an acceptable toxicity profile. Similar OS and rPFS benefits for enzalutamide were seen among men age ≥ 75 years.[43] With respect to patient-reported outcomes,[44] median time to deterioration in Functional Assessment of Cancer Therapy–Prostate total score was significantly longer for patients administered enzalutamide (11.3 months; 95% CI, 11.1 to 13.9 months) than placebo (5.6 months; 95% CI, 5.5 to 5.6 months; HR, 0.62; 95% CI, 0.54 to 0.72; $P < .001$). A significantly greater proportion of patients administered enzalutamide (*v* placebo) reported clinically meaningful improvements in the Functional Assessment of Cancer Therapy–Prostate total score (40% *v* 23%), the EuroQual Group Health Questionnaire utility index (28% *v* 16%), and the visual analog scale (27% *v* 18%; all $P < .001$).

In an open-label extended analysis of 787 of the 1,717 patients enrolled in the PREVAIL study, rPFS (as a post hoc analysis only) and OS were revisited after the prespecified number of deaths for the final analysis (n = 784) was reached.[45] With the inclusion of data from 5 months postcrossover for the placebo group, the median follow-up was 31 months. By this point, 52% of the original 872 patients in the enzalutamide arm and 81% of the original 845 in the placebo arm had received subsequent antineoplastic therapies (chemotherapy, abiraterone acetate, sipuleucel-T, or radium-223 dichloride) known to affect survival. Similar statistics were not provided for patients in the open-label extended analysis only. Nevertheless, patients who had been treated with enzalutamide had a 23% reduced risk of death compared with those treated with placebo (35.3 *v* 31.3 months; HR, 0.77; 95% CI, 0.67 to 0.88; $P < .001$). In the post hoc analysis, enzalutamide reduced the risk of radiographic progression or death by 68% compared with placebo (20.0 *v* 5.4 months; HR, 0.32; 95% CI, 0.28 to 0.37; $P < .001$).

In the supplemental literature, two related phase II trials (TERRAIN and STRIVE) compared enzalutamide (160 mg/day) to the antiandrogen bicalutamide (50 mg/day) for safety and efficacy among chemotherapy-naïve men with asymptomatic or mildly symptomatic progressive disease during treatment with ADT.[38,46] As mentioned under Research Question 2, STRIVE included patients with either M0N0/1 (n = 139) or M1N1 (n = 257) disease.[38] For the asymptomatic or mildly symptomatic M1 population, median PFS was significantly longer for enzalutamide (16.5 months) versus bicalutamide (5.5 months; HR, 0.24; 95% CI, 0.17 to 0.34). Patients with M1 disease treated with enzalutamide also had significantly greater PSA response ($P < .001$) irrespective of the definition of complete response (PSA decline ≥ 50% [or 90%] from baseline). Unlike STRIVE, TERRAIN randomly assigned only patients with M1 disease and radiographically confirmed metastases (n = 184

enzalutamide; n = 191 bicalutamide) but found similar results for the M1 population. Median PFS was significantly longer for enzalutamide (15.7 months) than for bicalutamide (5.8 months; HR, 0.44; 95% CI, 0.34 to 0.57; $P < .001$).

Although both are important phase II studies, neither STRIVE nor TERRAIN was designed to compare OS among patients with clinically defined CRPC. Thus, the question of whether earlier treatment with enzalutamide improves survival compared with the current practice of later treatment cannot be answered, but the similarity in results for PFS between the two studies is encouraging.

The remaining phase III randomized trials included a mix of asymptomatic and symptomatic patients[24,25,27] or all symptomatic patients.[26] No significant differences in survival outcomes were reported between treatment groups. However, Small et al[25] found that patients randomly assigned to AAWD and ketoconazole (AAWD/K) experienced higher rates of PSA decline ≥ 50% (27% *v* 11%; $P < .001$) and objective response (20% *v* 2%; $P = .02$) compared with those who underwent AAWD alone.[25] Of patients randomly assigned to AAWD who later had ketoconazole, the total PSA response rate was similar to those who received immediate AAWD/K, whereas the objective response rate was lower in those who received sequential therapy compared with immediate AAWD/K. The 11% PSA response results with AAWD alone varied from prior phase I and II studies that reported it as high as 40%. This lower rate may reflect shorter patient exposure to antiandrogens than in earlier reports.[47] In contrast, the 20% PSA response rate detected in the ketoconazole intervention arm is in line with a study by Trump et al[48] of 38 patients with CRPC and radiographic metastases treated with high-dose ketoconazole (400 mg three times a day) plus hydrocortisone wherein an objective response was observed in 17% of evaluable patients.

One additional phase III trial was identified in the systematic review of orteronel plus prednisone versus placebo among chemotherapy-naïve men with metastatic CRPC. The study does not inform our recommendations because of a lack of improvement in OS and a high adverse event rate (46%). Orteronel is no longer under development for treatment of metastatic CRPC.[49]

In the trials of prednisone versus flutamide,[26] high- versus low-dose megestrol acetate,[27] and diethylstilbestrol versus bicalutamide (single-facility phase II trial),[29] no meaningful objective differences in outcomes were detected between treatment groups. Three members of the Consensus Panel reported the use of high-dose bicalutamide in this setting, but data suggest possible excess mortality associated with this dose in a related context.[50]

No evidence provides guidance about the optimal order of second-line hormonal therapies for patients with M1 CRPC. In the trial by Ryan et al,[21] significant PFS and OS advantages and delay in clinical decline were detected in favor of abiraterone/prednisone compared with prednisone alone. A PSA response was seen in 62% of patients in the abiraterone treatment arm. The Beer et al[23] trial of enzalutamide versus placebo, which reported early significant rPFS and OS advantages, found a PSA decline of > 50% in 78% of men in the enzalutamide arm. A similar PSA response also has been reported in the phase III randomized trial that compared dexamethasone and aspirin with either immediate or delayed diethylstilbestrol.[24]

AAWD/K produced greater PSA and objective responses than AAWD alone but no differences in OS, and 21% of patients experienced a grade 3 and 4 adverse event.[25] Because ketoconazole usually is given with low-dose corticosteroids, this may influence PSA response. In the control arm of Ryan et al,[21] PSA response was seen in 24% of patients who received prednisone alone. In the Nakabayashi et al[51] retrospective review of 138 patients started on low-dose ketoconazole (200 mg three times a day), 28% had a PSA response. Fifty-five patients (40%) subsequently received high-dose ketoconazole (400 mg three times a day); 13% had an additional PSA response (*P* value not reported). In general, high-dose ketoconazole was associated with a greater risk of adverse effects, and six patients (11%) discontinued therapy as a result of worsening or new adverse effects from high-dose therapy. For patients who could not tolerate high-dose ketoconazole therapy, low-dose ketoconazole had similar efficacy.[51]

ASCO issued a systemic therapy guideline in 2014[9] that supports the use of immunotherapy (sipuleucel-T)[11] or chemotherapy (docetaxel and prednisone) in men with metastatic CRPC. The use of radium-223 was recommended for men with bone metastases.[52] Consult that guideline for the full recommendations.

Clinical interpretation. For chemotherapy-naïve patients who develop CRPC and have radiographic evidence of metastases, two second-line hormonal therapy options are supported by strong clinical trial evidence and are well tolerated. Abiraterone acetate plus prednisone extends rPFS and OS in addition to a variety of secondary end points, such as median time to opiate use, chemotherapy initiation, performance status deterioration, and PSA progression.

According to the manufacturer's warnings and precautions,[53] abiraterone acetate should be used with caution in patients with a history of cardiovascular disease. Drug safety was not established in patients with a left-ventricular ejection fraction < 50% or with New York Heart Association class II to IV disease. Abiraterone acetate can cause hypertension, hypokalemia, and fluid retention. Low risks of adrenocortical insufficiency or hepatotoxicity also are associated with abiraterone acetate use. A low risk of seizure associated with enzalutamide use exists[54]; however, among chemotherapy-naïve patients, the risk (0.1%) was similar between those who received enzalutamide and those who received placebo. Posterior reversible encephalopathy syndrome also has been associated with enzalutamide use, which required discontinuation of the drug.

According to the 2014 ASCO systemic therapy guideline for men with metastatic CRPC,[9] other treatment options include immunotherapy (sipuleucel-T) or chemotherapy (docetaxel and prednisone). The systemic therapy guideline specifically recommends radium-223 for men with bone metastases.[52] If none of the aforementioned hormonal therapy, immunotherapy, or chemotherapy options can be tolerated and/or accessed, other antiandrogens, prednisone, and ketoconazole/hydrocortisone may be offered. Enrollment in a clinical trial is always an option. The goal of treatment is symptom relief with extension and quality of life and deferral of chemotherapy for as long as possible. Palliative care should not be overlooked, particularly for patients who exhibit symptoms or decreased quality of life.[20]

Research Question 4

How often should patients with CRPC undergo PSA monitoring?

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

- For patients with no radiographic evidence of metastases and a slow PSA doubling time[18,19] or velocity, a PSA evaluation every 4 to 6 months is reasonable. If PSA levels rise, checking serum testosterone levels should be considered.
- For patients with a rapid PSA doubling time, velocity, or radiographic evidence of metastases, a PSA evaluation every 3 months is reasonable.

Literature review and analysis. Because no data inform this question, the Expert Panel relied on clinical experience, training, and judgment to formulate this PCO. Consideration was given to the inconvenience and anxiety introduced by more-frequent PSA testing versus potential harms that result from delayed recognition of a rapid PSA doubling time.

Clinical interpretation. Various PSA metrics are available and under evaluation for use in monitoring disease progression among patients with CRPC. Although some studies suggest that PSA doubling time is prognostic for OS, specifically among chemotherapy-naïve patients with metastatic CRPC, none of the available metrics or emerging biomarkers (eg, circulating tumor cells, androgen receptor splice variants, cancer stem cells) are as yet approved to serve as a surrogate metric for OS in clinical trials.[55,56]

Research Question 5

What imaging modalities are appropriate for patients with CRPC?

PCO 5.

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

Literature review and analysis. No trials that compared the utility of various imaging modalities for monitoring CRPC were identified by the systematic review. For patients with prostate cancer in general, early results from the National Oncologic PET registry are encouraging for ^{18}F-PET but are not yet definitive for the CRPC population because of a lack of data on past versus current ADT use, differentiation between initial and second-line hormonal therapy use, and PSA change. In the interim, clinical experience, training, and judgment were considered in formulating this PCO because of the lack of clinical trial data to inform the PCO. ^{18}F-PET appears to have greater sensitivity over bone scans, but evidence among patients with CRPC is evolving, and the impact on clinical outcomes remains undetermined. Whole-body magnetic resonance imaging to detect oligometastatic disease and radiotracers and imaging agents such as c-11 choline, prostate-specific membrane antigen, and ^{18}F-flucicovine currently are considered investigational.

Clinical interpretation. In the absence of clinical trial–based evidence, the panel considers bone scan and either computed tomography or magnetic resonance imaging of the abdomen and pelvis appropriate.

Research Question 6

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

PCO 6.

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

Literature review and analysis. No evidence provides guidance about how often patients with CRPC should undergo radiographic imaging. With no data to inform the question, the Expert Panel relied on clinical experience, training, and judgment to formulate the PCO. In addition to the potential inconvenience to the patient, discomfort, bother, and a small risk of complications can be associated with contrast agents or radiotracers administered during these tests. Finally, costs and overuse in busy health care sectors were considered.[57]

Clinical interpretation. The appropriate frequency of radiographic imaging is variable and largely depends on symptoms. In the absence of symptoms or some other clinical reason, radiographic imaging is not recommended.

Appendix Figure A1 (online only) shows a patient treatment algorithm if second-line hormonal therapy is considered. The Data Supplement provides recommendations from other guidelines for treatment considerations beyond second-line hormonal therapy.

Cost Implications

Few studies examined cost-effectiveness or the budgetary impact associated with second-line hormonal therapies for CRPC. The focus primarily is on patients with metastatic disease in the postchemotherapy setting. These cost studies are not directly comparable with one another because of differences in methodology and assumptions,[58-61] and the generalizability of the results to the chemotherapy-naïve population is questionable given differences in survival and total treatment costs. The two studies that provided estimates of 30-day treatment costs on the basis of average wholesale prices or reimbursement for the post-chemotherapy population suggested that abiraterone acetate is less expensive than enzalutamide.[9,58] These basic results may be similar for the chemotherapy-naïve population.

The only study that directly examined cost-effectiveness for the asymptomatic, chemotherapy-naïve population found that neither abiraterone nor sipuleucel-T were cost-effective compared with prednisone on the basis of a willingness-to-pay threshold of $150,000 per quality-adjusted life-year.[62] On the basis of findings from a survey of oncologists,[63] the authors suggested that $378,000 (2013 US dollars) may be a more accurate threshold. Although sipuleucel-T remains cost-ineffective at this new threshold, the

incremental cost-effectiveness ratio for abiraterone is nearly cost-effective at $389,000 per quality-adjusted life-year.

To the best of our knowledge, no studies have assessed the cost of follow-up after progression to CRPC. The few studies that assessed the costs of follow-up for patients with prostate cancer focused on the first 5 years after receipt of curative intent therapy.[64] Actual charges for 5 years of follow-up after curative therapy for prostate cancer varied by 7.3-fold.

Although most studies that addressed out-of-pocket (OOP) expenses for patients with prostate cancer generally focused on those with clinically localized disease, the findings of Jung et al[65] in 2012 are relevant. This study found that few patients fully understand the likely OOP costs in advance of the treatment decision. Also informative is a survey of factors that influence physician decisions to prescribe flutamide in conjunction with complete androgen blockade for patients with metastatic prostate cancer, which found that OOP costs were the most important factor.[66]

OOP costs, the potential adverse effects of OOP costs (referred to as financial toxicity),[67] and expected quality of life should be discussed with patients during the treatment decision-making process. Oncologists must continue to advocate for patient access to beneficial therapies while being responsible stewards of health care resources.

LIMITATIONS AND FUTURE DIRECTIONS

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

Another limitation of the literature was the definition of castrate levels of testosterone. Although < 50 ng/mL is the current accepted definition, this definition is based on older technology that was incapable of accurately measuring lower levels. Because newer technology is now available, studies have suggested that the cut point should be lower (< 32 ng/mL or even < 20 ng/mL to match surgical castration levels) and that perhaps free rather than total testosterone should be the focus.[68-70] However, no as-yet completed phase III randomized clinical trials support a change in definition, and how changing the definition would actually affect treatment patterns is unclear.

The focus of this PCO is on second-line hormonal therapy for the chemotherapy-naïve population with M0 and M1 CRPC. This PCO serves as a companion piece to the ASCO systemic therapy guideline that focuses primarily on the postchemotherapy M1 population.[9] Among patients with radiographic evidence of metastatic disease, the Prostate Cancer Clinical Trials Working Group 3 recommended that future RCTs characterize patients by number of lines of prior therapy rather than by pre- and post-chemotherapy.[19] As data from phase III RCTs that use this new nomenclature become available, the scope of updates to this PCO will likely narrow to focus solely on the M0 CRPC population. For new trials in the nonmetastatic CRPC state, the Prostate Cancer Clinical Trials Working Group 3 also recommends that future RCTs regularly include such outcome measures as time to symptomatic skeletal events, time to first metastasis, and time to progression.

As ongoing clinical trials reach completion and new evidence becomes available for more-sensitive imaging techniques and potentially more-potent hormonal agents, the PCO will be updated (Data Supplement).

Emerging evidence suggests that stereotactic body radiotherapy and stereotactic radiosurgery may soon be viable alternative treatment options for patients with oligometastatic prostate cancer. In addition, among men with newly diagnosed metastatic prostate cancer, a propensity score analysis of secondary data identified a significant association with improved OS for external-beam radiotherapy plus ADT versus ADT alone at a median follow-up of 5.1 years.[71] Prospective RCTs are needed. Similarly, cytoreductive prostatectomy after an excellent response to ADT or as initial therapy is under investigation at multiple centers.[72,73] Ongoing clinical trials may soon clarify the role of ablative therapy as hormone-free and chemotherapy-free survival rates increase among patients with oligo-recurrent prostate cancer.[74,75]

Phase III RCTs of related populations with implications for second-line hormonal therapy among chemotherapy-naïve men with CRPC include the ongoing STAMPEDE trial, which examines the use of five different treatments in combination with first-line hormonal therapy among chemotherapy-naïve men.[76] Because some of these treatments typically are reserved for second-line hormonal therapy use, earlier use of these therapies will affect clinical decisions in the second-line hormonal therapy space, which will eventually require an update of the existing PCO. Also of interest is the ongoing phase III PROSPER study (ClinicalTrials.gov identifier NCT02003924) that compares early use (before AAWD) of enzalutamide versus placebo among patients with nonmetastatic disease, with metastasis-free survival as the primary end point and OS and quality of life as two of several secondary end points. Also in the M0 CRPC space are the ongoing phase III SPARTAN and ARAMIS trials. SPARTAN (ClinicalTrials.gov identifier NCT01946204) compares apalutamide with placebo and ARAMIS (ClinicalTrials.gov identifier NCT02200614) compares darolutamide with placebo.

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

- Integration of Palliative Care Into Standard Oncology Practice[20] (ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)
- Systemic Therapy in Men With Metastatic CRPC[9] (ascopubs.org/doi/full/10.1200/JCO.2013.54.8404)
- Prostate Cancer Survivorship Care Guideline Endorsement[77] (ascopubs.org/doi/full/10.1200/JCO.2014.60.2557)

ADDITIONAL RESOURCES

More information, which includes a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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No relationship to disclose

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Appendix

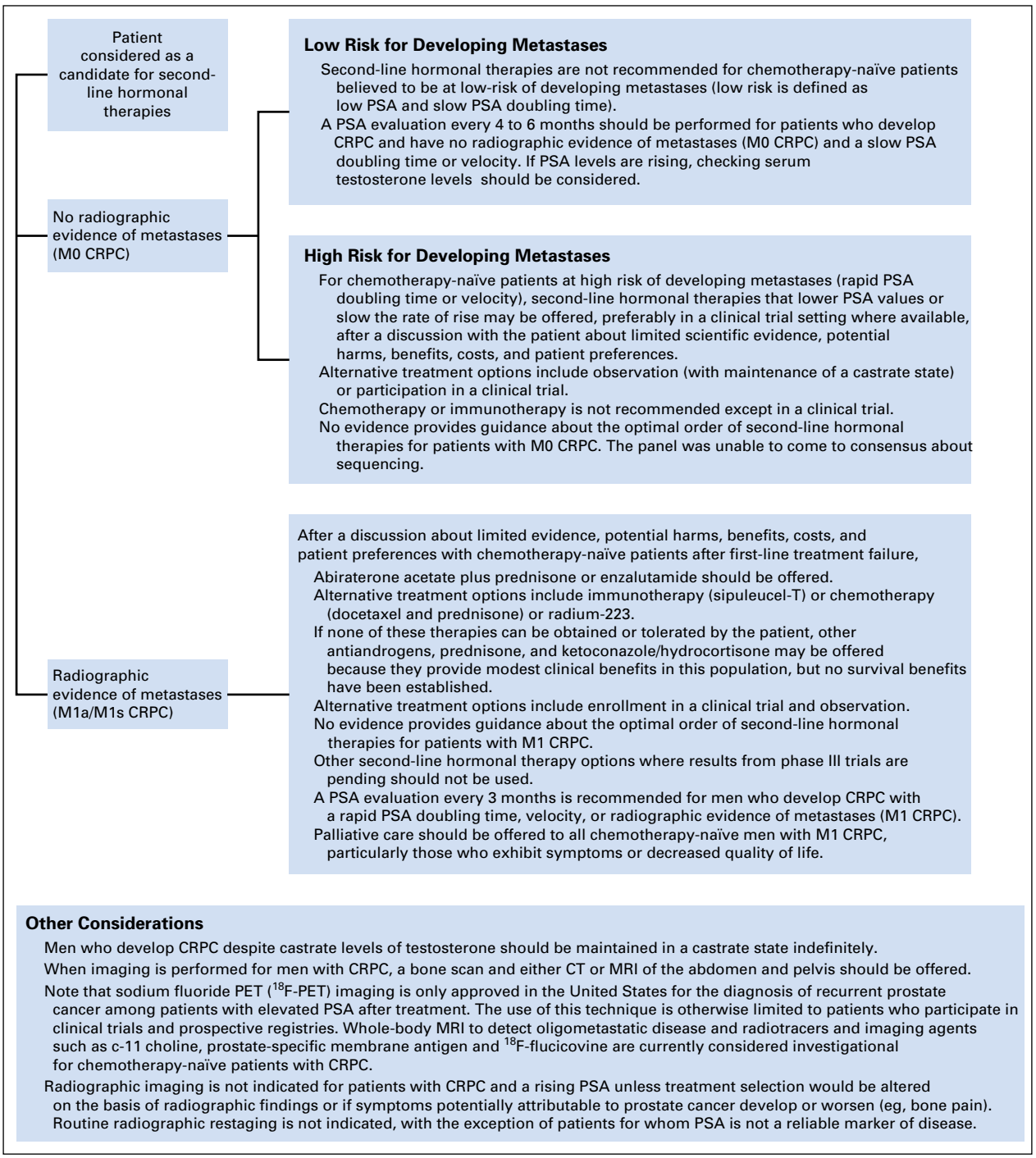

Fig A1. Algorithm for second-line hormonal castration-resistant prostate cancer (CRPC) treatment. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen.

Table A1. ASCO Castration-Resistant Prostate Cancer Expert Panel Membership

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