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"Non-metastatic, Castration-resistant Prostate Cancer: Diagnostic and Treatment Recommendations by an Expert Panel from Brazil"

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Abstract

A panel of Brazilian experts convened in order to provide recommendations regarding staging methods, antineoplastic therapy, osteoclast-targeted therapy, and patient follow-up in non-metastatic, castration-resistant prostate cancer. Key points include the reliance on prostate-specific antigen doubling time for treatment decisions, the absence of a clear preference between conventional and novel imaging techniques, and the increasing role of novel androgen-receptor signaling inhibitors.

Introduction: Non-metastatic, castration-resistant prostate cancer (nmCRPC) is an important clinical stage of prostate cancer, prior to morbidity and mortality from clinical metastases. In particular, the introduction of novel androgen-receptor signaling inhibitors (ARSi) has changed the therapeutic landscape in nmCRPC. Given recent developments in this field, we update our recommendations for the management of nmCRPC. **Methods:** A panel of 51 invited medical oncologists and urologists convened in May of 2021 with the aim of discussing and providing recommendations regarding the most relevant issues concerning staging methods, antineoplastic therapy, osteoclast-targeted therapy, and patient follow-up in nmCRPC. Panel members considered the available evidence and their practical experience to address the 73 multiple-choice questions presented. **Results:** Key recommendations and findings include the reliance on prostate-specific antigen doubling time for treatment decisions, the absence of a clear preference between conventional and novel (i.e., positron-emission tomography-based) imaging techniques, the increasing role of ARSis in various settings, the general view that ARSis have similar efficacy. Panelists highlighted the slight preference for darolutamide, when safety is of greater concern, and a continued need to develop high-level evidence to guide the intensity of follow-up in this subset of prostate cancer. **Discussion:** Despite the limitations associated with a consensus panel, the topics addressed are relevant in current practice, and the recommendations can help practicing clinicians to provide state-of-the-art treatment to patients with nmCRPC in Brazil and other countries with similar healthcare settings.

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Introduction

Prostate cancer is currently responsible for one out of seven new cancer cases in males worldwide.[1] For clinical practice, prostate cancer can be divided into clinical states, with specific diagnostic evaluation and therapeutic options. Progression during androgen-deprivation therapy (ADT) is a key milestone in that attempt, marking the onset of the castration-resistant state in a given patient.[2,3] When biochemical progression is detected in patients on ADT, generally after radical prostatectomy and/or radiotherapy to the prostate, and distant disease cannot be identified by imaging, non-metastatic, castration-resistant prostate cancer (nmCRPC) is defined.[3,4] More specifically, a 25% increase in prostate-specific antigen (PSA) levels from nadir (considering a starting value $\geq$1.0 ng/mL, and a minimum rise of 2.0 ng/mL) is required in the presence of castrate testosterone levels (<50 ng/dL) and absence of disease identified by computed tomography (CT) or magnetic resonance imaging (MRI), in lymph nodes beyond the true pelvis or in visceral organs, and by bone scan.[3]

The prevalence of nmCRPC is estimated to be between 2% and 8% in different countries.[5] In recent years, there has been an increased ability to identify these patients, partly as a result of more frequent PSA testing for men on treatment with ADT.[6] Moreover, there is growing interest in identifying patients with nmCRPC, for a variety of reasons. First, results from placebo arms in clinical trials among patients with nmCRPC suggest that up to 60% of these patients develop overt metastatic disease within 3 to 5 years.[4,7,8] The presence of clinical metastases is associated with morbidity from the disease and metastatic CRPC (mCRPC) is considered a lethal state of prostate cancer.[9] Based on the previously mentioned model, nmCRPC represents a patient population for whom preventing or delaying a transition to mCRPC is the primary therapeutic objective, with potential impact even in the public-health perspective.[9] Secondly, the introduction of the novel androgen-receptor signaling inhibitors (ARSi, apalutamide, darolutamide and enzalutamide)

has changed the therapeutic landscape in the various states along the continuum of prostate cancer progression and offered improved options in nmCRPC.[2,10] Finally, novel imaging methods are more accurate in detecting lymph-node and distant metastases in patients with biochemical recurrence, thus bringing a new perspective to disease staging in patients with CRPC.[2,6,11,12]

Our group has previously reviewed and provided recommendations for staging, diagnosis and treatment of nmCRPC in Brazil through a consensus conference.[13] Given recent developments in imaging and treatment modalities, we sought to update our recommendations for practicing physicians in Brazil, especially due to the epidemiological importance of prostate cancer in this country.[14]

Patients and Methods

Panel organization, composition, and goals

The expert panel was composed by 51 invited medical oncologists and urologists with expertise in genitourinary malignancies in Brazil. The number of experts in the panel was increased compared to prior consensus to better assess the regional differences in Brazil. In addition, specialists were selected based on local clinical practices, and usually urologists and oncologists assist patients with nmCRPC. Radiotherapy was discussed as part of the questions, but there were no radiotherapists as panel members, as no recommendations of radiotherapy were derived from first consensus edition. The meeting was organized and coordinated by the two senior authors (DLJ and FM) and aimed at discussing the most relevant issues concerning the diagnosis and treatment of patients with nmCRPC, including staging methods, antineoplastic therapy, osteoclast-targeted therapy, and patient follow-up. A total of 73 multiple-choice questions were developed on these topics. In a modified Delphi process, a scientific committee reviewed questions in three rounds for inputs and recommendations. Questions were presented to the expert panel, which convened in May of 2021 (see Supplementary Materials for the complete text of these questions, which appear in *Results* in an abbreviated format). In order to provide their recommendations, panel members considered the published scientific evidence and their practical experience on the issues discussed. For all the questions, it was assumed that the interventions discussed were approved and available, whereas those not yet approved in Brazil were not presented among the possible options.

Statistical analysis

Results were computed descriptively for each of the multiple-choice questions addressed by the panel. When answering each question, the option "abstain" was to be used when a panel member felt impeded to provide a qualified response for a lack of knowledge or the presence of conflicts of interest. The consensus was considered to be present for a question if at least 75% of the voting members selected a particular answer, considering the number of voters and the option "abstain" in the denominator of this proportion. When an answer garnered between 50.0% and 74.9% of votes, this was considered as a majority recommendation.

Results

Staging methods

As shown in Table 1, there was no consensus for any of the three questions on staging methods. Regarding imaging modalities for patients with nmCRPC, voters were equally divided between (1) positron-emission tomography (PET)-CT with prostate-specific membrane antigen (PSMA) (or PET-MRI with PSMA), with or without pelvic MRI and (2) chest CT or X-ray, CT of the abdomen and pelvis (or pelvic MRI) and bone scan, both in case of recurrences after radical prostatectomy and after curatively intended radiotherapy. Regarding the preferred method for calculating PSA doubling time (PSAdt), two-thirds of voters recommended using an electronic calculator and the last three PSA values above 0.1 ng/mL. Table 1 also shows a question addressing treatment options, which is presented here because the recommendation with the largest percentage of votes (45.2%) was for PSMA-based PET scanning in a hypothetical patient with small pelvic lymph nodes.

Antineoplastic therapy

There were 65 questions addressing systemic antineoplastic therapy for patients with nmCRPC, one of which presented in Table 1. The first eight of the remaining 64 questions elicited recommendations for a newly diagnosed patient with different combinations of PSA level, PSAdt, and life expectancy. The panel recommendations for these eight hypothetical patients are summarized in Figure 1. There was consensus for five of these questions, majority vote for one, and relatively similar division of votes between two different recommendations for two questions.

Table 2 presents recommendations regarding the specific choice of agents, particularly novel ARSi. There was consensus for only one of eight questions, namely about the adequacy of any novel ARSi when taking overall survival results into account. There was also a general trend for recommending any of these agents instead of anyone in particular, except for a preference for darolutamide when safety or tolerability was taken into account. Toxicity and access were the main reasons for recommendations regarding the choice of novel ARSi. Of note, there was a considerable lack of consensus about whether positive PSMA-based imaging should change management when conventional imaging has disclosed no metastatic disease, and on how to treat these patients.

The next series of questions addressed drug choice in view of concern with specific comorbidities or age groups among patients with a reasonable life expectancy. As shown in Table 3, voters generally indicated any ARSi as the first option for most groups of patients with specific comorbidities. Exceptions to this were the preference for darolutamide specifically for patients with mental impairment or a history of falls or of seizures, as well as the use of drugs that increase the risk of seizures. Of note, the panel emphasized the importance of checking for drug interactions before treatment decisions for patients on multiple medications.

The following 30 questions aimed to elicit the level of concern among panel members regarding specific types of toxicity from each of the three novel ARSi. The results are displayed graphically in Figure 2. For most combinations of toxicity types and agents, the level of concern indicated by the panel was low (green in Figure 2) or moderate (yellow). However, as a general rule, there was higher

Table 1 Questions related to staging methods.

Question	Recommendations and percentages									
Imaging for a nmCRPC patient after radical prostatectomy	PSMA PET-CT (or PSMA PET-MRI) +/- pelvic MRI	Whole-body MRI	Bone scan	Pelvic MRI	Pelvic MRI and bone scan	Chest CT/X-ray, CT of the A & P (or pelvic MRI), and bone scan	None	Abstain	–	–
	48.5%	0	0	0	3.0%	48.5%	0	0	–	–
Imaging for a nmCRPC patient after curatively intended radiotherapy	PSMA PET-CT (or PSMA PET-MRI) +/- pelvic MRI	Whole-body MRI	Bone scan	Pelvic MRI	Pelvic MRI and bone scan	Chest CT/X-ray, CT of the A & P (or pelvic MRI), and bone scan	None	Abstain	–	–
	47.2%	0	0	0	2.8%	50%	0	0	–	–
Calculation of PSA doubling time (based on values (>0.1 ng/mL)	Do not calculate it	Last 2 values, manually	Last 2 values, electronically	Last 3 values, manually	Last 3 values, electronically	At least 4 values, manually	At least 4 values, electronically	Abstain	–	–
	2.6%	0	15.4%	2.6%	66.7%	5.1%	7.7%	0	–	–
Approach to nmCRPC with pelvic lymph nodes <2.0 cm in minor axis	Apa	Enza	Daro	Apa or enza or daro	Bic or fluta or nilu	Pelvic radiotherapy	Stereotactic body radiotherapy for oligometastatic lymph nodes	Lymphadenectomy	PET-PSMA for therapeutic decision	Abstain
	2.4%	0	0	40.5%	0	2.4%	4.8%	0	45.2%	4.8%

Answers to some questions may not total 100% due to rounding.
A & P, abdomen and pelvis; Apa, apalutamide; Bica, bicalutamide; CT, computed tomography; Daro, darolutamide; Enza, enzalutamide; Fluta, flutamide; MRI, magnetic resonance imaging; Nilo, nilutamide; nmCRPC, non-metastatic, castration-resistant prostate cancer; PET, positron-emission tomography; PSMA, prostate-specific membrane antigen.

concern with enzalutamide, intermediate with apalutamide, and lower with darolutamide.

The final seven questions related to treatment addressed various decisions that are often required upon observation of clinical events (Table 4). There was consensus for only two of those questions: (1) docetaxel is the treatment of choice (90.7%) for patients developing clinical metastases during treatment for nmCRPC who previously progressed to castration resistance in less than 12 months; and (2) the ARSi should not be discontinued (81.8%) in patients with nmCRPC and a profound PSA response (<0.2 ng/mL). There was majority recommendation for three questions: (1) 51.2% of panel members indicated that two methods (among PSA, clinical and radiological) should be used to decide on changing treatment due to progression in patients with nmCRPC; and docetaxel was recommended as treatment of choice upon progression to mCRPC (2) for patients on ARSi with short metastasis-free survival (59.1%) and (3) for patients who progressed to mCRPC after previous progression to castration resistance in more than 12 months (56.8%). For the remaining two questions, there was considerable division of opinion among panel members.

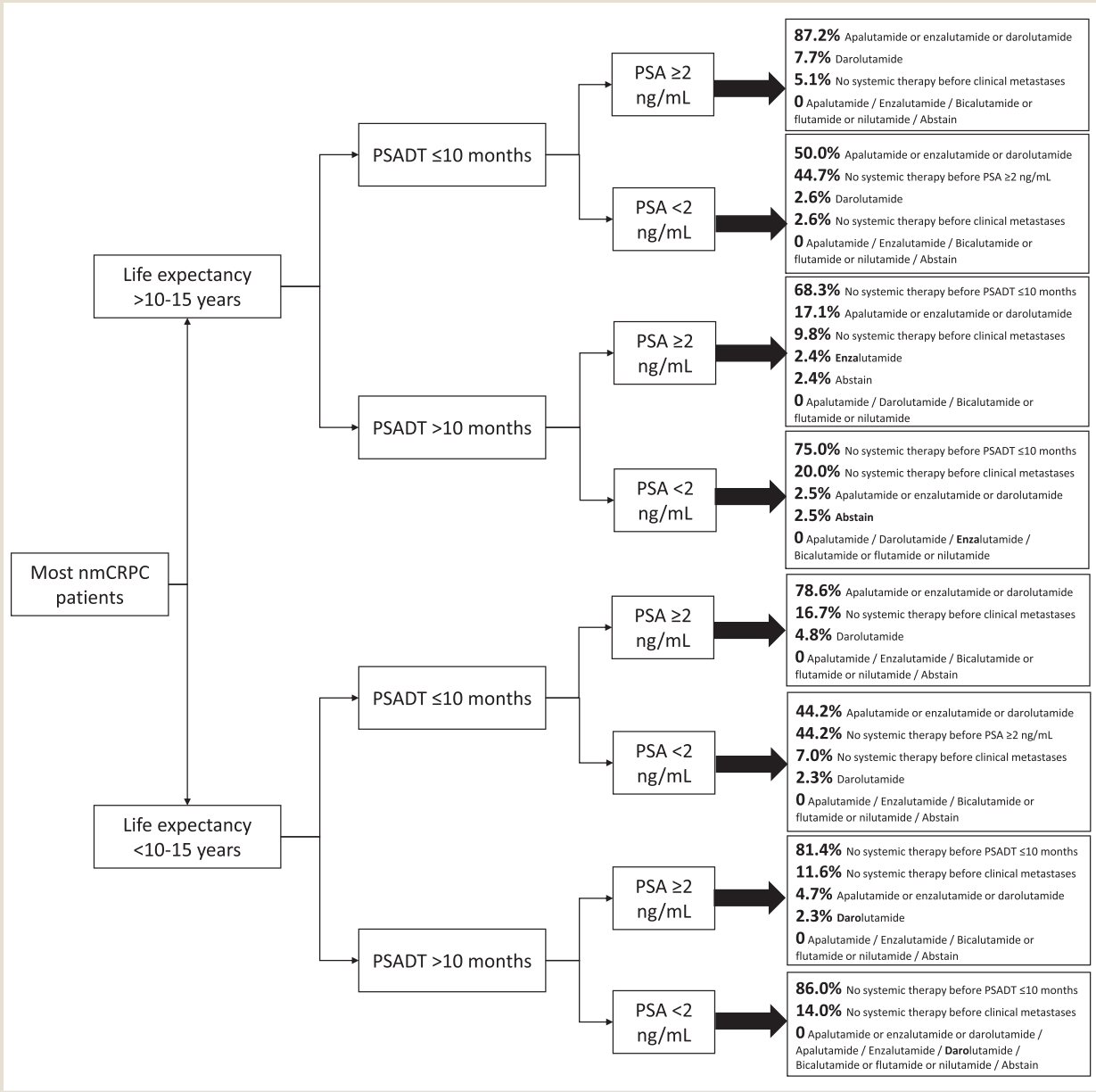
Osteoclast-targeted therapy

Four questions were posed to the panel to elicit recommendations on the use of osteoclast-targeted therapy to prevent skeletal-related events (SREs) in patients with nmCRPC (Table 5). Even though the percentage of panel members stating they do not recommend osteoclast-targeted therapy in this setting is below 75% for the first question, the other three questions make it clear that there was consensus that these agents are not indicated to prevent SREs in patients with nmCRPC.

Patient follow-up

Regarding the overall strategy for following-up patients with nmCRPC on active therapy, 50.0% of panelists recommended physical examination and PSA levels every 3-6 months and a bone scan every 3-6 months, whereas 37.5% recommended physical examination and PSA levels every 3-6 months and imaging only in the case of symptoms. Physical examination and PSA levels every 3-6 months and a bone scan every 3-6 months, plus a chest CT or X-ray and CT of the abdomen every 3-6 months was recommended by 5% of members. No panel members recommended PET-PSMA and whole-body MRI, and 2.5% of voters recommended either (1) physical examination and PSA levels every 3-6 months with abdominal ultrasound and chest X-ray every 3-6 months and bone scan annually or (2) physical examination and PSA levels every 3-6 months and a chest CT or X-ray and CT of the abdomen and pelvis every 3-6 months. Finally, the abstention rate was 2.5%.

Figure 1 Questions related to immediate management of patients with non-metastatic, castration-resistant prostate cancer. Answers to some questions may not total 100% due to rounding.
Abbreviations: nmCRPC, non-metastatic, castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.



Discussion

Staging methods

Likely because of its established role in risk stratification, the PSAdt is used by the vast majority of panel voters, notwithstanding differences in the number of PSA values used (Table 1). As in the previous edition of this expert panel, the predominant recommendation (66.7%) is to compute the PSAdt using the last three PSA levels and an electronic system. Interestingly, the lack of consensus—and dichotomy of recommendations between conventional and novel techniques—for the questions on imaging methods also recapitulates the results of the first version of this expert panel (Table 1).[13] These recommendations are consistent with individual clinical practice and likely related to the technology available in different institutions. PET-CT (or PET-MRI) imaging with PSMA is not available in public centers and is only available in some private

Table 2 Questions related to drug choice.

Question	Recommendations and percentages								
Antiandrogen preference in nmCRPC	Apa	Enza	Daro	Apa or enza or daro	Abiraterone	Bica or fluta or nilu	Abstain	–	–
	4.4%	2.2%	17.8%	68.9%	4.4%	2.2%	0	–	–
Change of management if positive PSMA-based and negative conventional imaging	Yes	No	Abstain	–	–	–	–	–	–
	52.3%	47.7%	0	–	–	–	–	–	–
Treatment if positive PSMA-based and negative conventional imaging	Apa	Enza	Daro	Apa or enza or daro	Bic or fluta nilu	Docetaxel (based on disease volume)	Local therapy if oligometastatic disease	Local therapy if oligometastatic disease plus Apa or enza or daro	Abstain
	0	8.8%	2.9%	38.2%	0	0	20.6%	23.5%	5.9%
Drug preference given survival data	Apa	Enza	Daro	Apa or enza or daro	Abstain	–	–	–	–
	2.4%	0	19.0%	76.2%	2.4%	–	–	–	–
Drug preference given QOL data	Apa	Enza	Daro	Apa or enza or daro	Abstain	–	–	–	–
	0	0	30.2%	67.4%	2.3%	–	–	–	–
Drug preference given safety	Apa	Enza	Daro	Apa or enza or daro	Abstain	–	–	–	–
	0	0	65.1%	27.9%	7.0%	–	–	–	–
Drug preference given tolerability	Apa	Enza	Daro	Apa or enza or daro	Abstain	–	–	–	–
	2.4%	0	58.5%	34.1%	4.9%	–	–	–	–
Reason for drug preference	Toxicity profile	Experience	Cost	Access	Abstain	–	–	–	–
	50.0%	4.8%	0	35.7%	9.5%	–	–	–	–
When to stop treatment and start a new one in nmCRPC	PSA progression alone	Clinical progression alone	Radiological progression alone	At least two criteria	Clinical and radiological progression	Any progression	Abstain	–	–
	2.3%	0	9.3%	51.2%	27.9%	9.3%	0	–	–

Answers to some questions may not total 100% due to rounding.
Apa, apalutamide; Bica, bicalutamide; Daro, darolutamide; Enza, enzalutamide; Fluta, flutamide; Nilo, nilutamide; nmCRPC, non-metastatic, castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; QOL, quality of life.

centers in Brazil, a country with a dual healthcare system whereby services are provided under government funding or through private insurance. However, it is conceivable that different opinions about the role of novel imaging methods stem from different philosophical perceptions about the role of systemic therapy in different stages of the continuum of prostate cancer, particularly the transition between the non-metastatic and the oligometastatic state. Since this possibility has not been addressed by the panel, it remains speculative.

Of note, the National Comprehensive Cancer Network (NCCN) guidelines support the use of conventional imaging in this setting.[15] Moreover, the definition of nmCRPC is not yet based on the need to rule out metastatic disease by more sensitive imaging modalities and is still largely based on conventional imaging.[2] In randomized trials of systemic therapy for patients with nmCRPC, eligibility was based on absence of metastases by conventional imaging.[16-18] However, this is an evolving field, and a recent randomized trial indicated that PET-CT with PSMA is superior to conventional imaging for detection of systemic disease in the setting of high-risk disease

Table 3 Questions related to comorbidities.

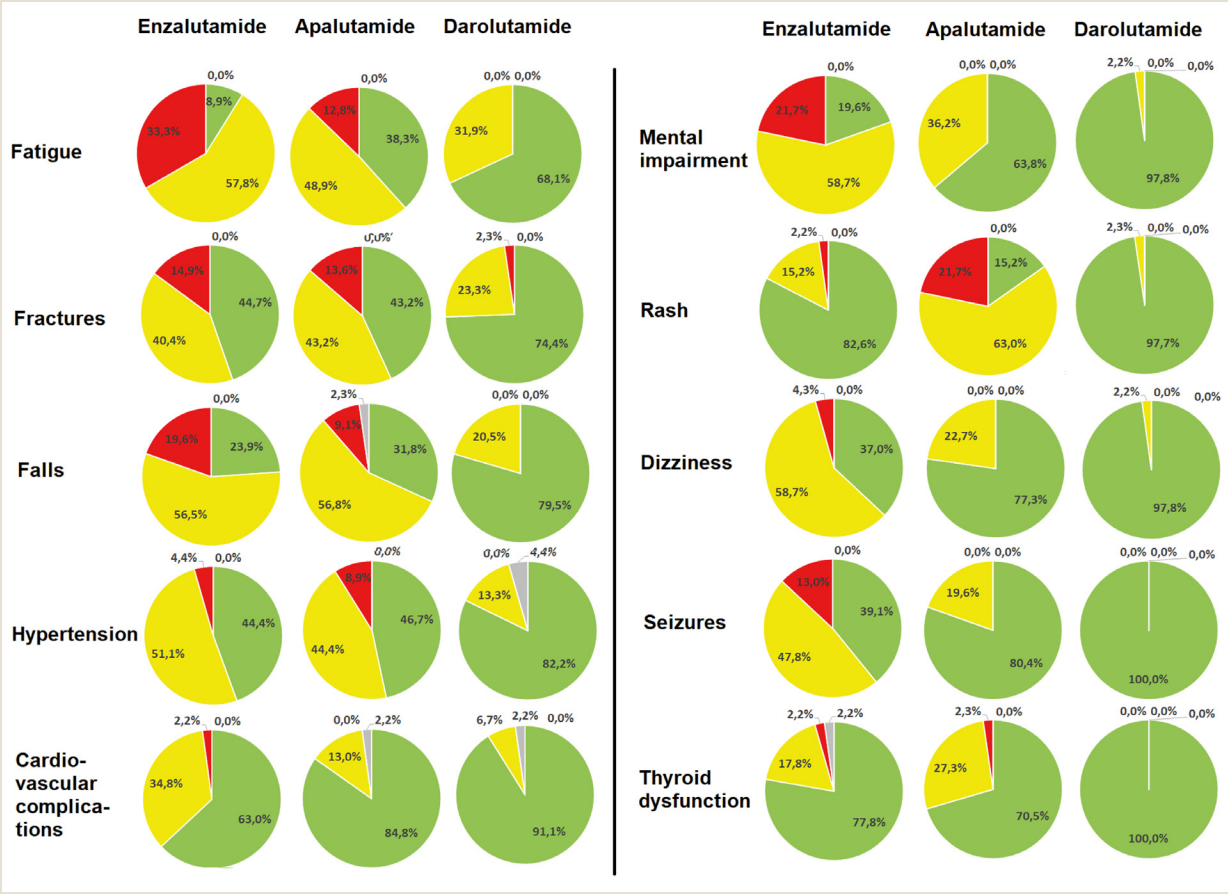
Question Drug choice for most patients with reasonable life expectancy and…	Recommendations and percentages						
Moderate/severe diabetes	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	81.0%	0	2.4%	9.5%	0	7.1%	–
Moderate/severe hypertension	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	54.8%	7.1%	0	35.7%	0	2.4%	–
Congestive heart failure ≥ Class II	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	59.1%	4.5%	0	29.5%	0	6.8%	–
Coronary artery disease	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	71.4%	4.8%	0	16.7%	0	7.1%	–
History of seizure or drugs that increase risk of seizure	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	11.1%	8.9%	0	71.1%	2.2%	6.7%	–
Mental impairment	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	15.6%	2.2%	0	73.3%	0	8.9%	–
Renal insufficiency	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	78.6%	0	2.4%	11.9%	0	7.1%	–
Age >75 years	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	78.6%	0	0	16.7%	0	4.8%	–
History of falls	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	34.9%	2.3%	2.3%	58.1%	0	2.3%	–
Osteopenia/osteoporosis	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Abstain	–
	75.0%	0	4.5%	13.6%	0	6.8%	–
On multiple medications	Apa or enza or daro	Apa	Enza	Daro	Bica or fluta or nilu	Checking drug interactions before deciding	Abstain
	17.4%	0	0	8.7%	0	73.9%	0

Answers to some questions may not total 100% due to rounding.
Apa, apalutamide; Bica, bicalutamide; Daro, darolutamide; Enza, enzalutamide; Fluta, flutamide; Nilo, nilutamide; nmCRPC, non-metastatic, castration-resistant prostate cancer.

before curative-intent surgery or radiotherapy.[19] Likewise, a meta-analysis assessing the role of ^{68}Gallium-PSMA scanning showed that, among patients with biochemical recurrence, the percentage of positive scans rises proportionally according to PSA levels.[12] Finally, a recent large retrospective study showed that PSMA-PET is able to detect M1 disease in 55% of patients previously diagnosed with nmCRPC.[20] Therefore, further studies are needed to clarify the role of PSMA-based imaging in defining nmCRPC.[21,22] Of note, as of today, no prospective trial demonstrated a clinical benefit in adding next-generation imaging for staging nmCRPC. Furthermore, there is no evidence that metastasis-directed therapy beside newer systemic treatments with novel ARSi will modify the natural course of nmCRPC.

Finally, the recommendation by nearly half of the panel members to consider PSMA-based imaging in patients with small pelvic lymph nodes was balanced by a similar percentage of recommendations for immediate treatment. It should be noted that the Selective Prostate Androgen Receptor Targeting with ARN-509 (SPARTAN) trial of apalutamide, the Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) trial of darolutamide, and the PROSPER trial of enzalutamide allowed the inclusion of patients presenting pelvic lymph nodes below the aortic

Figure 2 Level of concern regarding specific toxicities and agents. Green, low; yellow, moderate; red, high; grey, abstentions. Values of 0.0% more often indicate abstentions.



bifurcation (measuring <2 cm for SPARTAN and ARAMIS, and <1.5 cm for PROSPER).[16-18,23-25]

Antiandrogen therapy for nmCRPC

Considering a newly diagnosed patient with nmCRPC, there was consensus among panel members (87.2%) that any of the novel ARSi would be the treatment of choice for initial management of most men with a life expectancy >10-15 years, a PSAdt ≤10 months and a serum PSA ≥2 ng/mL. These characteristics are consistent with the criteria that led to eligibility to the three pivotal trials of these agents.[16-18,23-25] Likewise, there was also consensus for no systemic therapy in three other combinations of these patient characteristics which were not consistent with the eligibility criteria to the pivotal trials, as well as majority vote (68.3%) for no systemic therapy for a fourth combination. However, the specific setting of life expectancy <10-15 years PSAdt ≤10 months and a serum PSA ≥2 ng/mL also led to consensus recommendation (78.6%) of any of the novel androgen-signal inhibitors, even though life expectancy was not defined in this way as an entry criterion for the pivotal trials. Finally, for two combinations of PSAdt ≤10 months and a serum PSA <2 ng/mL, panel members were similarly divided between recommending any of the novel androgen-signal inhibitors or no systemic therapy until further PSA rises, something that reflects the current uncertainty in this field.

The panel reached consensus or majority vote for some of the various decisions that are often required during treatment of patients with nmCRPC. Chemotherapy plays a key role in the management of patients progressing to mCRPC, and consensus or majority recommendations were achieved for the use of docetaxel for patients who progressed to mCRPC (regardless of time to castration resistance of PFS while on ARSi). These results are supported in the literature by the description of cross-resistance between ARSi and findings of limited responses when sequencing treatment with two ARSi.[26-28] When asked about the decision to change treatment in patients with nmCRPC, nearly half of panel members indicated that two methods (PSA, clinical and radiological assessment) to ascertain progression should be used to trigger such a change, whereas nearly a third recommended clinical and radiological progression as the triggers. In ARAMIS, PROSPER and SPARTAN, the experimental agent (respectively darolutamide, enzalutamide and apalutamide) was discontinued when there was clinical or radiological progression, or given prespecified levels of toxicity.[16-18]

Table 4 Questions related to decisions during treatment.

Question	Recommendations and percentages							
When to stop treatment and start a new one in nmCRPC	PSA progression alone	Clinical progression alone	Radiological progression alone	At least two criteria	Clinical and radiological progression	Any progression	Abstain	–
	2.3%	0	9.3%	51.2%	27.9%	9.3%	0	–
Choice for a patient requiring interruption of ASI for toxicity	Discontinue ASI and maintain castration	Wait for resolution and re-initiate same ASI	Switch to a different antiandrogen	Abstain	–	–	–	–
	6.8%	47.7%	45.5%	0	–	–	–	–
Next choice for a patient on ASI for nmCRPC with short PFS	Enza if not used before	Abiraterone	Docetaxel	Radium-223 if only bone metastases	Cabazitaxel	Bic or fluta or nilu	PARPi if DDR positive	Abstain
	9.1%	15.9%	59.1%	9.1%	0	0	4.5%	2.3%
Next choice for a patient on ASI for nmCRPC with long PFS	Enza if not used before	Abiraterone	Docetaxel	Radium-223 if only bone metastases	Cabazitaxel	Bic or fluta or nilu	PARPi if DDR positive	Abstain
	7.0%	23.3%	44.2%	16.3%	0	0	4.7%	4.7%
Choice for a patient with clinical metastases after failing treatment for nmCRPC who previously progressed to CRPC in less than 12 months	Enza if not used before	Abiraterone	Docetaxel	Radium-223 if only bone metastases	Cabazitaxel	Bic or fluta nilu	PARPi if DDR positive	Abstain
	2.3%	2.3%	90.7%	2.3%	0	0	0	2.3%
Choice for a patient with clinical metastases after failing treatment for nmCRPC who previously progressed to CRPC in more than 12 months	Enza if not used before	Abiraterone	Docetaxel	Radium-223 if only bone metastases	Cabazitaxel	Bic or fluta or nilu	PARPi if DDR positive	Abstain
	4.5%	25.0%	56.8%	6.8%	0	0	4.5%	2.3%
Choice for a nmCRPC patient on ASI and PSA response to <0.2 ng/mL	Continue therapy	Discontinue antiandrogen after 1 year	Discontinue antiandrogen after 2 years	Consider intermittent therapy	Abstain	–	–	–
	81.8%	4.5%	2.3%	11.4%	0	–	–	–

Answers to some questions may not total 100% due to rounding.
ASI, androgen-signal inhibitor; Bica, bicalutamide; DDR, DNA-damage repair; Enza, enzalutamide; Fluta, flutamide; MFS, metastasis-free survival; Nilo, nilutamide; nmCRPC, non-metastatic, castration-resistant prostate cancer; PARPi, poly (ADP-ribose) polymerase inhibitor.

Choice of specific novel androgen-signal inhibitors

The lack of consensus about whether a positive PSMA-based imaging should change management when conventional imaging has disclosed no metastatic disease reflects the corresponding doubts in the current literature.[20,22] Regarding the specific choice of novel ARSi, only apalutamide and enzalutamide were approved by the Brazilian regulatory authority (Anvisa) when the first edition of this expert panel was conducted.[13] Likewise, another previous consensus-development panel from Brazil was conducted before the approval of darolutamide in this country.[29] Given the recent approval of darolutamide by Anvisa, there was considerable interest in assessing the comparative perception of these three agents. Interestingly, the panel indicated a seeming lack of clear preference for any specific agent when taking overall survival or quality of life into account, given positive results from all three agents.[23-25,30-32] Nevertheless, when one specific agent was indicated in light of considerations about safety, tolerability and quality of life, darolutamide was the drug garnering more votes, likely as a consequence of more

Table 5 Questions related to osteoclast-targeted therapy.

Question	Recommendations and percentages							
Choice of osteoclast-targeted therapy to prevent SREs in nmCRPC	Zoledronic acid	Denosumab	Either	Another osteoclast-targeted therapy	I do not use this therapy in this setting, but may supplement calcium and vitamin D	Abstain	–	–
	4.3%	6.5%	15.2%	0	71.7%	2.2%	0	–
Treatment frequency for zoledronic acid as prevention of SREs in nmCRPC	Every 12 months	Every 6 months	Every 3 months	Every month	I do not use this therapy in this setting	Abstain	–	–
	0	11.9%	2.4%	2.4%	81.0%	2.4%	–	–
Treatment frequency for denosumab as prevention of SREs in nmCRPC	Every 12 months	Every 6 months	Every 3 months	Every month	I do not use this therapy in this setting	Abstain	–	–
	0	7.3%	0	2.4%	82.9%	7.3%	–	–
Duration of osteoclast-targeted therapy for SRE prevention in nmCRPC	1 year	2 years	Until first SRE	Until second SRE	Indefinitely	Until disease progression	I do not use this therapy in this setting	Abstain
	0	0	2.5%	0	2.5%	0	87.5%	7.5%

Answers to some questions may not total 100% due to rounding.
nmCRPC, non-metastatic, castration-resistant prostate cancer; SRE, skeletal-related event.

impactful results in these domains in comparison with placebo in the ARAMIS trial[31] and in indirect comparison with apalutamide and enzalutamide.[33-36]

Even though novel ARSi are generally safe, toxicity is a major consideration when choosing treatment for this patient population, asymptomatic from the viewpoint of prostate cancer and typically with a long life expectancy. Apalutamide, darolutamide and enzalutamide are associated with variable rates of decreased appetite, fatigue, nausea, hot flashes, fractures, falls, skin rash, hypertension, cardiovascular complications, mental impairment, seizures, among other adverse events. For example, apalutamide was associated with rash of any grade in 23.8% of patients in the SPARTAN trial (versus 5.5% for placebo).[17] Fatigue was reported in 30.4% of nmCRPC patients treated with apalutamide, 33% of those treated with enzalutamide, and 12.1% of those treated with darolutamide, in all cases at higher rates than placebo.[16-18] The panel recommendations according to specific types of toxicity from each of the three novel ARSi mirror the recommendations related to safety and tolerability discussed above, and are generally supported by indirect comparisons between the agents, which as a rule have shown a better safety profile for darolutamide than the other two agents.[33-36]

Prevention of skeletal-related events

Bone is the leading metastatic site and a major cause of morbidity for patients with mCRPC, among whom both zoledronic acid and denosumab play a key role in delaying SREs.[37] Only denosumab has been assessed in a randomized trial among patients with nmCRPC, and it significantly increased bone-metastasis-free survival when compared with placebo, although by only 4.2 months.[8] Nevertheless, denosumab has not been approved for this patient population, given the unclear clinical relevance of the results. Although the literature in this regard is still relatively scant, there is no solid evidence that osteoclast-targeted therapy improves patient-relevant outcomes in patients with nmCRPC.[4,8] Probably as a reflection of the literature, there was consensus among panel members that neither zoledronic acid nor denosumab are indicated to prevent SREs in patients with nmCRPC.

Patient follow-up

There is no high-level evidence to guide the overall strategy for following-up patients with nmCRPC on active therapy. Nevertheless, physical examination and PSA levels every 3-6 months are recommended by the vast majority of panel members; nearly half would also add a bone scan every 3-6 months, whereas 37.5% recommended imaging only in the case of symptoms. Importantly, there is no perceived role for novel imaging methods currently.

Conclusion

As highlighted previously,[13] this type of survey has limitations. The opinions are elicited through a voting system, which assumes prior knowledge on the topics discussed. The recommendations by individual panel members may be influenced by individual access to newer diagnostic tools or treatment modalities; since that access may be subject to constraints in different healthcare settings in Brazil, there is a potential influence on recommendations. This may be particularly relevant for novel imaging methods. We also

Table 6 Areas of consensus (≥75% agreement) and important topics with no consensus in nmCRPC.

Topic	Result
Areas of Consensus	
Preferred systemic therapy considering survival data	Any of the ARSi (apalutamide, darolutamide, enzalutamide)
Drug of choice for most patients with nmCRPC and osteoporosis	Any of the ARSi (apalutamide, darolutamide, enzalutamide)
Choice for a patient with clinical metastases after failing treatment for nmCRPC, who previously progressed to CRPC in less than 12 months	Consensus was obtained for Docetaxel
What to do in patients with nmCRPC and PSA response to <0.2 ng/mL after ARSi	Continue therapy with no interruption
Consideration about osteoclast-targeted therapy in nmCRPC patients	Panelists recommended against osteoclast-targeted therapy to prevent SREs
Topics with no Consensus	
Staging imaging for nmCRPC patients	No consensus, with similar number of panelists recommending next generation imaging (PSMA-PET) and conventional imaging
Change of management if positive PSMA-based and negative conventional imaging	Half of the panel would change management in case of PSMA-only detected lesions
ARSi preference in nmCRPC	Any of the ARSi (apalutamide, darolutamide, enzalutamide) was generally recommended, with increase preference for darolutamide when safety, tolerability and mental impairment was considered

Abbreviations: ARSi: androgen receptor signaling inhibitor; SREs: skeletal-related events

consider that with advances in new imaging modalities a multidisciplinary team should be an optimal approach for nmCRPC, including discussions with radiotherapists for oligometastatic disease. We should point out, however, that the extent to which lack of consensus for some of the questions was due to characteristics at the country level or at the professional level, such as respectively specificities of the healthcare system or physician specialty, lack of sufficient data, has not been ascertained in the current work. Nevertheless, the low percentages of abstentions suggest that the topics chosen are relevant in current practice and that panel members indeed have variable preferences for many of the clinical issues discussed. Regardless of these limitations, we believe the current recommendations—and future updates in light of new knowledge—can help practicing clinicians best provide state-of-the-art treatment to patients with nmCRPC (Table 6).

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Clinical Practice Points

- Medical oncologists and urologists managing patients with non-metastatic, castration-resistant prostate cancer face in increasing number of choices to be made regarding staging methods, antineoplastic therapy, osteoclast-targeted therapy, and patient follow-up. Importantly, novel androgen-receptor signalling inhibitors are changing the therapeutic landscape for this disease. This paper reports recommendations of an expert panel convened to address these issues.

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