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The Role of Therapeutic Layering in Optimizing Treatment for Patients with Castration-Resistant Prostate Cancer (RADAR II)

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ABSTRACT

Objective: To offer recommendations on identification of disease progression, treatment management strategies, and suggestions on timing of initiating and discontinuing specific CRPC treatments.

Materials and Methods: The RADAR II [Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence] Working Group convened to provide guidance on sequencing, combination, or layering of approved treatments for mCRPC based on available data and clinical experience.

Results: A consensus was developed to address important questions on mCRPC patient management.

Conclusions: In the absence of large scale clinical trials, the Working Group recommends that patients may best be managed with a layered approach of approved therapies with unique or complimentary mechanisms of action.

Key Words: castration-resistant prostate cancer, guidelines, treatment, sequencing, combination, layering

(Main body word count limit: 4,000. Currently 3,929)

INTRODUCTION

Castration-resistant prostate cancer (CRPC) is a progressive disease (total testosterone <50 ng/dL) in men and is associated with one or more of the following: symptomatic, radiographic, or prostate-specific antigen (PSA)

progression.¹ Survival with CRPC has dramatically improved over the past decade due to the availability of multiple new therapeutics. These treatment options include an androgen biosynthesis inhibitor (abiraterone acetate) and an androgen receptor antagonist (enzalutamide), an immunotherapy (sipuleucel-T), a targeted alpha therapy (radium-223), and chemotherapeutic agents (docetaxel and cabazitaxel). Nevertheless, the management of metastatic castration-resistant prostate cancer (mCRPC) poses a significant challenge due to disease heterogeneity and the invariable development of molecular, proteomic, and genomic patterns of resistance.

While the recent therapeutic advances have shown a significant survival benefit in monotherapy trials in patients with mCRPC, optimal use (eg, combination and sequencing) of chemotherapy, second-generation androgen pathway inhibitors, immunotherapy, and a targeted alpha therapy to achieve maximum clinical benefit has not been established. There is a paucity of head-to-head trials to compare these new agents and no trials have yet been published comparing combinations to other combinations or monotherapy. As a result, there is no consensus in the current guidelines on the appropriate sequence of the available therapeutic options.²⁻⁴ In addition, the lack of validated predictive biomarkers of survival may delay treatment optimization. Therefore, decisions regarding treatment are made on the basis of limited nonrandomized comparisons, consideration of safety and tolerability, assumptions about the risks and benefits of combining agents with potentially complementary mechanisms of

action, potential for overlapping toxicities, and anecdotal experience. In addition, logistics regarding access to therapeutics as well as reimbursement policies may vary depending upon global and regional locations.

In the absence of a consensus on timing, methods, and frequency of imaging in clinical practice, the Working Group (Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence [RADAR I] Group) of medical oncologists, radiation oncologists, urologists, and a nuclear medicine radiologist convened to review available data and provide recommendations for early identification of metastases in patients with prostate cancer.⁵ Many of the same participants from the RADAR I Group collaborated in this consensus group to discuss the management of disease progression in patients with CRPC. One key objective of this Working Group was to provide a consensus regarding sequencing, combination, and “therapeutic layering.” Therapeutic layering is hereafter defined as a clinical point where one or more agent(s) are added onto an existing therapy. In forming these recommendations, the Working Group took into account the different treatment possibilities, trial data, existing guidelines, and real-world, practical considerations tempered by the clinical experience of the members.

REVIEW OF RADAR I RECOMMENDATIONS: IMAGING

Briefly, the RADAR I Group previously made recommendations regarding the timing and frequency of imaging among different patient groups with prostate cancer in order to identify metastatic disease early.⁵ The RADAR I Group cautioned against overutilization of imaging in clinical practice. Imaging in clinical practice should not reflect the timing or frequency of imaging in clinical trials, but rather should be utilized when therapeutic selection can be affected by results (ie, we emphasize the importance of diagnostic recommendations in order to optimize clinical utility). Imaging should be initiated when 1) considering starting therapy, 2) prior to changing therapy to establish a new baseline, and 3) after treatment has been completed to monitor disease progression. The discordance between the response of PSA and results of radiographic imaging has created confusion in identifying disease progression. The RADAR I Group recommends PSA trends and clinical context to be most important. For example, PSA doubling time (PSADT) is a very consistent predictor of aggressive disease progression in different disease states, but the greatest absolute utility of PSA is in the biochemical recurrence setting.⁶ Therefore, the recommendation by the RADAR I Group is to also perform subsequent imaging when clinical or consistent and convincing biochemical progression is identified. As a follow up to the previous recommendations, the RADAR II group recognizes that radiolabeled choline positron emission tomography/computed tomography (PET/CT) was recently determined to be more sensitive than conventional imaging (eg, ultrasound, CT of abdomen and pelvis, and bone scans) in select patients with biochemical recurrence.⁷ The 2016 National Comprehensive Cancer Network (NCCN)

guidelines provide updated recommendations for the use of radiolabeled choline PET/CT in these select patients.⁴ More recently, ¹⁸F-FACBC (Axumin) PET/CT was found to be superior in detection to ¹¹C-choline PET/CT scanning in patients with biochemical recurrence,⁸ and this new agent was approved by the Food and Drug Administration (FDA) in May 2016.

CURRENT TREATMENT LANDSCAPE

Currently, mCRPC is incurable. Therefore, the goal of treatment is to extend life and provide the best possible quality of life (QOL) for patients with mCRPC for as long as possible.² Since the approval of docetaxel in the United States in 2004, 5 new agents have achieved FDA approval for the treatment of mCRPC with an ability to prolong survival (**Table 1**). Although cabazitaxel is indicated only for the treatment of patients with mCRPC who have received prior treatment with a docetaxel-containing regimen, the other agents may be employed for first-line or subsequent therapy. Current treatment guidelines provide a list of available agents with limited recommendations regarding any order of sequence, combination, or layering (**Table 2**). The Working Group

recognizes that all treatment interventions for CRPC are technically layering of therapy since agents are added to the foundation of androgen deprivation therapy (ADT). ADT is continued even in the setting of CRPC where androgen-sensitive clones exist, and continuing ADT has become standard to avoid symptomatic and PSA progression from these clones.⁹ Hence, the term “therapeutic layering” was devised to describe a situation whereby a therapy is being used and one or more additional agent(s) are added. This is unique from “combination therapy” where 2 or more therapies are initiated simultaneously. At this time, the Working Group recommends considering therapeutic layering of certain new agents in patients with mCRPC when appropriate **(Figure)**.

QUESTIONS CONSIDERED BY THE WORKING GROUP

The RADAR II Working Group first addressed questions regarding disease progression:

- How is progression defined? What is the best way to determine progression while a patient is being treated with therapeutic agents with biologically distinct mechanisms of action?

The Working Group also made recommendations regarding initiating and discontinuing therapeutic agents:

- How early should treatment be initiated in patients with mCRPC? Which agents should be considered for use early in the disease process?
- When should therapy be changed? Should treatment continue beyond progression? If yes, with which agents?
- When should treatment be started and when should treatment be discontinued for each specific therapeutic agent?
- Should second-generation androgen pathway inhibitors (abiraterone or enzalutamide) be used sequentially?

The Working Group's recommendations are as follows:

How is progression defined? What is the best way to determine progression while a patient is being treated with therapeutic agents with biologically distinct mechanisms of action?

Recommendation: The Working Group defined progression of mCRPC as a convincing and consistent rise in PSA, evidence of radiographic progression, or the presence of clinical symptoms while the patient is on therapy. Recognizing that the different agents have unique mechanisms of action, **Table 3** outlines

recommended imaging and biomarkers to follow in order to determine progression while a patient is being treated with each therapeutic agent. In the absence of validated biomarkers for disease progression, close monitoring of patient symptoms and imaging are critical to ensure a patient is afforded the ability to receive alternative treatment to increase life expectancy and maintain or improve QOL.

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How early should treatment be initiated in patients with mCRPC? Which agents should be considered for use early in the disease process?

Recommendation: Although the topic of hormone-sensitive disease is technically outside of the topic of this consensus statement, recent data from the CHAARTED [ChemoHormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer], STAMPEDE [Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy], and GETUG-AFU-15 trials have potential to affect subsequent therapy in the mCRPC state. These 3 trials collectively demonstrate that the early use of docetaxel in patients diagnosed with metastatic androgen sensitive disease significantly improves progression-free survival²¹⁻²³ and OS.^{21,22} The trials were designed to add (therapeutically layer) docetaxel to (on top of) ADT, as patients were allowed to enroll within either 4 (CHAARTED), 3 (STAMPEDE), or 2 (GETUG 15-AFU-15) months of initiation of ADT. Although it is unclear whether early use of chemotherapy in the androgen-sensitive setting affect the survival gains of delayed use of chemotherapy in mCRPC, consideration of subsequent treatment when a patient does reach mCRPC was a discussion topic. Specifically, after a patient progresses after receiving prior ADT with docetaxel, should docetaxel be utilized again, and if so, when? Also if a patient has never received chemotherapy before, should chemotherapy be administered early in mCRPC, extrapolating from early use of chemotherapy in the androgen-sensitive setting?

The consensus from the Working Group is that chemotherapy should be initiated early in hormonally naive, newly diagnosed metastatic prostate cancer patients with high-volume disease.²¹ In low volume disease, chemotherapy has not shown a benefit in hormonally naive newly diagnosed patients.²⁴ For mCRPC, we generally do not recommend starting with chemotherapy first. The anticipated median survival benefit from docetaxel in the mCRPC setting is approximately 2 months,^{18,19} an absolute number much smaller than the median 13-month and 22-month benefit seen in CHAARTED and STAMPEDE for the metastatic populations, respectively. Therefore, to maintain good QOL, it may be logical to reserve chemotherapy for a more symptomatic mCRPC patient where survival benefit will be coupled with an additional pain palliative benefit. This recommendation is consistent with that of the St. Gallen Advanced Prostate Cancer Consensus Conference, which did not recommend docetaxel chemotherapy as first-line therapy for otherwise healthy asymptomatic/minimally symptomatic men with mCRPC.²⁵ However, the St. Gallen group did believe that docetaxel should be administered prior to other options in otherwise healthy symptomatic patients who had a short duration response (<12 months) to primary ADT.²⁵ If docetaxel was administered in the androgen sensitive setting previously, our Working Group recommends retreatment with docetaxel if the time to relapse was over 12 months and the patient does not have persisting neuropathy from the docetaxel, otherwise cabazitaxel should be considered. Because definitive clinical data does not exist, the Working Group recommends initiating basic investigations and clinical trials to fully establish if taxane resistance patterns exist or emerge in this population.

Immunotherapy

Immunotherapy with sipuleucel-T^a [**FOOTNOTE: ^aAvailable only in the US**] should be considered for first-line therapy in patients with mCRPC who are asymptomatic, have low disease burden, and who exhibit indolent disease characteristics.^{26,27} Early introduction of sipuleucel-T is supported by a posthoc analysis of results from the IMPACT [Immunotherapy for Prostate Adenocarcinoma Treatment] trial, which showed patients with lower baseline PSA values achieved a greater magnitude of OS benefit with sipuleucel-T.¹² In the postchemotherapy setting, sipuleucel-T can also be administered with survival benefit; however, it is important to recognize that this was a unique subset of patients from the IMPACT trial who had shown an excellent response to previous chemotherapy and were eligible to receive sipuleucel-T after a significant chemotherapy holiday.²⁸

The Working Group recommends that immunotherapy with sipuleucel-T be considered for all newly diagnosed asymptomatic/minimally symptomatic mCRPC patients with low tumor burden.¹² The duration of therapy is fixed with 3 doses and can be completed in 5 weeks (**Table 3**). In recent clinical trials, sipuleucel-T has been combined with enzalutamide (ClinicalTrials.gov Identifier: NCT01981122), abiraterone (ClinicalTrials.gov Identifier: NCT01487863), and radium-223.²⁹ The Working Group encourages continued clinical exploration of biologically rational combinations with sipuleucel-T including other immunotherapies.

Second-Generation Androgen Pathway Inhibitors

Current guidelines recommend the early initiation of androgen pathway inhibitors (ie, abiraterone or enzalutamide) for patients either with or without minimal symptoms in the prechemotherapy setting.⁴ The Working Group suggests initiating second-generation androgen pathway inhibitors (abiraterone, enzalutamide) following immunotherapy in the setting of biochemical or clinical progression in this prechemotherapy setting. Recognizing that not all patients are ideal candidates for sipuleucel-T, the Working Group suggests starting first with a second-generation androgen pathway inhibitor in that patient population.

Targeted Alpha Therapy

Following a second-generation androgen pathway inhibitor, radium-223 should be considered for patients with bone metastases upon the emergence of signs and symptoms (ie, fatigue, impaired mobility, previous or current bone pain). The risk of bone metastatic disease can be independently predicted by alkaline phosphatase (ALP) and PSA.³⁰ In phase 3 trials with enzalutamide and abiraterone, a subsequent decrement in QOL occurred soon after PSA progression, even in the absence of radiographic progression^{13,31}; therefore, it is reasonable to consider radium-223 during or soon after PSA progression on those agents. In the phase 3 ALSYMPCA trial, radium-223 demonstrated OS efficacy in patients with progressive mCRPC with 2 or more bone metastases detected on skeletal scintigraphy and no known visceral

metastases.³² Subgroup analysis indicated that radium-223 had a significant OS benefit in patients with and without prior docetaxel treatment.³² In posthoc and retrospective analyses, improved results have been observed in patients who receive 5 or 6 doses of radium-223 compared with those who receive only 1 to 4 doses.³³⁻³⁵ Patients who receive radium-223 early in the course of disease are also more likely to receive all 6 doses compared with those who are treated later in the disease process.³⁶ Radium-223 has an excellent safety profile and low risk for adverse effects on hematopoiesis,³² making it worthwhile to consider in a minimally symptomatic patient prior to administration of chemotherapy. Radium-223 has also been tested concomitantly with chemotherapy,^{37,38} but more extensive trials are ongoing with radium-223 and second-generation androgen pathway inhibitors (ClinicalTrials.gov Identifiers: NCT02043678; NCT02034552, NCT02194842).^{39,40} The Working Group advises that consideration be given to adding (therapeutic layering) radium-223 to androgen pathway inhibitors in patients with bone metastases and symptoms.

When should therapy be changed? Should treatment continue beyond progression? If yes, with which agents?

Recommendation: The Working Group recommends that changes in therapy should depend upon careful consideration of the mechanism of the therapeutic agent being used with the type of progression the patient is experiencing. For example, agents that do not directly induce tumor cell apoptosis or inhibit the androgen axis may not have direct effect on PSA. Specifically, this would include agents like sipuleucel-T and

radium-223, as both offer survival benefit without consistent PSA declines. Changes based on PSA alone are not generally recommended, particularly in the setting of favorable PSA kinetics (ie, long PSADT). This view is also in agreement with the suggestions of the St. Gallen Advanced Prostate Cancer Consensus Conference, which cautioned against stopping treatments with a proven survival benefit on the basis of PSA progression alone.²⁵ Additionally, the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) emphasized the importance of distinguishing between first evidence of disease progression (perhaps by PSA rise) vs stopping treatment when there is no longer a clinical benefit.¹ Altogether, the Working Group believes that symptomatic or radiographic progression are more reliable triggers for either therapeutic layering or change. PSA progression alone should prompt reimaging and may be a more reliable biologic indicator for therapeutic alteration or layering for the androgen pathway inhibitors.

When should treatment be started and when should treatment be discontinued for each specific therapeutic agent?

Recommendation: The recommendations of the Working Group also consider augmentation rather than switching treatment. These recommendations are based on the clonal diversity of mCRPC⁴¹ and the understanding that sequencing (ie, discontinuing current treatment when a new therapy is initiated) may allow clones suppressed by the current treatment clones to re-emerge or expand. Similar to therapeutic layering of (adding) a new agent to ADT with the development of CRPC, the

Working Group also considers therapeutic layering with agents used for known mCRPC.

Table 3 outlines recommendations for when treatment should be added, stopped, or switched for each therapeutic agent.

Should second-generation androgen pathway inhibitors (abiraterone or enzalutamide) be used sequentially?

Recommendation: There is no advice in the current guidelines regarding the sequential use of second-generation androgen pathway inhibitors.⁴ The ideal sequence of abiraterone and enzalutamide has not yet been established, but several prospective trials are comparing single agent to double agent therapy. Retrospective studies suggest that the antitumor activity of abiraterone or enzalutamide is reduced when administered sequentially.^{42,43} The activity of abiraterone also appears to be reduced after prior treatment with either docetaxel or enzalutamide.⁴⁴ Even when responses by PSA occur, the magnitude and duration of response to the second-line androgen pathway inhibitor may be diminished, relative to the first androgen pathway inhibitor. Although there are less data in the prechemotherapy setting, enzalutamide has shown limited activity when administered subsequent to abiraterone.⁴³ Preclinical evidence suggests that cross-resistance may also exist between cabazitaxel and the androgen pathway inhibitors.⁴⁵ The cross-resistance between taxanes and abiraterone or enzalutamide may not be distinct, particularly as microtubules may have an important role of shuttling androgen receptor to the nucleus.⁴⁶ Taxane efficacy may be reduced in tumors that have developed resistance to androgen receptor pathway inhibition, as

demonstrated in patients with mCRPC who had early development of castration resistance (<12 months), had a shorter time to progression, and shorter OS with docetaxel treatment compared with patients with more prolonged sensitivity to androgen axis suppression.⁴⁷ The Working Group, however, noted that the shorter efficacy of subsequent therapy to docetaxel may also be due to more advanced disease rather than prior therapeutic exposure. A prospective evaluation showed an association between detection of androgen-receptor splice variant 7 (AR-V7) in messenger RNA circulating tumor cells and resistance to enzalutamide or abiraterone from patients with CRPC.⁴⁸ The results from a recent cross-sectional cohort study demonstrated circulating tumor cell nuclear expression of AR-V7 protein in men with mCRPC as a treatment-specific biomarker, which is associated with superior survival on taxane therapy over second-generation androgen pathway inhibitors.⁴⁹ Technologies to detect AR-V7 may soon be commercially available for use, although the utility of AR-V7 as a “predictive biomarker” still requires further validation. Based on the current state of the data, the consensus from the Working Group was that switching therapy from one second-generation androgen pathway inhibitor to another after progression on the first agent is not recommended in most situations. However, a switch from one second-generation androgen pathway inhibitor to another may be considered if there is a prolonged treatment response (>12 months) to the first agent, or if the patient is a poor candidate for, or declines on, taxane therapy. The question of whether to switch from one second-generation androgen pathway inhibitor directly to another, or whether to move on to an agent which does not target the androgen pathway (radium-223 or chemotherapy) needs to be answered in prospective, randomized clinical trials. The

Working Group also recommends the layering of radium-223 to a second-generation androgen pathway inhibitor upon first sign of progression as an option. It is also possible that if chemotherapy is administered between one novel hormonal agent and another, there may be resensitization of the patient's tumor to second-generation androgen pathway inhibitors.

FOCUS ON THERAPEUTIC LAYERS

Important questions remain unanswered, such as what constitutes the most effective sequence, combination, or therapeutic layer in mCRPC. With 6 approved agents that prolong survival for mCRPC, exploration of every single duo in a combination or layering trial is not possible. However, the potential benefit of combining agents for the treatment of patients with mCRPC has been assessed in several small-scale studies and additional larger trials are currently ongoing. Trials are ongoing to determine optimal timing, sequence, and combination of these agents (ClinicalTrials.gov Identifiers: NCT01650194, NCT02522715, NCT01308567, NCT02254785, NCT02379390). Therefore, clinical trial participation should be offered to patients to advance the understanding of the efficacy of combinations, and more effort should be placed into therapeutic layering to attempt to further improve patient outcomes.

The Working Group believes that the easiest agents to therapeutically layer are the androgen pathway inhibitors. These agents are currently layered on top of ADT at

the outset of CRPC. The Working Group believes that second-generation androgen pathway inhibitors form an additional layer of therapy that can be combined with other partners, and may be generally less toxic in additional combinations. Several such combination trials in men with mCRPC are ongoing with chemotherapy, such as enzalutamide in combination with cabazitaxel (ClinicalTrials.gov Identifier: NCT02522715).

Concurrent administration of radium-223 and second-generation androgen pathway inhibitors appears to be well tolerated with similar toxicities compared with standard administration of radium-223 alone.⁵⁰ Data from 2 expanded access studies provided preliminary evidence that OS may be significantly longer in patients treated with concomitant radium-223 and abiraterone (vs radium-223 alone), as well as patients treated with concomitant radium-223 and denosumab (vs radium-223 alone).^{39,50} A randomized phase 2a study of radium-223 with abiraterone or enzalutamide in patients with mCRPC is underway (ClinicalTrials.gov Identifier: NCT02034552). Two phase 3 trials of radium-223 in combination with abiraterone or enzalutamide in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant mCRPC are also currently ongoing (ClinicalTrials.gov Identifier: NCT02043678, NCT02194842).⁴⁰ Evidence from a posthoc analysis of concomitant bone-targeted supportive therapy (BTT) in chemotherapy-naive mCRPC patients treated with abiraterone acetate plus low-dose prednisone vs prednisone alone revealed that concomitant BTT significantly improved OS, increased the time to Eastern Cooperative Oncology Group (ECOG) deterioration, and time to opiate use for cancer-related pain.⁵¹

Sipuleucel-T is also being evaluated as part of combination treatment with newer agents. A phase 2 open-label study has assessed the effects of concurrent or sequential administration of abiraterone acetate plus prednisone on sipuleucel-T manufacture and immune response in 69 patients with mCRPC. Results indicated that sipuleucel-T can be successfully administered during concurrent administration of abiraterone plus prednisone without altering the immunologic effects or parameters that have been correlated with survival benefit from sipuleucel-T.⁵² An ongoing randomized, open-label study is also evaluating the effects of sipuleucel-T when administered concurrently or sequentially with enzalutamide (ClinicalTrials.gov Identifier: NCT01981122).⁵³ Sipuleucel-T is also being combined with radium-223 in a trial of asymptomatic or minimally symptomatic patients with CRPC and bone metastases.²⁹

CONCLUSIONS

There have been great strides in the management of mCRPC in the past 5 years.⁵ However, clinicians who evaluate and manage patients with mCRPC face the challenging task of selecting a treatment approach that will optimize their patient's outcomes. These selections must often be made without the results from large-scale randomized, controlled clinical trials evaluating combination, sequential, or direct comparator protocols. Given the approved therapeutics and their phase 3 registrational trials, extrapolation of clinical data to a real-world setting is difficult due to the specific inclusion and exclusion criteria for these clinical studies. There is no agreement on an

ideal therapeutic CRPC sequence for all patients. We believe that patients with mCRPC will ultimately be best managed with different agents, particularly those with unique and complementary mechanisms of action that may be used together in order to avoid inducing cross-resistance. Providing additional evidence about the efficacy, safety, and tolerability of combination regimens, and enhanced approaches for identifying patients most suited for specific treatments, remain an important clinical trial need.

Combining antineoplastic agents is not a novel concept. Successful cure rates for lymphoma, testis, gastrointestinal, lung, and breast cancers, and certain leukemias have been attained by utilizing combination therapy. Ultimately, selection of optimal treatment may increasingly depend on molecular characterization and genotyping as well as patients' clinical characteristics.

The RADAR II Working Group believes that the guidance provided in this paper is consistent with currently available clinical trial results, and we anticipate additional data to further inform combining and/or sequencing CRPC therapeutic agents. When initiating treatment early, consideration should be given to how any chosen therapy may potentially impact subsequent treatments. However, it must be acknowledged that clinical trials might never address all possible options for patient management given the large number of agents now available as well as the potential addition of other unique therapeutics. Therefore, while the recommendations of the RADAR II group are based

on the available trial literature and real-world experience, optimal patient care will continue to demand the clinical judgment of each treating physician.

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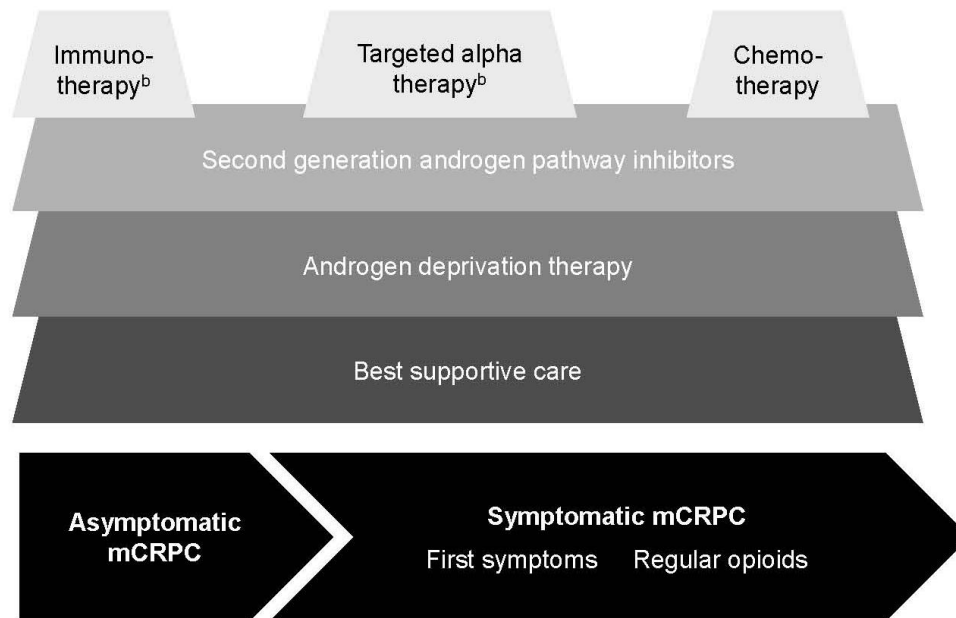
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Figure. Opportunities for therapeutic layering in mCRPC^a

^aClinicalTrials.gov Identifiers:

NCT01487863, NCT01981122, NCT02034552, NCT02288247, NCT02522715.

^bNot eligible if visceral metastasis is present.

mCRPC, metastatic castration-resistant prostate cancer.

Table 1. Agents approved for the treatment of mCRPC in the US

Therapy	Sipuleucel-T	Docetaxel	Abiraterone acetate	Enzalutamide	Radium-223
Indication	M1 CRPC: asymptomatic, minimally symptomatic	M1 CRPC	M1 CRPC	M1 CRPC	M1 CRPC: symptomatic with bone metastases and no visceral metastases
Class of therapy	Autologous immunotherapy	Chemotherapy	Hormonal therapy	Hormonal therapy	Targeted alpha therapy
Efficacy parameter					
OS	✓	✓	✓	✓	✓
PFS		✓	✓ (radiographic)	✓ (radiographic)	
Reduced time to first SSE					✓
Steroids required	No	Yes	Yes	No	No
Liver/kidney monitoring or dose	No	Yes	Yes	No	No

adjustment required					
Dosing schedule	3 cycles (leukapheresis + infusion) about 2 weeks apart	10 cycles, every 3 weeks	4 tablets once daily with BID concomitant steroids	4 capsules once daily	6 cycles, every 4 weeks
Route of administration	Intravenous	Intravenous	Oral	Oral	Intravenous

BID, twice daily; CRPC, castration-resistant prostate cancer; M1, evidence of metastatic disease; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; SSE, symptomatic skeletal event; US, United States.

Table 2. Current guidance for the treatment of CRPC

Stage	National Comprehensive Cancer Network (NCCN) ⁴	American Urological Association (AUA) ³	American Society of Clinical Oncology (ASCO) ²	European Society for Medical Oncology (ESMO) ¹⁰	Canadian Urological Association - Canadian Urologic Oncology Group (CUA-CUOG) ¹¹
M0				Docetaxel (patients with local progression and no possibility for local treatment)	
M1	Docetaxel Mitoxantrone Sipuleucel-T Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)	Docetaxel Mitoxantrone Sipuleucel-T Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)	Docetaxel Mitoxantrone Sipuleucel-T Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)	Docetaxel Abiraterone ^a Enzalutamide ^a Cabazitaxel Sipuleucel-T ^a Radium-223 ^b	Docetaxel Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)

^aPatients who are asymptomatic/mildly symptomatic men with chemotherapy-naive mCRPC.

^bPatients with bone-predominant, symptomatic mCRPC.

CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer.

Table 3. Treatment recommendations for patients with mCRPC TxNx-M1

	Initiate/Add	Imaging/Biomarkers to Follow	Stop/Switch/Add Treatment	Consensus Commentary
Immunotherapy (sipuleucel-T)	<ul style="list-style-type: none"> Should be considered for all newly metastatic CRPC patients with low tumor burden (asymptomatic/minimally symptomatic patients) <ul style="list-style-type: none"> Can be used after other therapies if patient had an outstanding response to the prior therapy 	<ul style="list-style-type: none"> PSA<22 prior to initiation may provide best survival outcomes¹² Improvements in PSA or imaging should generally not be expected 	Duration of therapy is fixed to 3 doses	<ul style="list-style-type: none"> Anti-PAP antibody may be detectable for 8 to 10 years postvaccination¹³
Androgen pathway inhibitors (abiraterone acetate and enzalutamide)	<ul style="list-style-type: none"> Upon consecutive PSA rises Early initiation is associated with greater benefit⁴ Consider initiating therapy following sipuleucel-T upon 	<ul style="list-style-type: none"> Consecutive rise in PSA levels^a indicative of resistance AR full length and AR splice variant expression in circulating tumor cells are potential biomarkers still under 	<ul style="list-style-type: none"> Symptomatic progression Radiographic progression Consider reimaging with consecutive and convincing PSA rises and either proceed with 	<ul style="list-style-type: none"> Therapeutic layering with radium-223 as appropriate Switch to taxane-based therapy PSA and ALP may rise before falling

	<p>biochemical or clinical progression</p> <ul style="list-style-type: none"> • If patient not a good candidate for sipuleucel-T, start with abiraterone or enzalutamide 	<p>evaluation and requiring validation</p>	<p>therapeutic layering or switch</p>	<p>with abiraterone (wait 3 months before making decision on these markers)</p> <ul style="list-style-type: none"> • Bone scan healing flare has been described¹⁴
<p>Targeted alpha therapy (radium-223)</p>	<ul style="list-style-type: none"> • Can be introduced at the first sign of progression on androgen pathway inhibitors for patients with bone metastases and symptoms • Strong consideration for use prior to chemotherapy <ul style="list-style-type: none"> - Favorable safety profile and low risk for adverse effects on hematopoiesis 	<ul style="list-style-type: none"> • PSA changes do not correspond with survival outcomes • ALP is a potential response biomarker 	<ul style="list-style-type: none"> • May be therapeutically layered onto abiraterone or enzalutamide • All 6 cycles should be given for maximal benefit • If given just with ADT, therapeutic layering of abiraterone or enzalutamide can be considered with: <ul style="list-style-type: none"> - Appearance of new symptoms - Rapid growth of lymph nodes - Emergence of visceral disease 	<ul style="list-style-type: none"> • Consider radium-223 earlier in therapy • Palliative radiotherapy can be used before, during, or after radium-223

<p>Chemotherapy</p>	<ul style="list-style-type: none"> • Generally administer after abiraterone and/or enzalutamide and radium-223 <ul style="list-style-type: none"> - Consider starting earlier in patients with visceral metastases, rapidly progressive symptomatic disease, or those with no or very short response to ADT/second-generation androgen pathway inhibitors - Early chemotherapy may influence the efficacy of latter lines of treatment • For neuroendocrine/small cell carcinoma or aggressive variants, use platinum 	<ul style="list-style-type: none"> • Imaging, PSA, ALP, LDH should be obtained prior to therapy • Imaging if clinical deterioration, regardless of PSA⁵ • For patients with a known DNA damage repair alteration (eg, BRCA1 or 2),^{15,16} agents that induce double-strand DNA breaks should be considered (eg, platinum, radium-223 or mitoxantrone).¹⁷ PARP inhibitors are being explored in this setting (ClinicalTrials.gov Identifier NCT01972217; NCT02500901). 	<ul style="list-style-type: none"> • Stopping point is with radiographic or clinical progression, but it is unclear if PSA progression should be used as well • Phase 3 docetaxel trials allowed up to 10 cycles^{18,19} • Cabazitaxel should be administered in patients who previously progressed or were intolerant of docetaxel 	<ul style="list-style-type: none"> • May have activity in patients with AR splice variants²⁰ • PSA may first rise before falling
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	combination chemotherapy regimens			
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^aPSA alone should not be used.

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; AR, androgen receptor; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; PAP, prostatic acid phosphatase; PARP, poly ADP ribose polymerase; PSA, prostate-specific antigen.

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