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Managing Patients With Metastatic Hormone-Sensitive Prostate Cancer: A Shared-Care Approach to Combination Therapy

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Abstract: The treatment landscape for metastatic hormone-sensitive prostate cancer has evolved significantly over the past decade. Androgen deprivation therapy (ADT) was once the first-line standard of care, but the introduction of combination therapies, including ADT with chemotherapy or antiandrogens, has markedly improved overall survival. Multiple studies have demonstrated that doublet therapies offer substantial survival benefits. More recently, triplet therapy—combining ADT with docetaxel and second-generation antiandrogens—has further improved patient outcomes. Selecting the appropriate combination therapy requires balancing efficacy and toxicity, particularly for older patients or those with comorbidities. Optimal management of these patients demands a multidisciplinary approach that integrates expertise from oncologists, urologists, and other specialists. The shared-care model enhances patient outcomes by facilitating collaboration and optimizing individualized treatment plans. Strengthening communication between oncologists and urologists, particularly regarding the implementation of triplet therapies, is critical for improving patient care.

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Table of Contents

Selecting Patients With Metastatic Hormone-Sensitive Prostate Cancer for Combination Therapy

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Introduction

The treatment of metastatic prostate cancer has significantly evolved over the past decade. Like most other nonhematologic malignancies, treatment for metastatic disease is palliative and the goals of treatment are to prolong survival and optimize quality of life. Metastatic hormone-sensitive prostate cancer (mHSPC) is defined as disease that is still responsive to androgen deprivation therapy (ADT); in contrast, metastatic castration-resistant prostate cancer (mCRPC) is disease that has progressed despite castrate testosterone levels. For prostate cancer, both survival and disease morbidity are significantly better for patients who have hormone-sensitive disease than for those who have castration-resistant disease. For example, the annual all-cause mortality rate is 16% for patients who have mHSPC, compared with 56% for patients who have mCRPC.[1] It has also been shown that there is a significant decrease in quality of life and a concomitant increase in health care costs associated with progression to mCRPC.[2-4] Thus, recent novel treatment approaches to metastatic prostate cancer have focused on delaying progression from hormone-sensitive to castration-resistant disease, and prolonging overall survival (OS).

Historical Treatment and the Introduction of Doublet Therapy

Prior to the results of the pivotal CHAARTED trial in 2013, ADT alone had long been the first-line standard of care (SOC) for patients with mHSPC. The results of this trial showed that in patients with newly diagnosed mHSPC, the addition of 6 cycles of docetaxel to ADT improved OS by 28% compared with ADT alone (hazard ratio [HR], 0.72; 95% CI, 0.59-0.89; *P*=.0018), with a median survival extension of 10.4 months at long-term follow-up (57.6 vs 47.2 months, respectively).[5,6]

The results of the CHAARTED study were followed shortly by those of other studies, including the LATITUDE, STAMPEDE, TITAN, ARCHES, and ENZAMET trials. Together, these studies demonstrated comparable OS benefit with doublet therapy that combined ADT with second-generation antiandrogens vs ADT plus placebo (or vs ADT plus a standard nonsteroidal antiandrogen for ENZAMET), including abiraterone (LATITUDE: HR, 0.62; 95% CI, 0.51-0.76; *P*<.001; STAMPEDE: HR, 0.63; 95% CI, 0.52-0.76; *P*<.001), apalutamide (TITAN: HR, 0.67; 95% CI, 0.51-0.89; *P*=.005), and enzalutamide (ARCHES: HR, 0.66; 95% CI, 0.53-0.81; *P*<.001 and ENZAMET: HR, 0.67; 95% CI, 0.52-0.86; *P*=.002).[7-11]

Triplet Therapy

Doublet therapy with either ADT plus docetaxel or ADT plus an antiandrogen remained the first-line SOC for mHSPC until the results of the PEACE-1 and ARASENS studies were published in 2022. These studies each demonstrated that triplet therapy with ADT plus docetaxel plus a second-generation antiandrogen (abiraterone or darolutamide, respectively) further improved OS by an additional 20% to 30% when compared with ADT plus docetaxel alone. These results established triplet therapy as a new SOC regimen for mHSPC, as recommended by both the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology (category 1, preferred) and the American Urological Association (strong recommendation; evidence level: grade B).[12,13]

PEACE-1

The PEACE-1 study was conducted by a European consortium with the goal of evaluating the efficacy and safety of the addition of abiraterone, with or without radiotherapy, to the SOC, which consisted of ADT alone or with docetaxel.[14] This open-label, randomized, active-controlled, phase 3 trial was conducted at 77 sites across 7 European countries.

For inclusion, men were required to have histologically or cytologically confirmed prostate adenocarcinoma that was deemed to be de novo metastatic by bone scan, computed tomography (CT) scan, or magnetic resonance

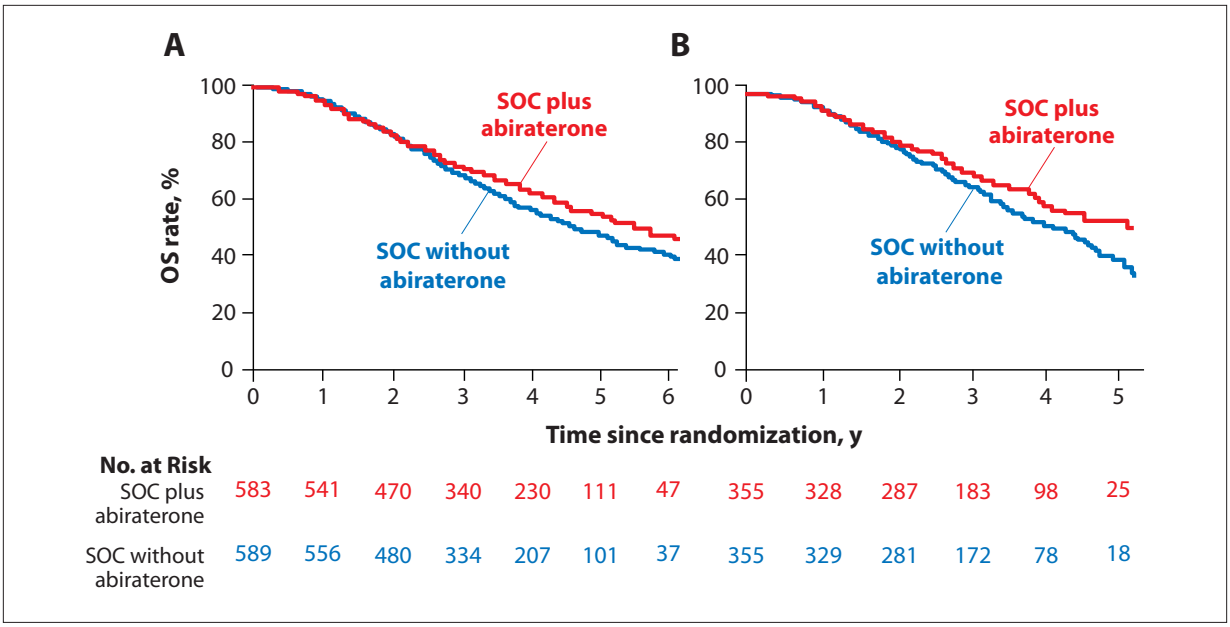

Figure 1. Kaplan-Meier estimates of OS in the overall population (A) and in the ADT with docetaxel population (B) in the PEACE-1 trial. HR for death: 0.82 (95.1% CI, 0.79-0.98; *P*=.030) in the overall population and 0.75 (95.1% CI, 0.59-0.95; *P*=.017) in the ADT with docetaxel population.

ADT, androgen deprivation therapy; SOC, standard of care; y, years.

Adapted from Fizazi K et al. *Lancet*. 2022;399(10336):1695-1707.[7]

imaging (MRI). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (a performance status of 2 because of bone pain was also permitted). Patients were excluded if they had previous prostate cancer treated by a definitive local treatment. Additionally, patients were not permitted to have received ADT for more than 3 months prior to randomization and were required to have at least 6 weeks between the initiation of ADT and the first docetaxel dose.

Two major protocol amendments occurred over the course of the study. First, the treatment protocol was modified to account for an update to the SOC treatment, which at the start of the study in 2013 had been ADT alone. In 2015, the protocol was amended to allow for the addition of docetaxel to ADT as the SOC after this combination was found to improve OS.[5,15] Subsequently, in 2017, after the addition of abiraterone to ADT was shown to result in superior OS compared with ADT alone,[7,8] the use of docetaxel was made mandatory for the remainder of patients to be accrued, so that the efficacy and safety of this triplet combination could be evaluated.

PEACE-1 had a 2 × 2 factorial design, randomizing 1173 patients in equal ratios across 4 treatment arms: (1) SOC (n=296); (2) SOC plus radiotherapy (n=293); (3) SOC plus abiraterone (n=292); or (4) SOC plus radiotherapy plus abiraterone (n=291). The SOC was either ADT alone (n=462) or ADT plus docetaxel (n=710). Patients assigned to receive abiraterone also received prednisone. Abiraterone was continued until disease progression to castration resistance, withdrawal of consent, unacceptable toxicity, or death.

At the time of randomization, patients were stratified according to several factors, including study site, ECOG performance status (0 vs 1 or 2), type of ADT (gonadotropin-releasing hormone [GnRH] agonist vs GnRH antagonist vs bilateral orchiectomy), planned administration of docetaxel (yes vs no), and extent of metastatic disease (lymph node metastases only vs bone metastases [with or without lymph node metastases] vs visceral metastases).

The PEACE-1 study had 2 coprimary endpoints: (1) radiographic progression-free survival (PFS), which was evaluated by bone scan, CT scan, or MRI; and (2) OS. The publication of the PEACE-1 study results in 2022 described the final planned analysis of these coprimary endpoints, as no interim analysis was conducted. Secondary endpoints were also defined for the study, including CRPC-free survival, prostate cancer–specific survival, event rate per 100 person-years, and toxicity. Several other secondary endpoints are planned to be reported at a later time.

Among the overall study population, after adjusting for the stratification factors, there was no statistical

interaction between abiraterone and radiotherapy for either coprimary endpoint: radiographic PFS (*P*=.64) or OS (*P*=.86). The same was true for the secondary endpoints of CRPC-free survival (*P*=.56) and prostate cancer–specific survival (*P*=.54). There was also no interaction between abiraterone and radiotherapy for any of these endpoints in the ADT plus docetaxel population. In response to these results, further evaluation of the efficacy of abiraterone was determined by pooling treatment groups without regard to radiotherapy (ie, SOC alone [with or without radiotherapy] vs SOC plus abiraterone [with or without radiotherapy]).

In this pooled analysis of the overall population, SOC plus abiraterone was associated with a decrease in the number of radiographic progression events or deaths compared with SOC alone. This resulted in a median radiographic PFS of 4.46 years with SOC plus abiraterone, double the 2.22 years experienced by the SOC-alone groups. Therefore, it was determined that the addition of abiraterone to SOC reduced the relative risk of radiographic progression or death by 46% compared with patients who did not receive abiraterone (adjusted HR, 0.54; 99.9% CI, 0.41-0.71; *P*<.001). The pooled overall population groups also showed improved median OS with the addition of abiraterone to SOC vs SOC alone (5.72 vs 4.72 years, respectively). This difference was associated with an 18% reduction in the risk of death by any cause (adjusted HR, 0.82; 95.1% CI, 0.69-0.98; *P*=.030; Figure 1A). Both coprimary outcomes were improved with SOC plus abiraterone vs SOC alone across most predefined subgroups, with the exception of those patients who had bilateral orchiectomy and those who did not receive docetaxel based on the investigator's decision. The improvement in OS with SOC plus abiraterone was especially pronounced in those patients who had a high volume of metastatic disease.

The addition of abiraterone to SOC was further evaluated within the ADT-plus-docetaxel subpopulation. Among these patients, median radiographic PFS was also improved in those treated with SOC plus abiraterone compared with SOC alone (4.46 vs 2.03 years; adjusted HR, 0.50; 99.9% CI, 0.34-0.71; *P*<.001). Median OS was also significantly higher with SOC plus abiraterone vs SOC alone in this subpopulation of patients (not reached vs 4.43 years; adjusted HR, 0.75; 95.1% CI, 0.59-0.95; *P*=.017; Figure 1B).

The extent of metastatic disease burden was also an important factor in the effect of SOC plus abiraterone vs SOC alone among the ADT-plus-docetaxel subpopulation. Those patients with a low-volume burden reached a median radiographic PFS of not reached with SOC plus abiraterone vs 2.7 years with SOC alone (adjusted HR, 0.58; 99.9% CI, 0.29-1.15; *P*=.0061). Patients with a high-volume burden reached a median radiographic PFS of 4.1 years with SOC plus abiraterone vs 1.6 years with SOC alone (adjusted HR, 0.47; 99.9% CI, 0.30-0.72; *P*<.001). Although the OS data for patients with a low-volume burden were immature at the time of reporting, those with a high-volume burden showed a median OS of 5.14 years with SOC plus abiraterone vs 3.47 years with SOC alone (adjusted HR, 0.72; 95.1% CI, 0.55-0.95; *P*=.019).

In the ADT-with-docetaxel subpopulation, secondary endpoints also showed statistical improvement with SOC plus abiraterone compared with SOC alone. For instance, the addition of abiraterone delayed castration resistance (median CRPC-free survival was 3.21 years vs 1.45 years with SOC alone; HR, 0.38; 95% CI, 0.31-0.47; *P*<.001). Median prostate cancer–specific survival was also prolonged with the addition of abiraterone to SOC vs SOC alone (not reached vs 4.72 years; HR, 0.69; 95% CI, 0.53-0.90; *P*=.0062).

The addition of abiraterone to ADT plus docetaxel did not affect the number of docetaxel cycles that were administered. Abiraterone was discontinued in 61% of the 226 patients treated with ADT plus docetaxel and in 53% of 347 treated only with ADT (of these, 21% and 17%, respectively, discontinued owing to toxicity).

It was determined that patients treated with the triplet combination of ADT plus docetaxel and abiraterone did not experience an increase in the incidence of severe or fatal adverse events. Among patients treated with ADT plus docetaxel, grade 3 or higher adverse events were reported by 63% of patients who additionally received abiraterone and by 52% of patients who did not (fatal adverse events occurred in 7 vs 3 patients, respectively). In patients treated with ADT without docetaxel, 66% of those patients treated with abiraterone had at least 1 severe adverse event, and 8 patients had a fatal adverse event.

The most frequent severe adverse events (grade ≥3) reported in at least 5% of patients were generally reported at similar incidences in the SOC-plus-abiraterone and SOC-alone groups. Two exceptions to this were hypertension (22% vs 13%) and hepatotoxicity with increased aminotransferases (6% vs 1%), both of which were more frequent in the SOC-plus-abiraterone group compared with the SOC-alone group. There was also a difference in the incidence of severe neutropenia, which occurred more frequently in the SOC-plus-abiraterone group (10%) compared with the SOC-alone group (0%).

Based on these results, the PEACE-1 study investigators concluded that the triplet combination of ADT plus docetaxel plus abiraterone was superior to the doublet of ADT plus docetaxel in both radiographic PFS and OS, and that these benefits came at the cost of a

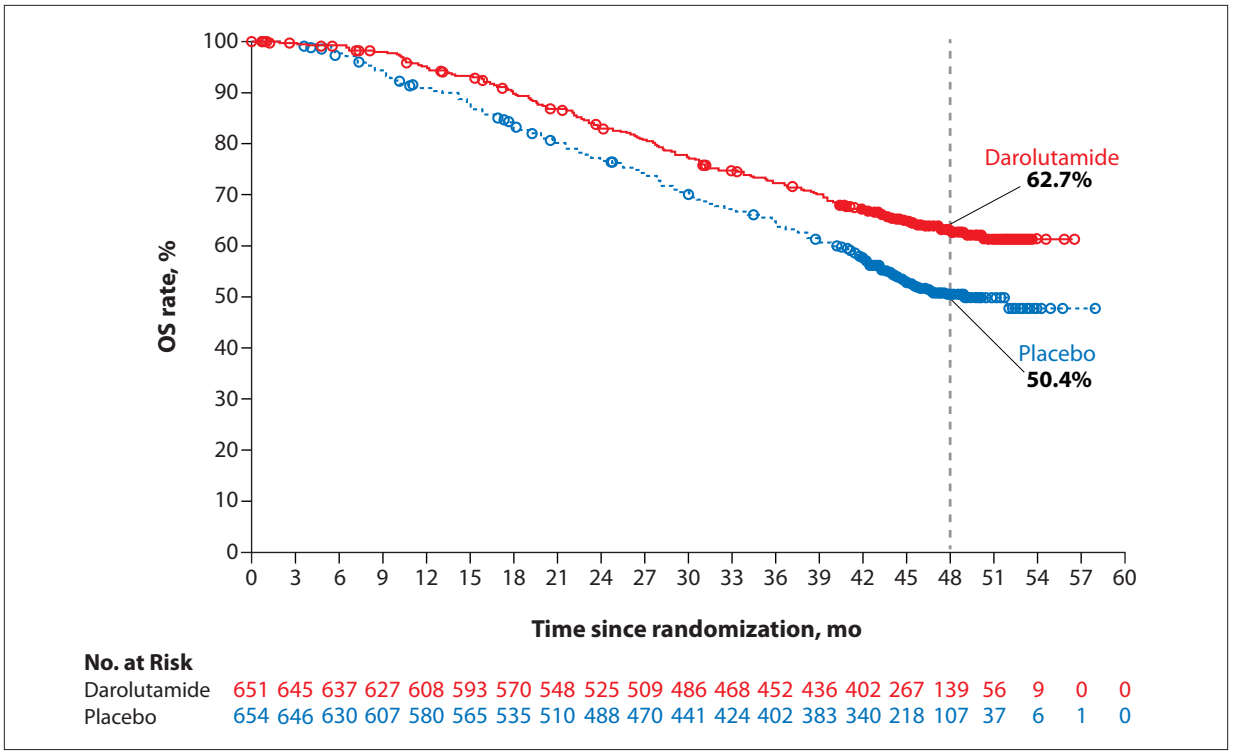

Figure 2. Kaplan-Meier estimates of OS in the ARASENS trial. HR for death, 0.68 (95% CI, 0.57-0.80; *P*<.001).

HR, hazard ratio; mo, months; OS, overall survival.

Adapted from Smith MR, et al. *N Engl J Med.* 2022;386(12):1132-1142.[16]

modest increase in toxicity. The investigators did note that the PEACE-1 trial was not designed to determine if the triplet combination was superior to the addition of ADT plus a second-generation androgen receptor axis inhibitor.

ARASENS

The ARASENS study was an international, randomized, double-blind, placebo-controlled, phase 3 trial.[16] This study aimed to evaluate the efficacy and safety of triplet therapy with darolutamide added to ADT plus docetaxel in patients with mHSPC. The ARASENS study was conducted in 286 centers across 23 countries.

To be eligible for study inclusion, adult patients had to have histologically or cytologically confirmed prostate cancer with metastases detected by bone scan, CT scan, or MRI. Patients were required to have an ECOG performance status of 0 or 1, and had to be candidates for SOC with ADT plus docetaxel. Regional lymph node involvement only (N1, below the aortic bifurcation) was an exclusion criteria, as was receipt of prior ADT more than 12 weeks before randomization. Other exclusion factors included prior use of second-generation androgen receptor pathway inhibitors, chemotherapy, immunotherapy, or radiotherapy within 2 weeks before randomization.

All 1306 patients received ADT or underwent orchiectomy within 12 weeks prior to randomization and also received docetaxel, with prednisone/prednisolone administered at the investigator's discretion. Patients were then randomized in a 1:1 ratio to additional treatment with either darolutamide (n=651) or matched placebo (n=655). At the time of randomization, patients were stratified according to the metastasis stage (nonregional lymph node metastases only [M1a], bone metastases with or without lymph node metastases [M1b], or visceral metastases with or without lymph node or bone metastases [M1c]) and according to the alkaline phosphatase level (< vs ≥ at the upper limit of the normal range). Darolutamide (or matched placebo) was continued until symptomatic disease progression, change in antineoplastic therapy, unacceptable toxic effects, patient or physician decision, death, or nonadherence.

The primary endpoint of the ARASENS study was OS. Secondary endpoints included time to CRPC, time to pain progression, symptomatic skeletal event–free survival, time to first symptomatic skeletal event, time to initiation of subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms,

time to initiation of opioid treatment for 7 or more consecutive days, and safety. Data from the primary analysis were reported in the 2022 publication.

The primary analysis of OS revealed that the risk of death was significantly lower with the addition of darolutamide to ADT plus docetaxel (32.5% lower risk of death vs the placebo plus ADT plus docetaxel arm; HR, 0.68; 95% CI, 0.57-0.80; *P*<.001; Figure 2). Significantly improved OS was achieved in the darolutamide arm despite a high percentage of patients in the placebo arm (75.6%) who received subsequent life-prolonging systemic therapies. The 4-year OS was 62.7% in the triplet combination arm with darolutamide compared with 50.4% in the placebo arm. The benefit of the addition of darolutamide was observed across most patient subgroups.

Darolutamide was associated with significantly greater benefits compared with placebo across several secondary endpoints that were tested in a hierarchical fashion. For example, the time to development of CRPC was significantly longer with the addition of darolutamide vs placebo (HR, 0.36; 95% CI, 0.30-0.42; *P*<.001). Other secondary endpoints that were prolonged with darolutamide vs placebo included the time to pain progression (HR, 0.79; 95% CI, 0.66-0.95; *P*=.01), symptomatic skeletal event–free survival (HR, 0.61; 95% CI, 0.52-0.72; *P*<.001), time to first symptomatic skeletal event (HR, 0.71; 95% CI, 0.54-0.94; *P*=.02), and time to the initiation of subsequent systemic antineoplastic therapy (HR, 0.39; 95% CI, 0.33-0.46; *P*<.001).

Incidences of adverse events were similar with the addition of darolutamide vs placebo. The most common adverse events in the darolutamide vs placebo arms, respectively, were alopecia (40.5% vs 40.6%), neutropenia (39.3% vs 38.8%), fatigue (33.1% vs 32.9%), and anemia (27.8% vs 25.1%). Grade 3 or 4 adverse events were reported in 66.1% of patients in the ADT plus docetaxel plus darolutamide arm, compared with 63.5% of patients in the ADT plus docetaxel plus placebo arm. Of these, neutropenia was the most common (in 33.7% and 34.2%, respectively). A total of 44.8% of patients in the darolutamide arm experienced a serious adverse event, compared with 42.3% of patients in the placebo arm. Many of the most frequently reported adverse events (≥10% of patients) were known toxicities of docetaxel, and indeed were highest during docetaxel administration, tapering in frequency thereafter.

Grade 5 adverse events were also reported at a similar frequency in both arms (4.1% in the darolutamide arm and 5.0% in the placebo arm). A total of 13.5% of patients discontinued darolutamide and 10.6% discontinued placebo owing to adverse events.

Several adverse events of special interest for patients receiving androgen receptor pathway inhibitors were monitored, most of which showed a similar incidence between the darolutamide and placebo arms. These included fatigue, falls, fractures, mental impairment, and cardiovascular events. Exceptions to this were rash (16.6% vs 13.5%) and hypertension (13.7% vs 9.2%).

The ARASENS study investigators concluded that based on these results, the triplet combination of ADT plus docetaxel plus darolutamide resulted in a significantly superior benefit in OS compared with the ADT plus docetaxel doublet. This benefit did not seem to result in greater toxicity over the combination of ADT and docetaxel alone. They further noted that the ARASENS study was not designed to compare the efficacy of the doublet combination of ADT plus darolutamide vs ADT plus docetaxel.

Selecting Patients for Doublet vs Triplet Therapy

Although US Food and Drug Administration labeling allows doublet and triplet therapy for all patients with mHSPC, in practice we often select patients based on their age, comorbidities, performance status, and extent of disease. At a minimum, all patients with mHSPC should be offered doublet therapy with ADT plus an antiandrogen, given the consistent and significant survival benefits across multiple trials evaluating this combination. Antiandrogens also have relatively low toxicity profiles compared with traditional chemotherapy. These medications are oral, and therefore can be easily dose-reduced or discontinued at any time should patients encounter significant adverse effects.

With regard to triplet therapy, focus should be placed on whether the patient is likely to tolerate docetaxel. Although docetaxel is one of the more tolerable cytotoxic chemotherapeutic agents, it can still cause significant myelosuppression, fatigue, gastrointestinal symptoms, and neuropathy. To be considered for triplet therapy, patients should exhibit adequate organ function, particularly liver and bone marrow function. From a risk-vs-benefit standpoint, many oncologists make stronger recommendations for triplet therapy in those patients with high-volume disease (as defined by the CHAARTED trial as the presence of visceral metastases, or ≥4 bone metastases with at least one outside of the spine and pelvis).[5] The initial CHAARTED trial did demonstrate a greater effect on survival for ADT plus docetaxel in those patients with high-volume disease vs low-volume disease. However, exploratory subgroup analyses of both the PEACE-1 and ARASENS trials did not find significantly different mortality reductions for triplet therapy comparing high-volume vs low-volume disease. Despite similar hazard ratios, the results were more statistically significant for the high-volume patient

population.[17] NCCN Guidelines currently recommend both doublet therapy and triplet therapy as a category 1 option for patients with high-volume disease, as well as patients with low-volume but synchronous metastases.[11] In contrast, only doublet therapy is recommended for those patients with low-volume metachronous metastases.

Disclosures

Dr Lam has consulted for Bayer.

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A Shared-Care Approach to the Management of Patients With mHSPC: The Urology Perspective

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Defining Multidisciplinary Care

For me, multidisciplinary care often means getting on the phone and talking to my oncology colleagues. Moving forward, changes in the science will necessitate further involvement of different subspecialties. For example, as the indications for the use of radionucleotides broaden, greater consultation with radiation oncologists will be needed. An improved understanding of the use of genomic testing in prostate cancer will lead to greater involvement with geneticists.

Role of Multidisciplinary Care in the Management of Patients With mHSPC

The shared-care approach is very important in the management of patients with mHSPC. As an example, several new poly(ADP-ribose) polymerase (PARP) inhibitors recently have become available for the treatment of patients with mCRPC, and few urologists have experience with these agents. These treatments soon will be available in the mHSPC space. Involving our medical oncology colleagues who have experience with these agents and their unique

toxicity profiles is valuable, as is the involvement of geneticists who can aid in the identification of patients who might benefit from these novel therapies. Patients benefit from this multidisciplinary approach because it means they are getting the best chance for an optimal therapy that fits their individual needs and profile.

Unique Role of the Urologist in mHSPC Management

Urologists are the primary care provider for the vast majority of patients with mHSPC. This is particularly true for those patients with recurrent disease. Typically, patients with de novo elevated prostate-specific antigen levels and metastatic disease on imaging will be referred to a urologist for biopsy. After the biopsy results are available, that patient typically will have a conversation with the urologist who, if he or she is experienced in uro-oncology, will set out for them the landscape of available treatments.

Barriers to Treatment Using a Multidisciplinary Care Approach

Certainly there is a need to bridge the gap of collaboration between urologists and oncologists. Urologists will often send patients to their medical oncologist colleagues only when they develop advanced mCRPC, seeking help with these particularly challenging-to-treat patients. On the other hand, medical oncologists may refer patients suspected of having mHSPC to a urologist only for biopsy. Making the time for conversations between urologists and their medical oncologist colleagues can certainly enhance that collaboration in a way that goes beyond simply referring patients. Urologists and medical oncologists need to figure out a way to create a shared/team approach rather than silos of patients.

Disclosures

Dr Cahn has consulted for Johnson & Johnson.

A Shared-Care Approach to the Management of Patients With mHSPC: The Oncology Perspective

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Defining Multidisciplinary Care

The multidisciplinary approach is defined as using multiple specialists. For the management of a patient with mHSPC, these specialists can include urologists, medical oncologists, radiation oncologists, pathologists, and radiologists. We have at least one representative from every one of those disciplines in our weekly tumor boards, and often more than one, so these teams can become fairly large. As a result, our meetings tend to not be skewed by any one individual and allow for the presentation of multiple opinions and perspectives. This is particularly true within medical oncology. For example, I may be very focused on one aspect of a patient's case, whereas a different medical oncologist colleague may provide a different perspective. Even within pathology, where the default may be for a single individual to perform the histologic analysis, it can be helpful to have multiple pathologists with different backgrounds evaluate the tissue. These specialists can either concur or offer a different perspective.

Role of Multidisciplinary Care in the Management of Patients With mHSPC

The shared-care approach is particularly important for patients with mHSPC, where we have a lot of newer imaging modalities that are being used. In the past, imaging studies were limited to bone scans, positron emission tomography (PET)/CT scans, and MRI, and clinical decision-making based on these modalities was clear. With the advent of PET/prostate-specific membrane antigen (PSMA) scans, patient management decisions have become more challenging. We are detecting more cases

of advanced disease earlier than we would have otherwise.

This really does require a multidisciplinary approach, partly because this aids in the understanding of the extent of the disease. For example, if a patient with prostate cancer has just one involved lymph node, the disease is considered stage IV. But how we treat that individual is highly divergent compared with another patient who has stage IV disease and has extensive liver metastasis, retroperitoneal disease, or bone metastasis. When do we think about using radiotherapy? When do we think about using doublet therapy vs triplet therapy? When do we think about clinical trials for the hormone-sensitive setting? These are all factors that are evolving in real time. Thus, taking a multidisciplinary approach that incorporates opinions from all the experts to determine the best available therapy ensures the most reasonable and optimal treatment on an individual patient basis.

What this means in terms of patient outcomes is 2-fold. First, a multidisciplinary care approach means that there is automatically a second opinion from many different specialists across the board, without the patient having to go to another facility or institution. Second, patients can receive an improved delivery of care as well as access to the most advanced therapeutics. As a result, patients can benefit from the formation of an individualized plan of care based on the expertise of many physicians who are in that room or on that call.

Unique Role of the Medical Oncologist in mHSPC Management

The medical oncologist offers many perspectives to the multidisciplinary care team. Many newer therapies are available and in development for which medical oncologists can offer experienced opinions. This is particularly true in the case of managing toxicities, as many side effects are nuanced and their management can be quite challenging. Additionally, medical oncologists tend to have a deep understanding of genetic testing and genomic sequencing and can provide insight into their application to the different settings of metastatic prostate cancer.

Barriers to Treatment Using a Multidisciplinary Care Approach

In a true community setting, I think that one of the main barriers is that the clinicians making up the multidisciplinary team are not all under the same roof. This separation can trickle down to the patient, who may have to travel from a urology office to a medical oncology office and a radiation oncology office in order to gain these perspectives. This process is much easier in an academic setting because these teams tend to be colocated in the same or nearby buildings, allowing them to meet in one place at a given time.

One way to overcome this separation is for the clinicians to find a common ground, such as between medical oncology and urology. Historically, urologists were the primary specialists managing prostate cancer, with general medical oncologists brought in only at the salvage therapy or palliative therapy stage. That mindset needs to change, which will take time. From a medical oncology standpoint, I would urge my own colleagues to say, "Look, there's actually a lot that you can offer even earlier in the course of disease. Help your urology colleagues to manage these toxicities that you are well-versed in as well." I think this comanagement will lead to better patient outcomes.

Another issue is insurance. Because clinicians from different specialties tend to participate in separate practices, insurance coverage can vary. Fortunately, nurse navigators can help assist with deconflicting this, although it may not be the easiest challenge to overcome in many true community settings.

Disclosures

Dr Bupathi has received honoraria from Agendia, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Johnson & Johnson, Sumitovant, and Pfizer; has served in a consulting or advisory role to AstraZeneca, Bristol Myers Squibb, and Exelixis; and has served on the speakers' bureau of Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Exelixis, Johnson & Johnson, and Pfizer.

The Importance of the Shared-Care Approach When Triplet Therapy Is Selected in mHSPC: Q&A

Anthony P. Lam, MD, MHS; David J. Cahn, MD; and Manojkumar Bupathi, MD, MS

Dr Lam: After a patient is referred to an oncologist, when should they see their urologist again? What delineations exist to avoid redundancies?

Dr Bupathi: In the community, we certainly run into this problem where patients have to commute back and forth between the specialties. Patients always ask this—once they are referred to an oncologist, do they still need to see the urologist? When do they need to see the urologist? Some patients are of the opinion that this is redundant for them.

In our practice, patients with newly diagnosed metastatic disease will often be referred to medical oncology from their urologist. In these cases, it tends to be more of a second opinion needed. When I see these patients, I usually let them know that I reviewed their case with their urologist. In addition, I am often able to let them know that I have reviewed their imaging results at our tumor board and concur with the multidisciplinary team's decision. I then make sure they know that I consider them a patient of mine, meaning I am available to them in case they develop any issues. However, their urologist will be the primary point of their care. We generally set an appointment for a 6-month follow-up as a way to check in. I tell them that if they are doing well at that point they are not required to see me, but I want them to know they have that option in case any issues arise. My experience is that patients find reassurance in this approach.

Dr Cahn: To a large extent, I think this depends upon the expertise and interest of both the urologist and the oncologist in treating prostate cancer, as well as the relationship the urologist has with the oncologist.

Dr Lam: Does the urologist continue to be the primary caregiver in the case of a patient with mHSPC who is a candidate for triplet therapy?

Dr Cahn: Again, this is practice- and patient-dependent. I believe that all patients with newly diagnosed mHSPC should be provided an overview of the full gamut of care that they might expect to receive. This should include a discussion of triplet therapy. If I have a patient considering triplet therapy, I will generally initiate ADT and a novel hormonal agent and will arrange consultation with an oncologist in my area who is an expert in the treatment of prostate cancer. The majority of these patients will return to our clinic for ongoing care, but sometimes they will seek follow-up with the oncologist. I think that both scenarios are appropriate.

Dr Bupathi: In general, we will have an initial appointment with the patient during which we talk to them about the benefits and drawbacks of triplet therapy. If the patient elects to proceed with the triplet combination, we complete the docetaxel chemotherapy portion in our office. We continue to follow patients for 6 weeks after they finish their chemotherapy to ensure that there are no residual cytopenias or other significant toxicities that remain untreated. During that time, they will also see their urologist to begin treatment with the ADT and a second-generation antiandrogen.

Dr Lam: At your center, do urologists retain care of the patient until a patient develops mCRPC?

Dr Bupathi: In general, yes, the patient is referred to the medical oncologist as the primary provider when they have gone on to develop mCRPC. Now, if I have an amazing trial for mHSPC, I make sure the urologists know about it, and they often send some eligible patients my way to explore it as an alternative option.

Dr Cahn: In the vast majority of cases, yes. Sometimes a patient may already have a relationship with an oncologist—perhaps their wife or a relative was treated by that individual, and they will seek care with them. Aside from chemotherapy, our center offers the full spectrum of care for mHSPC, plus trials in the space.

Dr Lam: In community practice, have you seen a difference of opinion between urologists and oncologists in terms of determining which patients are candidates for triplet therapy?

Dr Cahn: I think it is fair to say that urologists have a bit of a jaundiced view toward chemotherapy. Although docetaxel is a very well tolerated chemotherapy, we tend to focus on the side effects of chemotherapy, and the fact that there are some ambiguities in the data supporting the use of docetaxel in mHSPC. The concept of identifying chemo-eligible candidates is a new challenge for urologists. Gaining more experience with these therapies, not only with toxicities but with outcomes, will affect how often we recommend them to our patients. But I do, again, believe that every patient should be made aware that triplet therapy is an option, assuming chemo-eligibility and appropriateness.

Dr Bupathi: To generalize, some community urologists may not be as familiar as oncologists with the toxicities of chemotherapy, and we can see that manifest as some hesitancy in terms of who should be getting treated with triplet therapy. There are chemotherapy toxicity tools that can be utilized.

It is important to remember that in patients where it may be questionable to begin chemotherapy, it remains an option to just start the patient on a doublet therapy, such as darolutamide plus ADT, and see how they do. If they do well, we have up to 12 weeks to get the patient started on chemotherapy. This means we can see how the first 6 weeks go, evaluate how they are doing, and then get them plugged into medical oncology.

Dr Lam: Who should be screening patients for triplet therapy: the urologist or the oncologist?

Dr Cahn: I think the correct answer here is, both. It is important for urologists to become aware of those patients who are eligible for chemotherapy and triplet therapy, meaning that they will be able to get through the treatment with minimal comorbidities and experience a survival and quality of life benefit.

Dr Bupathi: It really depends on the urologist, and it also depends on the patient's age and extent of disease. For example, a younger patient in their 50s or 60s with extensive disease will often be referred immediately from the urologist to begin triplet therapy. However, for an older patient in their 70s or 80s, this decision may not be as clear. For these patients, the urologist may ask me to evaluate and provide my opinion.

Overall, most physicians can evaluate a patient in terms of fitness regardless of their specialty. I often think of it as, if a patient can be safely operated on, then that patient is probably safe enough to get chemotherapy. Now, that is just an initial consideration—certainly other factors such as liver and kidney function tests must be evaluated, as well as things like concomitant medications.

Dr Lam: Is there anything you would like to add?

Dr Bupathi: Communication is probably one of the biggest things that can make patients get frustrated—"didn't they send you the records?," or "didn't he or she call you?," or "how do you not know?" I think communication is the key thing we can do to maintain that relationship from a patient standpoint as well as from a colleague standpoint. I text my urology colleagues multiple times throughout the day. I find that when I push these lines of communications, the patients are very happy. We are all on the same page, and the next visit goes by much more smoothly, and I already know the plan before I see the patient.

Dr Cahn: I agree, and I also think it is important to reemphasize the benefit that a patient can experience with collaborative care. There does seem to be some tension between the urology and oncology specialties. Some of these patients have had decades-long relationships with their urologist prior to seeking care for mHSPC. That said, that does not mean that the urologist is the best physician to treat that patient's prostate cancer. If the patient's urologist has expertise in treating advanced prostate cancer, then perhaps that patient should stay under their care. But we all need to keep open minds, and check our egos at the door to maintain a willingness to be collaborative. The patient must always come first.

Slide Library

Historical Treatment of mHSPC and the Introduction of Doublet Therapy

- ADT alone was the SOC for mHSPC prior to CHAARTED in 2013
- CHAARTED established that the addition of docetaxel to ADT improved OS[1,2]
- The LATITUDE, STAMPEDE, TITAN, ARCHES, and ENZAMET trials found that the addition of second-generation antiandrogens (abiraterone, apalutamide, and enzalutamide) to ADT demonstrated comparable OS benefit[3-7]

ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; SOC, standard of care.
1. Sweeney CJ et al. *N Engl J Med*. 2015;373(8):737-746. 2. Kyriakopoulos CE et al. *J Clin Oncol*. 2018;36(11):1080-1087. 3. Fizazi K et al. *N Engl J Med*. 2017;377(4):352-360. 4. James ND et al. *N Engl J Med*. 2017;377(4):338-351. 5. Chi KN et al. *N Engl J Med*. 2019;381(1):13-24. 6. Armstrong AJ et al. J Clin Oncol. 2022;40(15):1616-1622. 7. Davis ID et al. *N Engl J Med*. 2019;381(2):121-131.

Triplet Therapy for mHSPC

- Doublet therapy with either ADT plus docetaxel or ADT plus an antiandrogen remained the SOC for mHSPC until PEACE-1 and ARASENS published in 2022
- These studies each demonstrated that triplet therapy with ADT plus docetaxel plus a second-generation antiandrogen further improved OS compared with ADT plus docetaxel alone
- These results established triplet therapy as the new SOC regimen for mHSPC, as recommended by the NCCN and AUA[1,2]

ADT, androgen deprivation therapy; AUA, American Urological Association; mHSPC, metastatic hormone-sensitive prostate cancer; NCCN, National Comprehensive Cancer Network; OS, overall survival; SOC, standard of care.
1. National Comprehensive Cancer Network. Prostate Cancer. Version 4.2024. Updated May 17, 2024. Accessed October 6, 2024. 2. Lowrance W et al. *J Urol*. 2023;209(6):1082-1090.

Triplet Therapy: PEACE-1

- Open-label, randomized, active-controlled, phase 3 trial conducted at 77 sites across 7 European countries[1]
- 1173 patients randomized across 4 treatment arms: SOC (n=296), SOC + RT (n=293), SOC + abiraterone (n=292), and SOC + RT + abiraterone (n=291)
- The addition of of abiraterone to SOC led to an 18% reduction in the risk of death by any cause

RT, radiotherapy; SOC, standard of care.
1. Fizazi K et al. *N Engl J Med*. 2017;377(4):352-360.

Triplet Therapy: ARASENS

- International, randomized, double-blind, placebo-controlled, phase 3 trial[1]
- 1306 patients received ADT or orchiectomy and also received docetaxel. Patients were then randomized in a 1:1 ratio to darolutamide (n=651) or matched placebo (n=655)
- Risk of death significantly lower with the addition of darolutamide to ADT plus docetaxel (32.5% lower risk of death vs the placebo plus ADT plus docetaxel arm)

ADT, androgen deprivation therapy.
1. Smith MR et al. *N Engl J Med*. 2022;386(12):1132-1142.

Selecting Patients for Doublet vs Triplet Therapy

- FDA labeling allows doublet and triplet therapy for all patients with mHSPC
- At a minimum, all patients with mHSPC should be offered doublet therapy with ADT plus an antiandrogen
- To be considered for triplet therapy, patients should exhibit adequate organ function
- NCCN Guidelines recommend both doublet therapy and triplet therapy for patients with high-volume disease, as well as patients with low-volume but synchronous metastases[1]

ADT, androgen deprivation therapy; FDA, US Food and Drug Administration; mHSPC, metastatic hormone-sensitive prostate cancer; NCCN, National Comprehensive Cancer Network.
1. National Comprehensive Cancer Network. Prostate Cancer. Version 4.2024. Updated May 17, 2024. Accessed October 6, 2024.

Shared Care: The Urology Perspective

- Multidisciplinary care involves collaboration among urologists, oncologists, and other subspecialties like radiation oncologists
- The shared-care approach is crucial in managing patients with mHSPC, particularly in integrating new treatments like PARP inhibitors
- Urologists are the primary care provider for the vast majority of patients with mHSPC
- Making the time for conversations between urologists and medical oncologists can enhance collaboration

mHSPC, metastatic hormone-sensitive prostate cancer; PARP, poly(ADP-ribose) polymerase.

Shared Care: The Oncology Perspective

- The shared-care approach is particularly important for patients with mHSPC, where many newer imaging modalities are being used
- A multidisciplinary care approach means that there is automatically a second opinion from many different specialists
- Medical oncologists have particular experience in managing toxicities, and tend to have a deep understanding of genetic testing and genomic sequencing
- In a true community setting, the clinicians making up the multidisciplinary team are not all under the same roof and insurance coverage can vary

mHSPC, metastatic hormone-sensitive prostate cancer.

Referral of Patients From Urology to Oncology

- The urologist will often refer patients with newly diagnosed mHSPC to oncology for consideration of triplet therapy
- Referrals can depend on the interest and expertise of both the urologist and the oncologist in treating prostate cancer
- The medical oncologist often becomes the primary provider when a patient develops mCRPC, but this depends on the patient

mHSPC, metastatic hormone-sensitive prostate cancer.

Difference Between Urologists and Oncologists Regarding Triplet Therapy

- Urologists may be more concerned about the toxicities of chemotherapy
- Oncologists may have more experience managing the toxicities of chemotherapy, which may lead to less hesitancy regarding triplet therapy
- In patients where beginning triplet therapy may be questionable, it remains an option to start the patient on a doublet therapy and see how they do

Screening Patients for Triplet Therapy

- Both the urologist and the oncologist should screen patients for triplet therapy
- The urologist may immediately refer a younger patient for triplet therapy, and may ask the oncologist for their opinion regarding triplet therapy in an older patient
- Most physicians can evaluate a patient's fitness for treatment, taking into account factors such as liver function, kidney function, and concomitant medication use

For a free electronic download of these slides, please direct your browser to the following web address:

http://www.hematologyandoncology.net

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