AUA **Update Series** 2020

Lesson 6 Volume 39

The Evolving Treatment of Metastatic Hormone Sensitive Prostate Cancer*

Learning Objective: At the conclusion of this continuing medical education activity, the participant should be able to select an appropriate treatment plan for metastatic hormone sensitive prostate cancer based on currently approved combination chemohormonal therapeutic agents, and identify the mechanisms of action, side effects and appropriate indications in this setting.

Tariq A. Khemees, MD

Disclosures: Nothing to disclose

Urologic Oncology Fellow

Department of Urology

David F. Jarrard, MD

Disclosures: Nothing to disclose

Professor, Department of Urology

Associate Director, UW Carbone Cancer Center

Glenn Liu, MD

Disclosures: Nothing to disclose

Professor, Division of Hematology/Oncology

UW Carbone Cancer Center

and

The University of Wisconsin-Madison

Madison, Wisconsin

***This AUA Update addresses the Core Curriculum topic of Oncology - Adult and the American Board of Urology Module: Oncology, Urinary Diversion and Adrenal.**

This self-study continuing medical education activity is designed to provide urologists, Board candidates and/or residents affordable and convenient access to the most recent developments and techniques in urology.

Accreditation: The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation: The American Urological Association designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Other Learners: The AUA is not accredited to offer credit to participants who are not MDs or DOs. However, the AUA will issue documentation of participation that states that the activity was certified for *AMA PRA Category 1 Credit*™.

American Urological Association

Education and Research, Inc.
1000 Corporate Boulevard
Linthicum, MD 21090

Evidence-Based Content: It is the policy of the AUA to ensure that the content contained in this CME enduring material activity is valid, fair, balanced, scientifically rigorous, and free of commercial bias.

AUA Disclosure Policy: All persons in a position to control the content of an educational activity (i.e., activity planners, presenters, authors) provided by the AUA are required to disclose to the provider any relevant financial relationships with any commercial interest. The AUA must determine if the individual's relationships may influence the educational content and resolve any conflicts of interest prior to the commencement of the educational activity. The intent of this disclosure is not to prevent individuals with relevant financial relationships from participating, but rather to provide learners information with which they can make their own judgments.

Resolution of Identified Conflict of Interest: All disclosures will be reviewed by the program/course directors or editors for identification of conflicts of interest. Peer reviewers, working with the program directors and/or editors, will document the mechanism(s) for management and resolution of the conflict of interest and final approval of the activity will be documented prior to implementation. Any of the mechanisms below can/will be used to resolve conflict of interest:

- Peer review for valid, evidence-based content of all materials associated with an educational activity by the course/program director, editor and/or Education Conflict of Interest Review Committee or its subgroup.
- Limit content to evidence with no recommendations
- Introduction of a debate format with an unbiased moderator (point-counterpoint)
- Inclusion of moderated panel discussion
- Publication of a parallel or rebuttal article for an article that is felt to be biased
- Limit equipment representatives to providing logistics and operation support only in procedural demonstrations
- Divestiture of the relationship by faculty

Off-label or Unapproved Use of Drugs or Devices: The audience is advised that this continuing medical education activity may contain reference(s) to off-label or unapproved uses of drugs or devices. Please consult the prescribing information for full disclosure of approved uses.

Disclaimer: The opinions and recommendations expressed by faculty, authors and other experts whose input is included in this program are their own and do not necessarily represent the viewpoint of the AUA.

Release date: March 2020

Expiration date: March 2023

Key Words: prostatic neoplasms; receptors, androgen; neoplasms, hormone-dependent; docetaxel; antineoplastic agents, hormonal

INTRODUCTION

An estimated 174,650 cases of prostate cancer were projected to be diagnosed in the United States in 2019, resulting in an estimated 31,620 deaths.[1] While the majority of newly diagnosed prostate cancers are clinically localized, the number of patients with de novo metastatic disease has been increasing, with an overall incidence of around 7% reported in 2013.[2] The overall 5-year survival rate for PC is 98.2%, while metastatic hormone sensitive prostate cancer carries a 5-year survival rate of only 30%. However, recent developments targeting this disease space have led to significant improvements in cancer specific survival.

mHSPC is heterogeneous with clonal cell populations including androgen receptor positive and negative cell subsets. Since androgen deprivation therapy was first described by Huggins et al in 1941, it has been the foundational approach for treatment of newly diagnosed metastatic PC.[3, 4] ADT for mHSPC leads to initial disease regression and stabilization but a clonal selection of cells capable of surviving testosterone withdrawal results.[5] Until recently cases of mHSPC would rapidly progress to castration resistant prostate cancer. However, with the introduction of newer therapeutic agents the time to castration resistance state has been prolonged.[6] Patients with metastatic CRPC have significant deterioration in quality of life and invariably die of the disease.[7]

Efforts directed at improving response to ADT and decreasing treatment related side effects have been an area of ongoing research. While multiple approaches have been explored, including the use of intermittent androgen deprivation therapy, addition of antiandrogens to medical or surgical castration and use of antiandrogens as monotherapy, none of these approaches results in meaningful improvements in 5-year survival beyond several months.[8] Despite these discouraging results, treatment continues to evolve. Recently there has been a major paradigm shift toward application of either cytotoxic chemotherapy or combination therapies using androgen signaling inhibitors at the initiation of ADT to delay progression to the lethal CRPC state.

Recently, there have been several phase III clinical trials evaluating combination therapy for mHPSC. The addition of docetaxel at initiation of ADT for mHSPC was recently evaluated in GETUG-AFU (Groupe d'Etude des Tumeurs Uro-Genital and Association Française d'Urologie) 15, a randomized phase III trial comparing hormonal treatment with and without docetaxel in patients with metastatic prostate cancer; [9, 10] CHAARTED (ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer);[11] and STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy).[12] CHAARTED and STAMPEDE were positive and indicated markedly improved overall survival when administering early chemohormonal therapy for mHSPC.

In addition, 3 large phase III clinical trials explored the combination of abiraterone and enzalutamide (androgen signaling inhibitors) with ADT for treating mHSPC.[13-15] LATITUDE is a randomized, double-blind, comparative study of abiraterone acetate plus low dose prednisone plus ADT vs ADT alone in newly diagnosed subjects with high risk, metastatic hormone naïve prostate cancer.[13] In the abiraterone arm of STAMPEDE abiraterone was assessed in patients with prostate cancer not previously treated with hormone therapy.[14] ARCHES is a phase III study of ADT administered with enzalutamide or placebo in patients with mHSPC.[15] All 3 trials of oral agents resulted in improved survival when combining androgen signaling inhibitors with ADT for mHSPC. In this Update we review the recent chemohormonal and combination trials that have driven a change in the paradigm for treatment of mHSPC. We will also examine the clinical applicability to current practice as well as discuss ongoing clinical trials and future directions.

CHEMOHORMONAL THERAPY TRIALS

Docetaxel chemotherapy was initially approved for the treatment of metastatic CRPC in 2004 after results from 2 phase III trials indicated 1.9 and 2.4-month improvements in survival.[16, 17] Since then, emerging data have suggested that adding docetaxel to ADT earlier in the disease process may be a more effective strategy for mHSPC. The hypothesis behind earlier application of combined cytotoxic chemotherapy and ADT has been that some degree of prostate cancer cell resistance to ADT is already present at diagnosis and is proportional to the disease burden. Chemotherapy may lead to elimination of the hormone resistant clones, prolonging time to progression to CRPC. Eigl et al applied this combination strategy and found that engrafted mice receiving paclitaxel at the time of ADT exhibited a delayed median time to progression compared to those treated with sequential castration and chemotherapy.[18] In addition, Zhu et al observed that taxanes blocked microtubule mediated AR nuclear localization, further shutting down AR signaling pathways.[19] These studies provided the basis for the investigation of a synergistic effect of taxanes and ADT. Applying cytotoxic chemotherapy earlier in the disease process may also expand the number of eligible patients, since once progression to CRPC has occurred some men become too frail and may miss the opportunity to receive potent chemotherapy.[20]

GETUG-AFU15. In one of the earliest phase III open-label trials comparing ADT alone to ADT combined with docetaxel a total of 385 men with mHSPC were enrolled at 30 centers in France and Belgium between 2004 and 2008.[9] Patients were required to have biopsy proven PC with radiographic evidence of metastatic disease, good performance status (Karnofsky score ≥70) and a minimum life expectancy of 3 months. Androgen deprivation was achieved by bilateral orchiectomy or luteinizing hormone-releasing hormone analog alone or in combination with steroidal antiandrogens. A dose of 75 mg/m^2 docetaxel was given every 3 weeks for a maximum of 9 cycles.

The trial primary end point was OS, and secondary end

ABBREVIATIONS: ADT (androgen deprivation therapy), AR (androgen receptor), CRPC (castration resistant prostate cancer), HVD (high volume disease), LVD (low volume disease), mHSPC (metastatic hormone sensitive prostate cancer), OS (overall survival), PC (prostate cancer), PFS (progression-free survival), PSA (prostate specific antigen), RT (radiotherapy)

points were clinical PFS and biochemical PFS. Clinical PFS was defined as progression of preexisting lesions according to RECIST (Response Evaluation Criteria in Solid Tumors) or the appearance of new bone lesions, whichever occurred first. RECIST provide definitions of minimum size of measurable lesions, and instructions on how many lesions to follow (up to 10, maximum of 5 per organ site) and use of unidimensional, rather than bidimensional, measures for overall evaluation of tumor burden.[21] Biochemical PFS was defined as a prostate specific antigen decline of at least 50% and progression as a PSA increase of at least 50% above the nadir with an absolute increase of 5 ng/ml. For patients without PSA nadir less than 50% progression was defined as a PSA increase of at least 25% above the nadir.

Median number of docetaxel cycles received was 8, and fewer than half of the patients received 9 cycles.[9] At the initial reporting of the trial results (median follow-up 50 months) there was no significant difference in OS between the 2 arms (58.9 months for the chemohormonal arm vs 54.2 months for the ADT only arm, HR 1.01, 95% CI 0.75–1.36). However, biochemical PFS and clinical PFS were significantly longer in the chemohormonal arm vs the ADT only arm (22.9 vs 12.9 months, HR 0.72, 95% CI 0.57–0.91, p=0.005 and 23.5 vs 15.4 months, HR 0.75, 95% CI 0.59–0.94, p=0.015), respectively.

In a subsequent post hoc analysis of GETUG-AFU15 with extended median follow-up to 83.9 months Gravis et al reported a 20% improvement in OS for the chemohormonal arm, which did not quite reach statistical significance (HR 0.88, 95% CI 0.68–1.14, p=0.3).[10] The authors also stratified patients based on disease volume at the time of enrollment (given the recent positive CHAARTED results) where high volume disease was defined as the presence of visceral metastases and/or at least 4 bone lesions, including at least 1 lesion in any bony structure beyond the spine or pelvis. Other patients were considered to have low volume disease. This analysis again failed to reach statistical significance for OS in patients with HVD on docetaxel plus ADT compared to those with HVD on ADT alone (39.8 months vs 35.1 months, HR 0.78, 95% CI 0.56–1.09, p=0.14). Gravis et al concluded that adding docetaxel to ADT did not improve OS compared to ADT alone, although clinical PFS and biochemical PFS favored the docetaxel-ADT combination.[10]

CHAARTED. The ECOG-ACRIN Cancer Research Group was the first to report that the combination of ADT with 6 cycles of 75 mg/m^2 docetaxel every 3 weeks improved the outcomes of men with mHSPC.[11] A total of 790 patients were randomized to receive combination ADT and docetaxel or ADT alone. Patients were stratified based on multiple parameters, including age (<70 vs ≥70 years), ECOG (Eastern Cooperative Oncology Group) performance status (0 or 1 vs 2), prior use of zoledronic acid or denosumab, planned use of combined androgen blockade for >30 days, duration of prior ADT use (<12 vs ≥12 months) and tumor volume (HVD vs LVD). The primary end point of the trial projected median OS to be 33.3% longer among patients receiving docetaxel added to ADT.

Mean follow-up duration was 28.9 months, with 136 deaths in the ADT alone group and 101 deaths in the combination group. In both groups approximately 65% had HVD and 60% had a Gleason score of 8 or higher. **Median OS was 57.6 months in the chemohormonal arm versus 44 months in the ADT alone arm, thus conferring an improvement of 13.6 months in OS (HR 0.61, 95% CI 0.47–0.80, p <0.001) for combination therapy.** The improvement in OS was even more pronounced in the HVD subgroup (49.2 months vs 32.2 months, HR 0.60, 95% CI 0.45–0.81, p <0.001). In contrast, there was no statistically significant difference in OS with the addition of docetaxel in the LVD group (median OS not reached in either group, HR 0.6, 95% CI 0.32–1.13, p=0.11). In addition to OS, the median time to CRPC was also prolonged in the chemohormonal arm compared to the ADT alone arm (20.2 months vs 11.7 months, HR 0.61, 95% CI 0.51–0.72, p <0.001), as well as the median time to clinical progression (33 months vs 19.8 months, HR 0.61, 95% CI 0.50–0.75, p <0.001), respectively.

The results from CHAARTED were recently updated with a longer duration of follow-up (53.7 months).[22] The initial trial results were confirmed (OS 57.6 months for ADT plus docetaxel vs 47.2 months for ADT alone, HR 0.73, range 0.59–0.89, p=0.0018). Patients with HVD benefited more from the addition of docetaxel (OS 51.2 months vs 34.4 months, HR 0.63, range 0.50 to 0.79, p <0.0001), while those with LVD again did not experience any survival benefit by adding docetaxel (OS 63.5 months vs not reported for ADT alone, HR 1.04, range 0.70–1.55, p=0.86). **Kyriakopoulos et al concluded that the addition of 6 cycles of docetaxel to ADT during the initiation of treatment for high volume mHSPC was associated with significant improvement in OS, longer time to development of CRPC, better PSA control at 1 year of follow-up and longer cancer specific survival.**

STAMPEDE. This unique phase II/III trial was designed to investigate new agents under the umbrella of a single trial.[12] Additional arms are added to STAMPEDE as new approaches evolve.[23] The docetaxel plus ADT trial enrolled patients with newly diagnosed metastatic, node positive PC or high risk locally advanced disease with at least 2 features from T3/4 disease, Gleason score 8-10 and PSA ≥40 ng/ml.[12] Patients with relapsing PC previously treated with radical surgery and/or radiotherapy were also included in the trial. The primary end points were OS and failure-free survival, defined as time from randomization to onset of biochemical failure, local or systemic progression, or death from PC. A total of 2962 previously untreated patients with metastatic or non-metastatic PC were randomly assigned in a 2:1:1:1 ratio to receive ADT only (1184), ADT plus zoledronic acid (593), ADT plus docetaxel (592) or ADT plus zoledronic acid and docetaxel (593). Docetaxel was given in 75 mg/m^2 dose along with prednisolone for six 3-weekly cycles. Trial therapy was discontinued in the event of intolerable side effects or disease progression.

After a median follow-up of 43 months the primary end point of OS showed a significant 10-month improvement for patients treated with docetaxel plus ADT vs ADT alone (81 months for the combination arm vs 71 months for the ADT only arm, HR 0.78, 95% CI 0.66–0.93, p=0.006). OS also improved in patients treated with docetaxel plus zoledronic acid vs neither docetaxel nor zoledronic acid (76 months vs 71 months, HR 0.82, 95% CI 0.69–0.97, p=0.022).[12] Maximum benefit was seen in the subset of patients with metastases, with a 15-month improvement in OS (60 months vs 45 months; HR 0.76, 95% CI 0.62–0.92, p=0.005). The secondary end points of median failure-free survival, 5-year failure-free survival and time to first skeletal related events were improved in the chemohormonal arm vs the ADT only arm (37 months and 38% vs 20 months and 28%).

SAFETY PROFILES AND OUTCOMES COMPARISON

A summary of the toxicities and safety profiles for the 3 chemohormonal trials is shown in table 1. In GETUG-AFU15 and CHAARTED side effects were more common in the chemohormonal therapy arm. The most common grade ≥3 adverse events were neutropenia, febrile neutropenia and fatigue. Diarrhea, stomatitis, and motor and sensory neuropathy developed in less than 1% of the population in CHAARTED. In contrast, STAMPEDE had higher toxicity in the chemohormonal therapy arm vs ADT alone with grade ≥3 adverse events reported in 52% vs 32% of patients mostly in the first 6 months of therapy and due to toxicity related to docetaxel dose. At 1 year after treatment an analysis of 1998 cases with available profiles revealed a balanced rate of grade ≥3 adverse events of 10% in each of the STAMPEDE arms. Two deaths were recorded in the chemohormonal therapy arm and 72 patients (13%) discontinued treatment. In all of these studies grade ≥3 adverse events were negligible in the ADT only arm.

Importantly, quality of life assessment was done 3, 6, 9 and 12 months after randomization in CHAARTED using the FACT (Functional Assessment of Cancer Therapy)-Prostate score.[24] Although quality of life scores with docetaxel decreased at 3 months, they were better at 12 months in patients who received docetaxel plus ADT vs ADT alone. Thus, the shorter term increased risk of side effects due to chemohormonal therapy was offset by an improved quality of life.

Response rates and outcomes demonstrated some variation between the trials. The 10-month improvement in median OS in STAMPEDE supported the CHAARTED findings that the addition of docetaxel to standard ADT alone results in improved survival for men presenting with mHSPC. However, GETUG-AFU15, which also compared chemohormonal therapy to ADT alone, did not indicate improved outcomes. Patient characteristics appear to have differed between trials. In GETUG-AFU15 the control arm receiving ADT alone had better overall survival compared to the control arms of CHAARTED and STAMPEDE (54 months in GETUG-AFU15 vs 44 months in CHAARTED and 45 months in STAMPEDE metastatic subgroup), suggesting differences in the baseline characteristics of these patients.

Among these 3 phase III trials CHAARTED used stratification based on tumor volume to show statistically significant improvement in OS for patients with HVD but not for the LVD group. A reason GETUG-AFU15 may have indicated no improvement in survival was that 52% of patients had LVD.[10] However, in a post hoc analysis of GETUG-AFU15 focusing on patients with HVD the ADT plus docetaxel arm experienced a non-significant 9.6-month improvement in median OS compared to the ADT only arm (p=0.3). In a recent meta-analysis of aggregate data on patients with HVD from CHAARTED and GETUG-AFU15 Gravis et al noted consistent effects and improved OS in those receiving docetaxel with ADT, with a pooled HR of 0.68 (95% CI 0.56–0.82, p <0.001).[25] They concluded that chemohormonal therapy is more likely to benefit patients with HVD, whereas patients with LVD have longer survival with ADT alone and docetaxel toxicity risks may outweigh the benefits. To date, no comparisons based on tumor volume have been reported for STAMPEDE.

The timing of chemotherapy initiation in patients with mHSPC may also have had a role in outcomes, although this effect is unclear. Each trial that indicated a survival advantage had a time delay between the start of ADT and chemotherapy, including 120 days in CHAARTED and 90 days in STAMPEDE. In GETUG-AFU15 patients were required to enroll within 2 months of starting ADT. In contrast, in animal models a closely timed sequence of chemohormonal therapy appears to induce maximum synergy by targeting hormone resistant PC cells when they are most vulnerable.[18] Increased toxicity has previously been suggested when ADT and docetaxel are started concurrently.[26] This timing may be partly due to decreased hepatic clearance of docetaxel before castration.[27]

Finally, the increased survival in CHAARTED and STAMPEDE could be confounded by treatment with newer antiandrogens. GETUG-AFU15 was the first of these reported trials and most participants had CRPC at a time when neither abiraterone nor enzalutamide was widely available. However, the majority of CHAARTED cases were also accrued before 2011, when abiraterone was initially approved.

ADT COMBINED WITH ANDROGEN SIGNALING INHIBITORS

Abiraterone is an androgen axis inhibitor, which decreases androgen biosynthesis by inhibiting the steroidal enzyme CYP17A1, and causes suppression of androgen synthesis in testicular, adrenal and prostatic tumor tissues. Its active D4A metabolite contributes to its antitumor effects through blockade of multiple steroidogenic enzymes and antagonism of the androgen receptor.[28] Approval of this drug in the pre-chemotherapy and post-chemotherapy CRPC states led to investigations of its applicability to an earlier disease state.[29] Resistance to ADT is partly driven by upregulation of AR signaling through adrenal androgen production, intratumoral testosterone production and modification of androgen receptors.[30] The neoadjuvant combination of abiraterone plus prednisone and ADT markedly reduced the tumor burden in men with newly

Table 1. Summary of toxicities in phase III chemohormonal trials

	GETUG-AFU15	CHAARTED	STAMPEDE
No. adverse events (%):	72 (38)	114 (29)	288 (52)
Neutropenia	40 (21)	47 (12.1)	84 (15)
Febrile neutropenia	6 (3)	24 (6.1)	66 (12)
Abnormal liver function tests	3 (2)	-	-
Fatigue	-	16 (4.1)	16 (4.1)
No. treatment related deaths (%)	4 (2)	1 (0.2)	2 (0.3)

diagnosed, high risk, localized PC, suggesting a potential role for inhibiting extragonadal androgen biosynthesis before the emergence of resistant clones.[31] These findings led to 2 randomized phase III trials testing the efficacy of abiraterone and ADT in mHSPC.

Enzalutamide is a second generation antiandrogen with multiple sequential actions in the AR pathway, including competitive inhibition of androgen binding to receptors, and inhibition of AR nuclear translocation and DNA interaction.[32] Enzalutamide has shown significant survival benefits in patients with metastatic CRPC before and after treatment with docetaxel.[33, 34] These results paved the way for studies investigating enzalutamide for the treatment of mHSPC in phase II and subsequent large phase III clinical trials.[15, 35, 36]

LATITUDE. This double-blind, placebo controlled, phase III trial was performed at 235 sites in 34 countries in Europe, the Asia-Pacific region, Latin America and Canada.[13] Eligible patients had high risk mHSPC documented by a positive bone scan or metastatic lesions on computerized tomography or magnetic resonance imaging at the time of diagnosis, according to RECIST. In addition, patients were required to have at least 2 of the 3 high risk factors associated with poor prognosis, which were Gleason score ≥8, at least 3 bone lesions and/or presence of measurable visceral metastasis. Patients were excluded from the trial if they had received previous chemotherapy or radiation therapy, or had undergone surgery for metastatic PC, with the exception of 3 months or less of androgen deprivation therapy. The 2 primary efficacy end points were OS and radiographic PFS.

A total of 1199 patients were randomly assigned to receive a combination of ADT plus 1000 mg abiraterone plus 5 mg prednisolone or ADT plus placebo.[13] **After a planned median follow-up of 30.4 months and 406 deaths, the median OS was significantly longer in the abiraterone group than in the placebo group (not reached vs 34.7 months, respectively, HR for death 0.62, 95% CI 0.51–0.76, p <0.001). Median radiographic PFS was 33 months in the abiraterone group and 14.8 months in the placebo group (HR for disease progression or death 0.47, 95% CI 0.39–0.55, p <0.001).** Significantly better outcomes in all secondary end points were observed in the abiraterone group, including time until pain progression, next subsequent therapy for prostate cancer, initiation of chemotherapy and PSA progression (p <0.001 for all comparisons), along with next symptomatic skeletal events (p=0.009). Given these results, there was a unanimous recommendation by the trial independent data and safety monitoring committee that the trial be unblinded and crossover be allowed for patients in the placebo group to receive abiraterone.

Abiraterone arm of STAMPEDE. This study used a multistage, multi-arm setting similar to that of previous trials to examine the combination of abiraterone and prednisone at the time of ADT initiation for patients with newly diagnosed metastatic, node positive or high risk locally advanced PC.[14] Cases of relapse with high risk features after previous radical surgery or RT were also included in the trial. A total of 1917 patients were enrolled, of whom 52% had metastatic disease, 20% node positive or node indeterminate non-metastatic disease and 28% node negative, high risk non-metastatic disease. Patients were randomized to receive ADT alone or ADT plus abiraterone. This trial also mandated RT in patients with node negative non-metastatic disease and provided the option of RT for those with node positive non-metastatic disease. Treatment continued until PSA, radiological or clinical progression. In patients in whom RT was planned treatment was administered for 2 years or until any type of progression occurred, whichever came first.

Results indicated improved OS at 3 years in the combination therapy group, with a 37% reduction in relative risk compared to ADT alone (death HR 0.63, 95% CI 0.52–0.76, p <0.001). Failure-free survival showed a 71% relative risk reduction (treatment failure HR 0.29, 95% CI 0.25–0.34, p <0.001). The rate of reported grade ≥3 adverse events was 47% in the combination group and 33% in the ADT only group. There were 12 grade 5 adverse events, of which 9 occurred in the combination group. Additional adverse events over and above the control therapy were hypertension, mild increases in aminotransferase levels and respiratory disorders.

ARCHES. In this multinational, double-blind, phase III study 1150 patients with mHSPC were randomized to 160 mg enzalutamide daily plus ADT (574 patients) or placebo plus ADT (576) stratified by disease volume (CHAARTED criteria) and prior docetaxel therapy.[15] The primary end point was radiographic PFS assessed centrally or death within 24 weeks of treatment discontinuation. Secondary end points included time to PSA progression, PSA and radiographic responses, and OS. Treatment continued until disease progressed or unacceptable toxicity occurred. Overall, 67% of patients had distant metastasis at initial diagnosis, 63% had HVD and 18% had received prior docetaxel therapy. Median follow-up was 14.4 months.

The combination of enzalutamide and ADT significantly improved radiographic PFS (HR 0.39, 95% CI 0.30–0.50, p <0.001). Similar significant improvements in radiographic PFS were reported in prespecified subgroups of disease volume, pattern of spread, region and prior docetaxel therapy (HRs 0.24–0.53). Secondary end points improved with enzalutamide plus ADT. At the time these results were reported the OS data were still immature. Grade 3–4 adverse events were reported in 23.6% of the enzalutamide arm vs 24.7% of the placebo arm, with no unexpected adverse events. Armstrong et al concluded that enzalutamide plus ADT significantly improved radiographic PFS and other efficacy end points compared to placebo plus ADT in men with mHSPC, with a preliminary safety analysis that appears consistent with the safety profile of enzalutamide in previous CRPC clinical trials.[15]

PATIENT SELECTION FOR COMBINATION THERAPY

In light of the published results from the aforementioned clinical trials, combined therapy now represents the standard of care for men with mHSPC. ADT plus docetaxel can be offered to patients with mHSPC who are eligible for chemotherapy, particularly those with a high metastatic burden or a rapid pace of disease (see figure). Barriers to docetaxel use include advanced age, poor performance status, comorbidities and patient preference. Hematological side effects, neuropathy and fatigue are more common with chemohormonal therapy than with ADT alone, and chemotherapy related deaths, although rare (1% to 3%), were seen in all 3 trials. In CHAARTED and the docetaxel arm of STAMPEDE an 18-week course of therapy (6 cycles, each consisting of 3 weeks) was administered, and 26% and 23% of patients, respectively, in the chemohormonal arms did not complete the full course of therapy.[11,12] This issue becomes even more important in community practice,

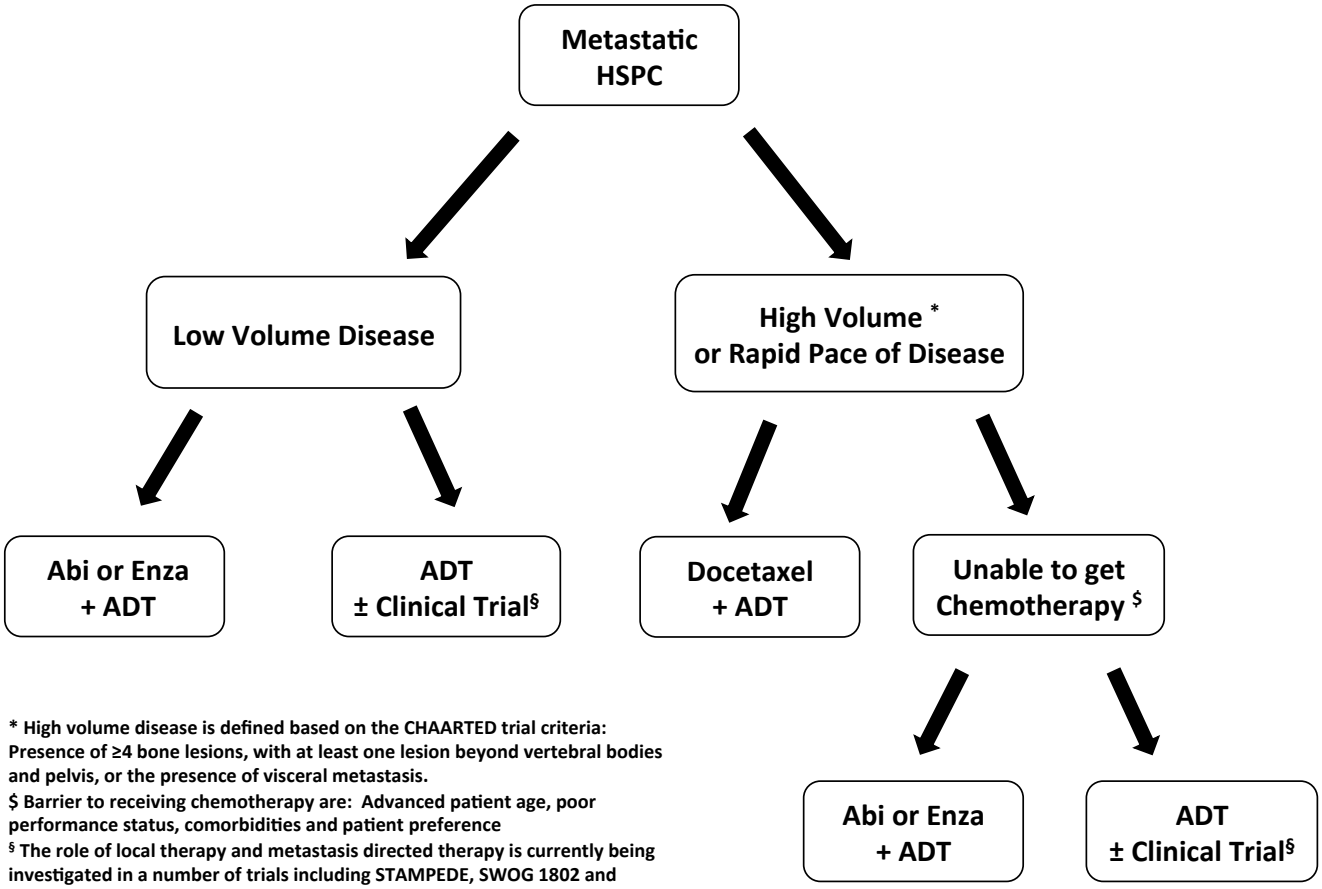

Figure. Proposed treatment algorithm for metastatic hormone sensitive prostate cancer (*HSPC*) based on currently approved therapies from most recent clinical trials. *Abi*, abiraterone. *Enza*, enzalutamide.

where patients with mHSPC are commonly older than those enrolled in CHAARTED and STAMPEDE.[37]

Abiraterone and enzalutamide have different side effect profiles than docetaxel. Furthermore, being oral agents, they are easier to administer in the office. In fact, based on data from a recent LUGPA (Large Urology Group Practice Association) annual meeting, more urology practices in the United States are now dispensing these medications to patients via a buy and bill model.[38] This strategy allows greater continuity of care and may improve patient adherence to therapy, reducing the barriers and abandonment rates by providing an easier path to treatment.

In LATITUDE 88% of patients completed therapy without a dose modification, with 63% reporting grade 3 or 4 adverse events in the abiraterone group compared to 48% in the placebo group.[13] In the abiraterone arm of STAMPEDE only a few patients discontinued therapy due to toxicity, and toxicity rates were similar to those seen in LATITUDE (47% for combination therapy vs 33% for placebo).[14] Most of the adverse events were related to mineralocorticoid side effects, including hypertension, fluid retention and hypokalemia. Altered liver transaminases also occur more frequently with abiraterone and must be monitored. A meta-analysis of these 2 trials revealed a threefold increase in grade 3 or higher cardiac and hepatic events, and a twofold increase in grade 3 or higher vascular events in the abiraterone combination group.[39] Enzalutamide side effects seen in ARCHES included grade 3–4 adverse events in a quarter of the patients.[15] In another meta-analysis of the safety profile of these combination therapies enzalutamide had no association with all grade or grade ≥3 cardiovascular events, while it was associated with about a 30% increased risk of all grade fatigue.[40] While rare (<1%), the risk of seizure should be monitored and enzalutamide should be avoided in patients with a history of seizure.

Quality of life and side effects are important to consider in most men who are otherwise asymptomatic. In patients with LVD or significant comorbid conditions ADT alone remains an appropriate treatment option and should be discussed during individualized counseling. The duration of treatment with abiraterone is long at 2 years or more, which raises concerns about safety, especially in patients with risk factors for cardiovascular disease and stroke. STAMPEDE excluded men with a significant cardiac history, limiting generalizations of benefit or toxicity in those patients. A short course of docetaxel might be preferred in patients with good performance status to avoid the long-term effects of steroids and the toxicity associated with abiraterone, including hyperglycemia, cardiovascular risks, and osteopenia and/or osteoporosis. The requirement for concurrent prednisone with abiraterone can limit its use in patients with brittle diabetes, chronic gastric ulcers or infection.

This information raises the question of the ideal therapeutic agent in the setting of mHSPC. To date, a direct head-to-head comparison of ADT plus abiraterone, enzalutamide and docetaxel has not been performed, limiting the ability to

generate conclusions. A recent analysis of STAMPEDE indicated that contemporaneously randomized patients showed no significant differences in overall or PC specific survival or symptomatic skeletal events between these therapies.[41] Interestingly, failure-free survival favored abiraterone, likely reflecting the PSA response and the mechanism of action. The docetaxel cohort had a more durable survival after failure. Toxicity was similar between the arms, with an 11% prevalence of grade 3 or 4 toxicity at 1 year. The question has been raised whether a combination of abiraterone plus docetaxel plus ADT may lead to an additive benefit in survival. Data on this issue will emerge from PEACE1 (Phase III Study for Patients with Metastatic Hormone-naïve Prostate Cancer), which is currently under way.

The cost of long-term treatment with abiraterone and enzalutamide is also a factor that physicians and patients should consider before starting therapy. While the cost of docetaxel for a 6-cycle course is estimated to be about $20,000, the cost of abiraterone for a 2-year course can exceed $120,000 per patient. The cost is even higher for treatment with enzalutamide.[42, 43] While cost analyses have been completed for abiraterone and enzalutamide in men with CRPC, to our knowledge they have not been reported in the hormone sensitive prostate cancer setting. Given the extended treatment duration with these medications in patients with hormone sensitive prostate cancer, often exceeding 2 years, the potential costs can be significant. The fluid nature of prescription drug coverage across different insurers, especially for oral agents, has made it difficult to predict year to year costs of these agents. It is noteworthy that patent protection for abiraterone acetate ended in 2018, which may impact the cost of this agent. Drug coverage represents a new world for many prescribers, in which monitoring patient costs for these agents is a critical issue requiring close collaboration with oncology pharmacists. The emergence of new assistance programs for these expensive therapies requires dedicated staff to guide patients through the application process.

FUTURE DIRECTIONS

There has been a paradigm shift in the therapeutic approach to mHSPC with recently published phase III studies confirming a survival advantage with chemohormonal and combination therapies. Furthermore, there are multiple ongoing phase III trials investigating other combined agents (table 2). The addition of docetaxel to ADT is now the standard of care as reflected by the updated NCCN® (National Comprehensive Cancer Network®) guidelines for men with mHSPC and LVD.[44] Cabazitaxel has proven efficacy in advanced CRPC and is most commonly used after docetaxel failure.[45] Cabazitaxel with ADT for mHSPC is being examined in an ongoing randomized phase III trial (SensiCab, NCT01978873). Other validated chemotherapy agents active in CRPC will likely be applied earlier in the disease course in the future based on the findings of CHAARTED and other trials.

Apalutamide, a potent antiandrogen similar to enzalutamide in its action, was recently approved for treatment of non-metastatic CRPC with rapidly rising PSA in patients on ADT.[46] The use of apalutamide for mHSPC during a phase II trial demonstrated a durable PSA response and safety, with 89% of patients having ≥50% PSA decline at 12 weeks, which was the primary end point, and median time to PSA progression was 24 months.[47] A phase III trial comparing apalutamide plus ADT to ADT alone (TITAN, NCT02489318) in the setting of mHSPC is ongoing. Orteronel is a selective non-steroidal inhibitor of 17,20 lyase, a key enzyme in androgen synthesis (similar to abiraterone). This agent has shown significant activity in the setting of CRPC.[48] A phase III trial comparing orteronel plus ADT to bicalutamide plus ADT (S1216, NCT01809691) is currently under way. Combination therapy with these additional androgen axis inhibitors is expected to contribute to the evolving landscape of mHSPC management.

The synergistic combination of less toxic agents that take advantage of metabolic changes occurring in susceptible PC cells after ADT has shown promise. Metformin for advanced

Table 2. Selected ongoing clinical trials of combination therapy with ADT for metastatic hormone sensitive prostate cancer

Trial Name	Trial ID	Trial Type	No. Pts (accrued or planned)	Intervention	Primary End Point	Estimated Completion
TITAN	NCT02489318	Hormonal	1000	ADT+apalutamide vs ADT+placebo	OS+radiographic PFS	2020
SWOG S1216	NCT01809691	Hormonal	1304	ADT+orteronel vs ADT+bicalutamide	OS	2022
ENZAMET	NCT02446405	Hormonal	1125	ADT+enzalutamide vs ADT+nonsteroidal anti-inflammatory	OS	2020
STAM-PEDE:	NCT00268476				OS	2020
Arm J		Hormonal	914	ADT vs ADT+abiraterone +enzalutamide		
Arm K		Metabolic	Not reported	ADT vs ADT+metformin		
PEACE1	NCT01957436	Chemo-hormonal	1168	ADT±docetaxel±abiraterone ±radiation	OS+radiographic PFS	2018
ARASENS	NCT02799602	Chemo-hormonal	1303	ADT+docetaxel+ darolutamide	OS	2022

hormone sensitive prostate cancer is gaining momentum in this realm. This oral glyburide effects systemic metabolic changes and directly acts on tumor cells by inhibiting the respiratory mitochondrial electron transport chain.[49] This action results in altered gluconeogenesis and decreased glucose uptake, as well as activation of AMPK, which is important in cell survival. Metformin also inhibits fatty acid synthesis, lipid peroxidation and the Krebs cycle, which are crucial for PC cell survival.[50] Finally, metformin represses AR mediated signaling in hormone sensitive cell lines,[51] and enhances the antiproliferative and apoptotic effects of the antiandrogen bicalutamide.[52] In a recently published retrospective study of more than 87,000 patients who were placed on ADT for advancing PC those receiving metformin had improved overall and cancer specific survival, and reduced skeletal metastases compared to men with diabetes on insulin and those without diabetes.[53] Metformin is currently being examined prospectively in combination with ADT in arm K of STAMPEDE.

The concept of local therapy for the primary tumor in mHSPC has been supported by several retrospective studies indicating better overall and disease-free survival with cytoreductive prostatectomy compared to RT, brachytherapy or no surgical treatment, with optimal benefit seen in cases of M1a disease.[54-56] Local therapy for metastatic disease is increasingly relevant given the improved length of survival for patients with CRPC in the modern era. Results from the recent HORRAD trial, which compared ADT with radiotherapy to ADT alone in men with metastatic PC, suggest that radiotherapy to the primary tumor may offer an OS advantage for patients with low volume disease.[57] These results were also supported by the recent findings in arm H of STAMPEDE (ADT plus radiotherapy).[58] A subgroup analysis of men with low volume disease according to CHAARTED criteria revealed that those receiving primary site RT had better OS compared to those who did not (81% vs 73%, respectively, HR 0.68, 95% CI 0.52–0.90, p=0.007). SWOG 1802, which is an ongoing randomized, phase III trial of standard systemic therapy with vs without definitive treatment of the primary tumor (surgery or radiation) in mHSPC, will potentially provide insights into cytoreductive treatment in addition to systemic therapy for patients with metastatic PC.[59] These trials will help stratify patients with metastatic disease who might benefit from local therapy. Of note, the advent of increasingly sensitive imaging for metastatic disease will further alter the landscape of mHSPC.

Interest has also arisen in examining the concurrent use of statins and ADT. Statins inhibit the HMG-CoA enzyme at the rate limiting step in the mevalonate pathway of cholesterol synthesis. Recent research has focused on the antineoplastic role of statins through their impact on cell proliferation, inflammation, membrane organization and steroidogenesis.[60] It is now recognized that castration resistance is at least partly related to the ability of PC cells to undergo intratumoral steroidogenesis sufficient to activate the AR.[60, 61] Statins may work synergistically with ADT by lowering cholesterol, hence decreasing the availability of the major substrate for androgen synthesis.[60] Furthermore, statins have been observed to downregulate androgen receptors via proteolysis, alter cell signaling pathways and induce apoptosis of proliferating cells.[60, 62] A recent retrospective study suggested that men taking statins while on ADT for advanced PC exhibit better oncologic outcomes compared to those not taking statins.[63] Statins and metformin have minimal side effects and low cost, making these commonly available agents an attractive adjunct in the management of mHSPC if a synergistic benefit is demonstrated in future randomized trials. Finally, ADT induces an AR specific T cell response, suggesting that ADT combined with AR directed immunotherapy may be an alternative approach to prevent the development of AR overexpressing CRPC clones.[64] In summary, these novel approaches represent an intriguing and potentially less toxic strategy that may be used in the near future.

ADDENDUM

Results of the recent ENZAMET trial of 160 mg enzalutamide daily plus ADT versus ADT alone have been reported, further supporting the role of second generation antiandrogens in the mHSPC setting.[65] After a median follow-up of 34 months enzalutamide plus ADT demonstrated significantly better OS than ADT alone (80% vs 72%, HR for death 0.67, 95% CI 0.52–0.86, p=0.002). Better results with enzalutamide and ADT were also seen for all of the secondary end points including PSA progression-free survival (174 and 333 events, respectively, HR 0.39, p <0.001) and clinical progression-free survival (167 and 320 events, respectively, HR 0.40, p <0.001). Shortly after publication of the ENZAMET trial results the U.S. Food and Drug Administration granted the medication a priority review which led to the subsequent approval of enzalutamide for the treatment of mHSPC in December 2019.

In addition, interim data from the TITAN trial demonstrated significantly longer overall survival and radiographic progression-free survival of mHSPC with the addition of apalutamide to ADT than with placebo plus ADT, and the side effect profile did not differ substantially between the groups.[66]

DID YOU KNOW?

- Recent phase III trials of combination cytotoxic chemotherapy (docetaxel) or combination therapies of androgen signaling inhibitors (abiraterone or enzalutamide) indicate improved survival and delayed progression to castration resistant PC.
- Docetaxel in combination with ADT at a dose of 75 mg/m^2 every 3 weeks in 6 cycles significantly improved overall survival and quality of life for patients with mHSPC. The effect is more pronounced in patients with high volume disease (≥4 bone metastases) and toxicity is generally better tolerated than in the CRPC setting.
- Early application of abiraterone, a CYP17 inhibitor, plus ADT prolongs progression-free survival and improves overall survival. Abiraterone must be administered with prednisone and has side effects related to hypokalemia, hypertension and liver enzyme increases.
- In combination with ADT, enzalutamide and the closely related apalutamide (both androgen receptor signaling inhibitors) improve progression-free survival of mHSPC. Side effects are related to fatigue and hypertension, and enzalutamide should be avoided in patients with a history of seizures, strokes and falls.
- Metastatic burden (high vs low), performance status, comorbidities, cost and quality of life are all factors to consider when selecting management pathways for mHSPC.
- Treatment of the prostate in patients with new mHSPC is evolving. Recent data suggest a survival benefit for low volume mHSPC treated with radiation therapy compared to no local therapy. Surgical trial data collection is ongoing.

REFERENCES

1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin 2019; **69:** 7.
2. Weiner AB, Matulewicz RS, Eggener SE et al: Increasing incidence of metastatic prostate cancer in the United States (2004–2013). Prostate Cancer Prostatic Dis 2016; **19:** 395.
3. Huggins C, Stevens RE Jr and Hodges CV: Studies on prostatic cancer. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941; **43:** 209.
4. Huggins C, Stevens RE Jr and Hodges CV: Studies on prostatic cancer. The effect of castration, of oestrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Arch Surg 1941; **43:** 293.
5. Attar RM, Takimoto CH and Gottardis MM: Castration resistant prostate cancer: locking up the molecular escape routes. Clin Cancer Res 2009; **15:** 3251.
6. Suzman DL and Antonarakis ES: Castration-resistant prostate cancer: latest evidence and therapeutic implications. Ther Adv Med Oncol 2014; **6:** 167.
7. Tangen CM, Hussain MH, Higano CS et al: Improved overall survival trends of men with newly diagnosed M1 prostate cancer: a SWOG phase III trial experience (S8494, S8894 and S9346). J Urol 2012; **188:** 1164.
8. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Prostate Cancer Trialists' Collaborative Group. Lancet 2000; **355:** 1491.
9. Gravis G, Fizazi K, Joly F et al: Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013; **14:** 149.
10. Gravis G, Boher JM, Joly F et al: Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2016; **70:** 256.
11. Sweeney CJ, Chen YH, Carducci M et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; **373:** 737.
12. James ND, Sydes MR, Clarke NW et al: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016; **387:** 1163.
13. Fizazi K, Tran N, Fein L et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; **377:** 352.
14. James ND, de Bono JS, Spears MR et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017; **377:** 338.
15. Armstrong AJ, Szmulewitz RZ, Petrylak DP et al: Phase III study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): the ARCHES trial. J Clin Oncol, suppl., 2019; **37:** 687.
16. Petrylak DP, Tangen CM, Hussain MH et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; **351:** 1513.
17. Tannock IF, de Wit R, Berry WR et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; **351:** 1502.
18. Eigl BJ, Eggener SE, Baybik J et al: Timing is everything: preclinical evidence supporting simultaneous rather than sequential chemo hormonal therapy for prostate cancer. Clin Cancer Res 2005; **11:** 4905.
19. Zhu ML, Horbinski CM, Garzotto M et al: Tubulin-targeting chemotherapy impairs androgen receptor activity in prostate cancer. Cancer Res 2010; **70:** 7992.
20. Kyriakopoulos CE and Liu G: Chemohormonal therapy for hormone-sensitive prostate cancer: a review. Cancer J 2016; **22:** 322.
21. Therasse P, Arbuck SG, Eisenhauer EA et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; **92:** 205.
22. Kyriakopoulos CE, Chen YH, Carducci MA et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018; **36:** 1080.
23. Carthon BC and Antonarakis ES: The STAMPEDE trial: paradigm-changing data through innovative trial design. Transl Cancer Res, suppl., 2016; **5:** S485.
24. Morgans AK, Chen YH, Sweeney CJ et al: Quality of life during treatment with chemohormonal therapy: analysis of E3805 chemohormonal androgen ablation randomized trial in prostate cancer. J Clin Oncol 2018; **36:** 1088.
25. Gravis G, Boher JM, Chen YH et al: Burden of metastatic

castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies. Eur Urol 2018; **73:** 847.
26. Sathianathen NJ, Philippou YA, Kuntz GM et al: Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. Cochrane Database Syst Rev 2018; CD012816.
27. Franke RM, Carducci MA, Rudek MA et al: Castration-dependent pharmacokinetics of docetaxel in patients with prostate cancer. J Clin Oncol 2010; **28:** 4562.
28. Li Z, Bishop AC, Alyamani M et al: Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature 2015; **523:** 347.
29. de Bono JS, Logothetis CJ, Molina A et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; **364:** 1995.
30. Yamaoka M, Hara T and Kusaka M: Overcoming persistent dependency on androgen signaling after progression to castration-resistant prostate cancer. Clin Cancer Res 2010; **16:** 4319.
31. Taplin ME, Montgomery B, Logothetis CJ et al: Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol 2014; **32:** 3705
32. Tran C, Ouk S, Clegg NJ et al: Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; **324:** 787.
33. Scher HI, Fizazi K, Saad F et al: Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; **367:** 1187.
34. Beer TM, Armstrong AJ, Rathkopf DE et al: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; **371:** 424.
35. Tombal B, Borre M, Rathenborg P et al: Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol 2014; **15:** 592.
36. Davis ID, Stockler MR, Martin AJ et al: Randomised phase 3 trial of enzalutamide in first-line androgen deprivation therapy for metastatic prostate cancer: the ANZUP ENZAMET Trial (ANZUP 1304). J Clin Oncol, suppl., 2017; doi: 10.1200/JCO.2016.34.15_suppl.TPS5090.
37. Gerritse FL, Meulenbeld HJ, Roodhart JM et al: Analysis of docetaxel therapy in elderly (≥70 years) castration resistant prostate cancer patients enrolled in the Netherlands Prostate Study. Eur J Cancer 2013; **49:** 3176.
38. Berberabe T: Physician dispensing of abiraterone and enzalutamide for mCRPC gains appeal. OncLive, November 7, 2015. Available at https://www.onclive.com/conference-coverage/lugpa-2015/physician-dispensing-of-abiraterone-and-enzalutamide-for-mcrpc-gains-appeal.
39. Rydzewska LHM, Burdett S, Vale CL et al: Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. Eur J Cancer 2017; **84:** 88.
40. Moreira RB, Debiasi M, Francini E et al: Differential side effects profile in mCRPC patients treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials. Onctotarget 2017; **8:** 84572.
41. Sydes MR, Spears MR, Mason MD et al: Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomized data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol 2018; **29:** 1235.
42. Ramaekers BLT, Riemsma R, Tomini F et al: Abiraterone acetate for the treatment of chemotherapy-naive metastatic castration-resistant prostate cancer: an evidence review group perspective of an NICE single technology appraisal. Pharmacoeconomics 2017; **35:** 191.
43. Pilon D, Queener M, Lefebvre P et al: Cost per median overall survival month associated with abiraterone acetate and enzalutamide for treatment of patients with metastatic castration resistant prostate cancer. J Med Econ 2016; **19:** 777.
44. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Prostate Cancer. Version 1.2019. Fort Washington, Pennsylvania: National Comprehensive Cancer Network 2019. Available at http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
45. de Bono JS, Oudard S, Ozguroglu M et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; **376:** 1147.
46. Smith MR, Saad F, Chowdhury S et al: Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; **378:** 1408.
47. Smith MR, Antonarakis ES, Ryan CJ et al: Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. Eur Urol 2016; **70:** 963.
48. Fizazi K, Jones R, Oudard S et al: Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. J Clin Oncol 2015; **33:** 723.
49. Owen MR, Doran E and Halestrap AP: Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000; **348:** 607.
50. Zadra G, Photopoulos C and Loda M: The fat side of prostate cancer. Biochim Biophys Acta 2013; **1831:** 1518.
51. Wang Y, Liu G, Tong D et al: Metformin represses androgen-dependent and androgen independent prostate cancers by targeting androgen receptor. Prostate 2015; **75:**1187.
52. Colquhoun AJ, Venier NA, Vandersluis AD et al: Metformin enhances the antiproliferative and apoptotic effect of bicalutamide in prostate cancer. Prostate Cancer Prostatic Dis 2012; **15:** 346.
53. Richards KA, Liou JI, Cryns VL et al: Metformin use is associated with improved survival in patients with advanced prostate cancer on androgen deprivation therapy. J Urol 2018; **200:** 1256.
54. Antwi S and Everson TM: Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. Cancer Epidemiol 2014; **38:** 435.
55. Fossati N, Trinh QD, Sammon J et al: Identifying optimal

candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. Eur Urol 2015; **67:** 3.
56. Gratzke C, Engel J and Stief CG: Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. Eur Urol 2014; **66:** 602.
57. Boeve LMS, Hulshof M, Vis AN et al: Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. Eur Urol 2019; **75:** 410.
58. Parker CC, James ND, Brawley CD et al: Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018; **392:** 2353.
59. Southwest Oncology Group: Standard Systemic Therapy with or without Definitive Treatment in Treating Participants with Metastatic Prostate Cancer, NCT03678025. Available at https://clinicaltrials.gov/ct2/show/NCT03678025.
60. Pelton K, Freeman MR and Solomon KR: Cholesterol and prostate cancer. Curr Opin Pharmacol 2012; **12:** 751.
61. Schweizer MT and Yu EY: Persistent androgen receptor addiction in castration-resistant prostate cancer. J Hematol Oncol 2015; **8:** 128.
62. Yokomizo A, Shiota M, Kashiwagi E et al: Statins reduce the androgen sensitivity and cell proliferation by decreasing the androgen receptor protein in prostate cancer cells. Prostate 2011; **71:** 298.
63. Anderson-Carter I, Posielski N, Liou JI et al: The impact of statins in combination with androgen deprivation therapy in patients with advanced prostate cancer: a large observational study. Urol Oncol 2019; **37:** 130.
64. Olson BM, Gamat M, Seliski J et al: Prostate cancer cells express more androgen receptor (AR) following androgen deprivation, improving recognition by AR-specific T cells. Cancer Immunol Res 2017; **5:** 1074.
65. Davis ID, Martin AJ, Stockler MR et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. New Engl J Med 2019; **381:** 121.
66. Chi KN, Agarwal N, Bjartell A et al: Apalutamide for castration sensitive prostate cancer. N Engl J Med 2019; **381:** 13.

Study Questions Volume 39 Lesson 6

1. The most clinically meaningful efficacy demonstrated in CHAARTED and STAMPEDE-docetaxel was
   a. disease-free survival
   b. metastases-free survival
   c. PSA-free only survival
   d. overall survival

2. A 61-year-old otherwise healthy man complains of back pain and is found to have a PSA of 226 ng/ml and >5 bone lesions in the lumbar spine and bilateral ribs. A prostate biopsy confirms high volume Gleason score 8 (4+4) disease. Computerized tomography reveals pelvic and retroperitoneal adenopathy. The therapy associated with the best overall survival in this situation is ADT and
   a. bicalutamide
   b. cabazitaxel
   c. docetaxel
   d. sipuleucel-T

3. The mechanism of action of docetaxel is
   a. interference with DNA repair mechanisms
   b. cross-linking of tumor cell DNA
   c. microtubule inhibition
   d. CYP17 inhibition

4. Abiraterone acetate is associated with a risk of
   a. hyperkalemia
   b. hypertension
   c. neuropathy
   d. seizure

5. An 82-year-old man with a PSA of 52 is found to have grade group 8 cancer on biopsy. Imaging reveals several 1 cm pelvic lymph nodes and a bony metastasis on the left 9th rib. He ambulates poorly due to hip pain. The most appropriate treatment option is
   a. observation
   b. leuprolide
   c. docetaxel and leuprolide
   d. abiraterone and leuprolide

Take this test online and claim CME at http://university.auanet.org.