The Rapidly Evolving Treatment Landscape of Metastatic Hormone-Sensitive Prostate Cancer

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ABSTRACT: The management of metastatic hormone-sensitive prostate cancer (mHSPC) or castration-sensitive prostate cancer (mCSPC) has become increasingly complex with the tremendous progress that has been made in this space within the past few decades. In the early days of androgen deprivation therapy (ADT), ADT monotherapy was the mainstay for treatment of advanced prostate cancer. However, novel hormone therapies in the form of androgen receptor pathway inhibitors (ARPI) have emerged; vaccine therapy, chemotherapy with docetaxel and cabazitaxel, and radioactive ligands have shaped the treatment of metastatic prostate cancer in the last decade. Following the initial approval of several drugs for use in metastatic castration-resistant prostate cancer (mCRPC) in combination with primary ADT, these agents were studied and subsequently approved for use in mCSPC. Therefore, ADT monotherapy no longer constitutes an optimal therapeutic option for otherwise fit patients who present with mCSPC. We focus on the treatment of first-line de novo mHSPC or mCSPC and explore frontline doublet and triplet therapy and the pivotal trials that led to their United States Food and Drug Administration approval.

KEYWORDS: Prostate cancer, metastatic hormone-sensitive prostate cancer, chemotherapy, androgen deprivation therapy, androgen receptor pathway inhibitors

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Introduction

In 2024, prostate cancer will be diagnosed in an estimated 299 010 men and approximately 35 250 men will die of this disease with a death rate of 11%, according to the 2024 Cancer Statistics.[1] While the management of prostate cancer typically entails surgery or radiation for curable and localized disease, a multimodality approach including androgen deprivation therapy (ADT) is the cornerstone of treatment for advanced or metastatic disease. While surgical castration was used in the remote past, it was supplanted by the development of gonadotropin-releasing hormone (GnRH) agonists in the 1970s. The 1990s saw the development of abiraterone acetate (AA), a novel 17α-hydroxylase/C17,20-lyase inhibitor that eventually proved its worth in the treatment of prostate cancer.[2,3] Since its initial United States Food and Drug Administration (US FDA) approval in 2011 for use in advanced metastatic castration-resistant prostate cancer (mCRPC), approved use of AA was expanded to the metastatic castration-sensitive prostate cancer (mCSPC) space in 2018 and other novel androgen receptor (AR) pathway targeting drugs subsequently followed suit.[4-6] Over the past 5 years, various doublet and triplet regimens have demonstrated efficacy and have been approved for use in mCSPC and treatment has become more individualized considering the nuances of de novo versus recurrent and low-volume versus high-volume mCSPC. In the future, we anticipate defining the role of targeted agents currently approved for use in mCRPC toward earlier in the mCSPC space, including Poly (ADP-Ribose) Polymerase inhibitors (PARPi) and PSMA radioligand therapy (RLT). We also look forward to the development of new drug targets, taking advantage of the pathways involved in prostate cancer pathogenesis in the castration-sensitive setting. This review will discuss seminal data that led to the approval of doublet and triplet therapy regimens which include the addition of androgen receptor pathway inhibitors (ARPI), docetaxel (DOC), and AA to primary ADT. In addition, future potential novel treatment combinations will be discussed herein.

Doublet Therapy Trials—Using ADT With ARPI Drugs

The doublet regimen of ADT and different ARPIs have been evaluated in multiple trials. One of the early combination doublet therapies came in the form of AA with ADT and was evaluated in the LATITUDE trial, which was a phase 3, double-blind, placebo-controlled trial which enrolled 1199 patients randomly assigned to receive ADT plus AA 1000 mg daily and prednisone 5 mg daily (n = 597) or ADT plus placebo (n = 602).[7] Only patients with newly diagnosed, high-risk mCSPC (defined by having at least 2 of 3 high-risk features including Gleason score of 8 or more, at least 3 bone lesions, and/or measurable visceral metastasis) were included in the trial. Overall survival (OS) and radiographic progression-free

survival (rPFS) were co-primary end points. The first interim analysis was performed after a median follow-up of 30.4 months. Results were positive with a median OS that was not reached (NR) in the AA/prednisone arm compared with 34.7 months in the placebo arm (hazard ratio [HR] for death = 0.62, 95% confidence interval [CI] = 0.51-0.76, $P < .001$). Overall survival rate at 3 years for the ADT + AA + prednisone arm was 66%, compared with 49% in the ADT + placebo arm. Overall survival benefit was seen across all evaluated subgroups including patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 and 1-2, visceral metastases, Gleason ⩾ 8 disease, and ⩾10 bone lesions. The median rPFS was also better in the AA arm as compared with the placebo arm, at 33 and 14.8 months, respectively (HR = 0.47, 95% CI = 0.39-0.55, $P < .001$). Abiraterone acetate was better than placebo in multiple other secondary end points like time to pain progression (HR = 0.70, 95% CI = 0.58-0.83), time to prostate specific antigen (PSA) progression (HR = 0.30, 95% CI = 0.26-0.35), time to subsequent prostate cancer therapy (HR = 0.42, 95% CI = 0.35-0.50), time to chemotherapy (HR = 0.44, 95% CI = 0.35-0.56), and symptomatic skeletal events (HR = 0.70, 95% CI = 0.54-0.92). However, side effects, including grade 3 or 4 adverse events (AEs), were higher in the AA arm (63%) as compared with the placebo arm (48%). A higher incidence of hypertension and hypokalemia was noted in the AA arm, as well, though these were expected on-target effects based on the mechanism of action for AA. The benefits were maintained despite cross-over which was seen in 72 patients who crossed over from the placebo arm to AA arm. An updated final analysis reported in 2019 after a median follow-up of 51.8 months showed continued OS benefit in the AA arm versus placebo arm at 53.3 and 36.5 months (HR = 0.66, 95% CI = 0.56-0.78, $P < .0001$), respectively.[8] Secondary end points like time to pain progression (HR = 0.72, 95% CI = 0.61-0.86), time to PSA progression (HR = 0.31, 95% CI = 0.27-0.36), time to subsequent prostate cancer therapy (HR = 0.45, 95% CI = 0.38-0.53), time to chemotherapy (HR = 0.51, 95% CI = 0.41-0.63), and symptomatic-skeletal events (HR = 0.75, 95% CI = 0.60-0.95) were all significantly improved in the AA arm. Time to progression on second therapy (PFS2) was assessed as an exploratory endpoint and it was also statistically improved on the AA arm as compared with the placebo arm (HR = 0.58, 95% CI = 0.49-0.68). Overall incidence of AEs was similar in both groups. There were no new safety signals, and AEs in each arm were similar to what had been reported in prior interim analyses. Post hoc analysis compared outcomes based on disease volume per CHAARTED criteria which showed an improvement in OS among patients with high-volume disease (49.7 vs 33.3 months, HR = 0.62, $P < .0001$) in contrast to those with low-volume disease (NR in either arm, HR = 0.72, $P = .12$), although the apparent lack of benefit among low-volume patients might be attributable to lower sample size. Improvement in radiographic failure-free survival (FFS) was statistically significant in both the high-volume (HR = 0.46, 95% CI = 0.39-0.54) and low-volume disease populations (HR = 0.59, 95% CI = 0.40-0.85). It is worth noting that 176 (30%) patients in AA arm and 345 (57%) in the placebo arm received subsequent life extending therapy in the intention-to-treat population suggesting improved survival rates with upfront use of AA and prednisone. Hence, these data solidified the role of AA and prednisone added to ADT in men with mCSPC with high-risk disease per the LATITUDE trial definition. On the contrary, the concept of adding AA to standard ADT regardless of the LATITUDE high-risk definition came in the form of the STAMPEDE trial, which was a novel multiarm, multistage trial that included multiple cohorts of patients randomized in different arms, among which was ADT with AA and prednisone.[9] The study enrolled 1917 patients predominantly in the United Kingdom with 957 patients randomized to ADT alone and 960 to combination therapy of ADT with AA. Results showed improvement in both FFS and OS in favor of the combination arms compared with ADT alone, with 3-year survival rates of 83% versus 76% (HR = 0.63, $P < .001$) and FFS of 75% versus 45% (HR = 0.29, $P < .001$), respectively.

The addition of enzalutamide, an oral ARPI, to ADT was further evaluated in the ARCHES trial [10] which was a phase III trial comparing 1150 men with metastatic hormone-sensitive prostate cancer (mHSPC) to either ADT with enzalutamide compared with ADT alone. The primary endpoint was rPFS which was met with a median rPFS of NR with enzalutamide plus ADT compared with 19.0 months in those who received ADT monotherapy (HR = 0.39, $P < .001$). Another trial that looked at enzalutamide was called ENZAMET, a phase III prospective, open-label, randomized controlled study that included 1125 men who were randomized 1:1 to receive enzalutamide at 160 mg daily plus ADT or a standard non-steroidal antiandrogen (bicalutamide, nilutamide, or flutamide) plus ADT.[11] The protocol was later amended after the enrollment of 88 patients to allow the administration of DOC, in response to the practice-changing data from the CHAARTED trial. Ultimately, a total of 359 patients with high-volume and 144 patients with low-volume mCSPC on study received DOC. However, it is important to point out that DOC use was not randomized and utilization was at the discretion of the investigator, making it difficult to predict subgroups who do not benefit from it. Regardless, stratification factors included age, volume of disease defined by CHAARTED criteria, and concurrent DOC use. The primary end point was OS and secondary end points included PSA progression-free survival (PFS), clinical PFS (based on imaging, signs and symptoms, and change in therapy), and AE. At a median follow-up of 34 months, OS was improved in the enzalutamide arm as compared with the control arm (HR = 0.67, 95% CI = 0.52-0.86). Three-year OS was 80% in the enzalutamide arm versus 72% in the control arm. Similar

statistically significant improvements were noted in PSA PFS (HR = 0.39, 95% CI = 0.33-0.47) and clinical PFS (HR = 0.40, 95% CI = 0.33-0.49) in the enzalutamide arm. However, AEs leading to treatment discontinuation were more common in the enzalutamide arm (33 events) versus control arm (14 events). Seven patients had seizures in the enzalutamide arm, compared with zero in the control arm. The effects of enzalutamide on health-related quality of life were analyzed separately and enzalutamide was associated with worse patient-reported ratings with regard to fatigue, cognitive function, and physical function. However, overall health-related quality of life was preserved due to delayed progression of disease and improved deterioration-free survival.[12] Updated analysis at a median follow-up of 68 months showed sustained statistically significant benefit in the enzalutamide arm (HR = 0.70, 95% CI = 0.58-0.84) with a 5-year OS of 67% in the enzalutamide arm compared with 57% in the control arm.[13] Median PSA PFS in the enzalutamide arm and control arm was 68 and 22 months, respectively (HR = 0.44, 95% CI = 0.38-0.52). Median clinical PFS was 81 and 25 months, respectively (HR = 0.45, 95% CI = 0.39-0.53). In subgroup analyses, the HRs were as follows: low-volume disease (HR = 0.54, 95% CI = 0.39-0.74), high-volume disease (HR = 0.79, 95% CI = 0.63-0.98), DOC use (HR = 0.82, 95% CI = 0.63-1.06), and no DOC use (HR = 0.60, 95% CI = 0.47-0.78). Better outcomes were noted for patients treated with DOC and enzalutamide in synchronous metastatic disease (HR = 0.73, 95% CI = 0.55-0.99) rather than metachronous metastatic disease (HR = 1.10, 95% CI = 0.65-1.86). The most frequently reported grade 3 to 4 AEs included febrile neutropenia, fatigue, and hypertension. Similar trends were seen in the ENZAMET trial with more patients in the control arm (n = 413) than experimental arm (n = 268) who received subsequent treatment for progression highlighting importance of using ARPI with ADT in the initial stages of disease to improve clinical outcomes.

Another ARPI plus ADT combination using apalutamide in mCSPC patients was studied in the TITAN trial.[14] Apalutamide is an orally administered nonsteroidal antiandrogen, which is similar to enzalutamide. It operates by directly binding to the ligand-binding domain of AR. Through this interaction, it hinders AR translocation, DNA binding, and the subsequent transcriptional activities mediated by AR. The primary end points of rPFS and OS were both met in the TITAN trial. Patients were assigned randomly in a 1:1 ratio to either receive apalutamide 240 mg daily or placebo with continuous ADT. A total of 525 patients were randomly assigned to receive apalutamide with ADT while 527 patients were assigned to receive a placebo in addition to ADT. About 16.4% of the patients had previously undergone prostatectomy or received radiotherapy for localized disease and 10.7% of patients had received prior DOC therapy for mCSPC but had not progressed during or after chemotherapy. Among all participants in the TITAN trial, 62.7% had high-volume disease and 37.3% had low-volume disease.

On conducting the first interim analysis with a median follow-up of 22.7 months, an rPFS improvement was observed with the apalutamide arm. At 24 months, rPFS was 68.2% in the apalutamide group and 47.5% in the placebo group. The HR for radiographic progression or death was 0.48 (95% CI = 0.39-0.60, $P < .001$). Furthermore, the OS at 24 months was higher in the apalutamide group compared with the placebo group, with rates of 82.4% and 73.5%, respectively. The HR for death was statistically significant at 0.67 (95% CI = 0.51-0.89, $P = .005$). The duration until the initiation of cytotoxic chemotherapy was notably extended in patients receiving apalutamide compared with those receiving the placebo with an HR of 0.39. Grade 3 or 4 adverse events were comparable with 42.2% in the apalutamide plus ADT arm and 40.8% in the placebo plus ADT arm. The final survival analysis of the TITAN study was later reported and with a median follow-up of 44 months, apalutamide plus ADT significantly reduced the risk of death by 35% compared with placebo and by 48% after accounting for crossover. Median OS was NR in the apalutamide arm versus 52.2 months in the placebo arm.[15] One hundred twenty (48.6%) patients of 247 alive at treatment discontinuation needed subsequent systemic therapy in the experimental arm as compared with 221 (64.1%) of 345 patients in the control arm reinforcing the concept of early use of ARPI to improve OS.

The CHART trial, which was conducted predominantly in China (with only 10% of patients enrolled outside of China including Poland, Czech Republic, and Bulgaria), randomized 654 patients with high-volume mCSPC to either ADT with rezvilutamide (n = 326) or ADT with bicalutamide (n = 328).[16] Rezvilutamide is another oral ARPI that showed significant improvement in rPFS over the comparator of bicalutamide, NR versus 25.1 months (HR = 0.44, 95% = CI 0.33-0.58, $P < .0001$) after a median follow-up duration of 21 months. Rezvilutamide was also found to improve OS compared with bicalutamide (HR = 0.58, 95% CI = 0.44-0.77, $P = .0001$). The safety profile of rezvilutamide appears to be consistent with other ARPIs, including observed AEs of hypertension, anemia, and hypokalemia. While rezvilutamide is approved in China for the treatment of mCSPC patients with high tumor burden,[17] it is unclear how the regulatory pathway would be paved in the United States for this drug. Table 1 summarizes doublet therapy with ADT and ARPI.

Doublet Therapies With Chemotherapy

The next doublet regimen of ADT studied with multiple clinical trials was with chemotherapy, specifically DOC. CHAARTED was a phase 3 trial that enrolled and randomly assigned 790 men with mCSPC to ADT alone (n = 393) or combination therapy of ADT plus DOC (n = 397).[18,19] The primary endpoint was OS. The interim analysis at a median follow-up of 28.9 months showed that the median OS was

Table 1. Selected phase III metastatic hormone-sensitive prostate cancer trials using doublet therapy with ADT and ARPI.

CLINICAL TRIAL NAME	LATITUDE	STAMPEDE ABIRATERONE	TITAN	ARCHES	ENZAMET	CHART
No of patients	n = 1199	n = 960	n = 1007	n = 1150	n = 1125	n = 654
Arms	ADT + abiraterone/ prednisone vs ADT + dual placebo	ADT + abiraterone and prednisolone vs ADT	ADT + apalutamide vs ADT + placebo	ADT + enzalutamide vs ADT + placebo	ADT + enzalutamide + docetaxel vs ADT + NSAA + docetaxel	ADT + rezvilutamide vs ADT + bicalutamide
Primary endpoint	OS and rPFS	OS	rPFS and OS	rPFS	OS	Independent review rPFS and OS
mOS (ADT + experimental arm)	Not reached	3-yr OS 83%	82.40%	NR	3-yr OS of 80%	NR; 2-yr OS: 81.6%
mOS (ADT alone or as SOC)	34.7 mos	3-yr OS 76%	73.50%	NR	3-yr OS of 72%	NR; 2-yr OS: 70.3%
HR	HR = 0.62; 95% CI = 0.51-0.76; $P < .001$	HR = 0.62; 95% CI = 0.51-0.76; $P < .001$	HR = 0.67; 95% CI = 0.51-0.89; $P = .005$	HR = 0.81; 95% CI = 0.53-1.25; $P = .3361$	HR = 0.67; 95% CI = 0.52-0.86; $P = .002$	HR = 0.58; 95% CI = 0.44-0.77; $P = .0001$
Metastatic burden percentage	98%	52%	100%; 62.7% high volume	93%	100%; 52% high	100%
mPFS	Median rPFS: 33 mos vs 14.8 mos (HR = 0.47; 95% CI = 0.39-0.55; $P < .001$)	3-year failure-free survival = 75%	Median rPFS 68.2% vs 47.5% placebo arm	Median rPFS NR vs 19 mos (HR = 0.39; 95% CI = 0.30-0.50; $P < .001$)	3-year EFS: 67% vs 37% (SOC arm) (HR = 0.39; 95% CI = 0.33-0.47; $P < .001$)	rPFS = NR vs 25.1 mos ADT + bicalutamide (HR = 0.44; 95% CI = 0.33-0.58; $P < .0001$)
Discontinuation d/t toxicity	12% vs 10%	17% vs 21%	8% vs 5.3% (placebo arm)	7.2% (vs 5.2% ADT arm)	16% (vs 4% SOC arm)	2% (vs 2% ADT + bicalutamide)

Abbreviations: ARPI, androgen receptor pathway inhibitors; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; mos, months; OS, overall survival; rPFS, radiographic progression-free survival; SOC, standard of care.

13.6 months longer with ADT plus DOC than with ADT alone (57.6 vs 44.0 months, HR = 0.61, 95% CI = 0.47-0.80, $P < .001$). Updated analysis at a median follow-up of 53.7 months confirmed this finding, with the median OS being 10.4 months longer in the ADT plus DOC group than in the ADT-alone group (57.6 vs 47.2 months, HR = 0.72, 95% CI = 0.59-0.89, $P = .0018$). Both the interim and updated analysis demonstrated the benefit in the OS for the combination therapy with ADT plus DOC versus ADT alone across all subgroups, including high-volume disease, ECOG 0, 1, and 2, and Gleason score ≥ 8, except for low-volume metastatic disease. Among the subgroups, the high-volume metastatic disease group had the most prominent median OS benefit of 16.7 months (51.2 vs 34.4 months, HR = 0.63, 95% CI = 0.50-0.79, $P < .001$).

Other secondary endpoints included the proportion of patients who experienced a decrease in the PSA level to less than 0.2 ng/mL, median time to mCRPC (biochemical, symptomatic, or radiographic), and the median time to clinical progression defined as increasing symptoms of bone metastasis, progression according to response evaluation criteria in solid tumors, version 1.0, or clinical deterioration from cancer based on the investigator's judgment. The proportion of patients who achieved a decrease in the PSA level to less than 0.2 ng/mL at 12 months was 27.7% in the ADT plus DOC group compared with 16.8% in the ADT alone group ($P < .001$). The median time to mCRPC was 20.2 months in the ADT plus DOC group and 11.7 months in the ADT alone group (HR = 0.61, 95% CI = 0.51-0.72, $P < .001$). Finally, the median time to progression was 33.0 months with ADT plus DOC compared with 19.8 months with ADT alone (HR = 0.61, 95% CI = 0.50-0.75, $P < .001$). The ADT plus DOC combination therapy demonstrated benefit for all 3 of the secondary endpoints compared with ADT alone. There were some minimal adverse events associated with the combination therapy. Treatment-related grade 3 or 4 allergic reactions occurred in 2% of the group, and grade 3 fatigue and grade 3 diarrhea, stomatitis, and motor and sensory neuropathy happened in the 4%, and 3% of the group, respectively. In addition, in the combination group, approximately 1% of patients experienced a thromboembolic event, 6% had neutropenic fever, and 2% had grade 3 or 4 infection with neutropenia.

Another clinical trial that studied the addition of DOC to standard of care (SOC), hormone therapy for at least 2 years, was the STAMPEDE trial.[20] The study enrolled and randomized 2962 patients in 2:1:1:1 ratio of SOC only (n = 1184), SOC plus zoledronic acid (ZA) (n = 593), SOC plus DOC (n = 592), and SOC plus ZA and DOC (n = 593). Eligible subjects included those with newly diagnosed metastatic, node-positive, or high-risk locally advanced prostate cancer, or those previously treated with either or both radical surgery and radiotherapy that had relapsed with high-risk features. One of the primary endpoints was OS. The median OS was 81 months for the SOC plus DOC group compared with 71 months for the SOC-only group (HR = 0.78, 95% CI = 0.66-0.93, $P = .006$). The SOC plus ZA and DOC group also showed a survival advantage with 76 months (HR = 0.82, 95% CI = 0.69-0.97, $P = .022$), but no survival advantage was observed for the SOC plus ZA group.

The other primary endpoint was FFS, defined as the time from randomization to the first evidence of at least biochemical failure (PSA rise of 50% above the within 24-week nadir and above 4 ng/mL), progression of cancer to local lymph nodes or distant metastasis, or death from prostate cancer. The SOC plus DOC group again showed evidence of improvement in FFS with 37 months compared with the SOC-only group with 20 months (HR = 0.61, 95% CI = 0.53-0.70, $P = .413 \times 10^{-13}$). Similarly, there was no evidence of improvement in the FFS for the SOC plus ZA group, but the SOC plus ZA and DOC group did demonstrate survival benefit (HR = 0.62, 95% CI = 0.54-0.70, $P = .134 \times 10^{-12}$). The proportion of grade 3 or higher adverse events was higher in the treatment groups with DOC. The SOC plus DOC group reported 288 (52%) patients, and the SOC plus ZA and DOC group reported 269 (52%) patients. In comparison, the SOC-only group reported 399 (32%) patients, and the SOC plus ZA group reported 197 (32%) patients. In conclusion, this study demonstrated an improvement in the survival of DOC in conjunction with long-term hormone therapy and supported the use of DOC as standard therapy.

An updated retrospective analysis of the M1 cohort from the STAMPEDE trial was completed to address the results of the CHAARTED trial showing no benefit in OS for low-volume metastatic disease.[21] There were 1086 M1 patients who were randomized to receive SOC (n = 724) and SOC plus DOC (n = 362), and from these population, metastatic burden was available for 830 patients (362 had low and 468 had high metastatic burden). With a median follow-up of 78.2 months, this long-term analysis reconfirmed the benefit of DOC over SOC on OS (59.1 vs 43.1 months, HR = 0.81, 95% CI = 0.69-0.95, $P = .003$). There was also a statistically significant benefit of adding DOC to SOC on FFS (HR = 0.66, 95% CI = 0.57-0.76, $P < .001$) and PFS (HR = 0.69, 95% CI = 0.59-0.81, $P < .001$). This analysis also demonstrated similar OS, PFS, and FFS benefits to adding DOC to SOC in both low- and high-volume mCSPC patients. Therefore, this updated long-term analysis supported the addition of DOC to ADT irrespective of metastatic cancer burden in the castration-sensitive setting. Table 2 summarizes the ADT and chemotherapy trials.

Treatment of mCSPC Using Triplet Therapy

After the benefits of doublet therapy were well-established in mCSPC, interest in further treatment intensification grew and led to the validation of 2 triplet therapy regimens to date (ADT, DOC, plus AA or darolutamide). The addition of darolutamide

Table 2. Selected phase III metastatic hormone-sensitive prostate cancer trials using doublet therapy with ADT and DOC.

CLINICAL TRIAL NAME	CHAARTED	STAMPEDE DOC
No of patients	n = 790	n = 2962
Arms	ADT + DOC vs ADT	ADT + DOC vs ADT
Primary endpoint	OS	OS
mOS (ADT + experimental arm)	57.6 mos	81.0 mos
mOS (ADT alone or as SOC)	44.0 mos	71.0 mos
HR	HR = 0.61; 95% CI = 0.47-0.80; $P < .001$	HR = 0.78; 95% CI = 0.66 to 0.93; $P = .006$
Metastatic burden percentage	100%; 65% high volume	62% (newly diagnosed); 48% (recurrent disease)
mPFS	mPFS: 20.2 mos vs 11.7 mos (HR = 0.61; 95% CI = 0.51-0.72; $P < .001$)	mFFS: 37 mos vs 20 mos (HR = 0.61; 95% CI = 0.53-0.70; $P = .413 \times 10^{-13}$)
Discontinuation d/t toxicity	NA	13% vs NA

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; DOC, docetaxel; mFFS, media failure-free survival; mos, months; mPFS, median progression-free survival; OS, overall survival; SOC, standard of care.

to ADT plus DOC was evaluated in the ARASENS trial, and likewise, the addition of AA to ADT plus DOC was studied in the PEACE-1 trial. Both of these practice-changing trials demonstrated significant improvements in the primary endpoint of OS and all other secondary endpoints in patients with mCSPC.[22,23]

PEACE-1 was a European phase III trial that used a 2 × 2 factorial design that enrolled 1173 mCSPC patients in a 1:1:1:1 fashion to the SOC arm (which in this trial was ADT plus DOC), SOC with radiation therapy (RT), SOC with AA, and SOC plus RT and AA. Patients were stratified by study location, ECOG performance status (0 vs 1-2), type of GnRH agonist or antagonist or surgical castration, planned treatment with DOC, volume of disease, and site of metastases (lymph node only, bone metastases with or without lymph node metastases, and visceral metastases). The dual primary endpoints included rPFS and OS. Progression was defined using the Prostate Cancer Working Group (PCWG2) criteria. There were many secondary endpoints, but some key ones included CRPC-free survival, time to serious genitourinary event–free survival, prostate cancer–specific survival, PSA response rate, time to chemotherapy for mCRPC, time to pain progression, and toxicity. A prognostic study of serum PSA measured 6–8 months after initiation of systemic therapy and correlation of biomarkers with outcome are also planned. The protocol underwent a few revisions to adapt to the changing standard-of-care at the time when abiraterone doublet therapy was validated. The initial protocol rolled out in 2013 and set out to enroll 916 patients. The planned sample size was increased in 2017 to 1173. The hypothesis was that adding abiraterone to SOC (ADT plus DOC) would improve OS by 30% over a median of 53 months and PFS by over 40% in a span of 30 months. Among enrolled patients, 296 patients were randomized to SOC only, 293 patients to SOC plus RT, 291 patients to SOC plus RT and AA and 292 patients to SOC plus AA. After a median follow-up of 3.5 to 4.4 years, the addition of abiraterone to SOC conferred an increase in rPFS from 2.22 to 4.46 years compared with those who did not receive AA. Treatment with AA resulted in a reduction of radiographic progression events or deaths from 371 to 252 and reduced the relative risk of progression or death by 46% (adjusted HR for rPFS = 0.54, 99.9% CI = 0.41-0.71, $P < .0001$). Overall survival was similarly improved with reduction in the number of deaths from 268 to 228, with an improvement in median OS from 4.72 to 5.72 years, translating to a reduction in risk of death by 18% (adjusted HR for OS = 0.82, 95.1% CI = 0.69-0.98, $P = .030$). While the addition of RT was not found to improve OS, it did increase time to serious genitourinary events. The subgroup of patients with high-volume disease showed vast improvement in survival from 3.47 years with SOC compared with 5.14 years in the SOC plus AA with a 28% reduction in relative risk of death from any cause (adjusted HR = 0.72, 95.1% CI = 0.55-0.95, $P = .019$). Overall survival was not significantly different in those with low disease burden of disease though data was not yet mature at the time of reporting.[24]

ARASENS was a phase III international trial that randomized 1306 men with mCSPC into 1 of 2 treatment arms, doublet therapy with ADT plus DOC (n = 655) or triplet therapy with ADT plus DOC plus darolutamide (n = 651), another ARPI.[22] The primary endpoint of OS was met with a 4-year OS of 62.7% for the triplet therapy arm of ADT versus 50.4% in the doublet therapy arm. There was a reduction in the risk of death by 32.5% with triplet therapy, compared with the doublet

Table 3. Selected phase III metastatic hormone-sensitive prostate cancer trials using triplet therapy.

CLINICAL TRIAL NAME	ARASENS	PEACE-1	ENZAMET
No of patients	n = 1305	n = 1172	n = 1125
Arms	ADT + docetaxel + darolutamide (n = 651) vs ADT + docetaxel + placebo (n = 654)	ADT + docetaxel + abiraterone/pred (with or without RT; n = 583) vs ADT + docetaxel without abiraterone (with and without RT; n = 589)	ADT + enzalutamide + docetaxel vs ADT + NSAA + docetaxel
Primary endpoint	OS	OS and PFS	OS
mPFS	NR; time to CRPC: HR = 0.36 (0.30-0.42); $P < .001$	HR = 0.54, 99.9% CI = 0.41-0.71; $P < .0001$	3-year EFS: 67% vs 37% (SOC arm); HR = 0.39; 95% CI = 0.33-0.47; $P < .001$
mOS (ADT + experimental arm)	HR = 0.68; 95% CI = 0.57-0.80; $P < .0001$	HR = 0.82, 95.1% CI = 0.69-0.98; $P = .030$	3-year OS of 80% vs ADT + SOC arm (HR = 0.67, 95% CI = 0.52-0.86, $P = .002$)
Metastatic burden percentage	M1—85.7%; 77% of 1005 pts—high v; 23%—low v;	100%; 57%—high v; 43%—low v;	100%; 52% high
Discontinuation d/t toxicity	13.5% in darolutamide vs 10.6% in placebo	NR	16% vs 4% (SOC arm)

Abbreviations: OS, overall survival; rPFS, radiographic progression-free survival; EFS, event-free survival; SOC, standard of care; mos, months; HR, hazard ratio; CI, confidence interval; v, volume; NR, not reported; NSAA, nonsteroidal antiandrogen.

of ADT plus DOC (HR = 0.68, 95% CI = 0.57-0.80, $P < .0001$). These results led to the FDA approval of darolutamide in combination with ADT and DOC in mCSPC in August 2022. Many other secondary endpoints were evaluated and almost all favored triplet therapy, including time to castration-resistant prostate cancer, 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, and time to initiation of opioid use for 7 or more days. While subgroups based on disease volume and risk were not prespecified at the time the ARASENS protocol was developed, these subgroup analyses were completed post hoc according to criteria for high-volume and high-risk disease in the CHAARTED and LATITUDE, respectively.[25] Further updates revealed men with high-volume disease (n = 497 in the darolutamide group; n = 508 in placebo) had improved OS (HR = 0.69, 95% CI = 0.57-0.82), whereas those with low-volume disease (n = 154 in the darolutamide group and n = 146 in the placebo group) had a less consistent OS benefit with CI showing wide variability (HR = 0.68, 95% CI = 0.41-1.19). However, the ARASENS trial demonstrated OS benefit with the addition of darolutamide in mCSPC patients with both de novo and recurrent disease (defined as patients who had prior prostate cancer treatment with curative intent but developed recurrent or progressive mCSPC at the time of inclusion in the study). Triplet therapy was generally well tolerated with discontinuation rates of 8% and 13.5% in the doublet and triplet therapy arms, respectively. Table 3 summarizes the triplet therapy trials.

The aforementioned phase III ENZAMET trial is generally regarded as a doublet therapy study, but it is important to note that this trial allowed for early administration of DOC with enzalutamide, hence its occasional inclusion as a triplet trial.[11] However, among patients who received DOC in this study, the effect of enzalutamide on OS was less robust (HR = 0.82, 95% CI = 0.63-1.06) than that observed for all patients (HR = 0.70, 95% CI = 0.58-0.84). In addition, there was also a notable increased risk of toxicity in those who received both enzalutamide and DOC in addition to ADT, which raises some concern regarding the use of enzalutamide as a triplet therapy regimen.

The number of treatment options that are available based on these doublet and triplet therapy trials in mCSPC makes it more challenging for oncologists and patients to make treatment decisions. Several meta-analyses exploring the benefits of doublet versus triplet therapy have been reported. One meta-analysis revealed that for patients with low-volume disease, there was no added benefit of a triplet regimen; therefore, doublet therapy is usually sufficient.[26] However, for patients with high-volume disease, triplet therapy with darolutamide and DOC scored the highest (P score .92), followed by AA with DOC (P score .85), followed by any doublet ARPI-based regimens. In addition, OS was favorable with the darolutamide triplet regimen (HR = 0.76, 95% CI = 0.59-0.97) compared with the ARPI-based doublet regimens in this pooled analysis. Conversely, in another systematic review and "living" meta-analysis, the abiraterone triplet regimen yielded the best OS in men with high-volume disease compared with the ADT and DOC doublet regimen (HR = 0.72, 95% CI = 0.55-0.95), but

not compared with any of the ARPI-based regimens including AA, enzalutamide, or apalutamide.[27] On the contrary, in men with low-volume mCSPC, no survival advantage was seen with receiving triplet therapy compared with any of the ARPI-based doublet regimens, emphasizing the importance of considering disease burden when deciding on therapy. Based on these analyses, patients who are fit for chemotherapy with high-volume mCSPC should be considered for triplet therapy.[28] On the contrary, there may not be a clear advantage for systemic treatment intensification for those who present with low-volume disease, metachronous, or recurrent/progressive rather than de novo mCSPC beyond using a ARPI-based doublet regimen.[29] In addition, while overall rates are low for toxic deaths, it is about 3 times higher (3.3%) for those who receive triplet therapy compared with those who receive DOC-based doublet therapy (0.9%), which is not inconsequential.

Clinical Trials Using Additional Targets

Radioligand therapy

The use of radiopharmaceuticals in metastatic prostate cancer dates back to the 1990s when Indium-11 was studied in imaging trials, but until the 2010s, there was not as much interest in their therapeutic potential.[30] The approval of alpha emitter, radium-223, in 2013 based on the OS results of ALSYMPCA therapy trial in mCRPC patients played a key role in reviving interest in RLT.[31] Lutetium-177 (^{177}Lu)-PSMA-617 subsequently gained traction as a promising RLT in advanced prostate cancer and was ultimately FDA-approved for use in PSMA-positive mCRPC in the post-ARPI and post-DOC setting based on the results of the VISION trial.[32-35] Currently, prospective data on the use of ^{177}Lu-PSMA-617 in mCSPC are relatively more limited, but one retrospective cohort study looking at the use of PSMA-RLT demonstrated promising efficacy in mCSPC patients. In this small study of 20 patients, 18 patients received ^{177}Lu-PSMA-617 and 2 patients received ^{225}Actinium-PSMA-617 (alpha emitter), although overall patients were heterogeneous. Median PFS was 12 months and 17 patients (85%) had a $\geqslant$50% PSA response following PSMA-RLT.[36] In one prospective pilot study, ^{177}Lu-PSMA-617 was administered to 10 patients with low volume (defined by $\leqslant$10 metastatic lesions on ^{68}Ga-PSMA-11 PET/CT) mCSPC who developed metastases following local therapy. All patients received 2 cycles of ^{177}Lu-PSMA-617. Five patients had a PSA response of greater than 50%, 1 patient had a complete response on PSMA-PET imaging, and 2 other patients had minimal residual disease.[37] PSMAddition (NCT04720157) and BULLSEYE (NCT04443062) are 2 prospective trials in progress investigating the use of ^{177}Lu-PSMA-617 in the mCSPC space.[38,39] PSMAddition is a randomized phase III trial studying ^{177}Lu-PSMA-617 in combination with SOC therapy. In this trial, SOC entails primary ADT plus the addition of an ARPI and approximately 1144 mCSPC patients were randomized to receive ^{177}Lu-PSMA-617 plus SOC versus SOC alone. Patients were required to have PSMA-positive metastatic disease as determined by ^{68}Ga-PSMA-11 PET/CT and they could not have received prior ADT for metastatic disease, although prior ADT use for up to 2 years in the adjuvant/neoadjuvant setting was permitted as long as it was completed over a year prior to consenting for the trial.[40] The primary outcome of the study is rPFS and patients randomized to the SOC-only arm will be allowed to crossover if they develop progression of disease. As of the writing of this article, recruitment for this trial is complete and study completion is expected by June 2026. The BULLSEYE trial is studying ^{177}Lu-PSMA-617 as a metastasis-directed therapy (MDT) in patients with oligometastatic (defined by 5 or less metastasis on PSMA-PET) CSPC. In this study, approximately 58 patients will be randomized to receive either 2 cycles of ^{177}Lu-PSMA-617 versus SOC and the primary outcome measure is disease progression defined by 100% PSA increase or clinical progression of disease.[41] Finally, the UpFrontPSMA trial, assessing the sequential use of ^{177}Lu-PSMA-617 after DOC compared with DOC alone in 130 mCSPC patients, is being conducted in Australia and has completed enrollment. The estimated study completion date is April 2024.[42] There are a number of novel radiolabeled PSMA-targeted monoclonal antibodies and small molecules in development that are being studied in mCRPC patients and it will be of interest to see whether these newer radiopharmaceuticals will move forward into mCSPC trials in the future.[43]

Poly (ADP-Ribose) Polymerase Inhibitors in mCSPC

The use of PARPi is already well-established in select mCRPC patients based on prior studies. Olaparib was first approved by the FDA in May 2020 for homologous recombination repair gene-mutated (HRRm) mCRPC following prior treatment with enzalutamide or abiraterone based on the results of the PROfound trial.[44] Initial ORR and PSA response results of the TRITON-2 trial led to the accelerated approval of rucaparib in BRCA-mutated mCRPC following prior treatment with ARPI and taxane-based chemotherapy in May 2020 and the final results of this trial were published in September 2023.[45,46] The confirmatory TRITON-3 trial demonstrated a statistically significant improvement in imaging-based PFS with rucaparib compared with a physician's choice control therapy (DOC or second-generation ARPI) in BRCA-mutated mCRPC after one prior ARPI regimen.[47] Several PARPi/ARPI combinations were FDA-approved for use in select mCRPC patients in 2023 based on the reported outcomes of the PROpel, TALAPRO-2, and MAGNITUDE trials.[48-50] However, there are unanswered questions, including the impact of intermittent ADT or enzalutamide monotherapy for nonmetastatic CSPC especially given data on EMBARK which would likely translate into clinical practice. On the contrary, there are known subsequent life-prolonging therapies that patients on all 3 trials have received with PFS benefit. For instance, PROpel showed about 68.9% of patients

who received abiraterone and olaparib received subsequent cytotoxic chemotherapy compared with 75.1% on the abiraterone and placebo arm. TALAPRO-2 showed 29% of the patients who received talazoparib and enzalutamide received subsequent antineoplastic treatment, of which majority (23%) was DOC compared with the enzalutamide and placebo arm of 44%, of whom 38% received DOC. MAGNITUDE showed only 31% in the niraparib and abiraterone group received further life-prolonging therapy compared with the placebo and abiraterone group where 58.9% underwent subsequent treatment. However, all imbalances were rectified by applying inverse probability censoring weighting to account for the differences in subsequent receipt of life-prolonging therapies between the 2 treatment groups.

Currently, several clinical trials are investigating the use of PARPi/ARPI combinations in mCSPC, including the TALAPRO-3 (NCT04821622), AMPLITUDE (NCT04497844), and ZZ-First (NCT04332744) trials. TALAPRO-3 is a phase III, double-blinded, randomized study of talazoparib plus enzalutamide versus placebo plus enzalutamide in mCSPC patients with alterations in DNA damage response genes involved in HRR (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, and *RAD51C*). The primary endpoint of this study is rPFS and secondary endpoints include OS, safety, and patient-reported outcomes.[51] Similarly, AMPLITUDE is a phase III, double-blinded, randomized study of niraparib plus AA and prednisone versus placebo plus AA and prednisone in germline or somatic HRRm mCSPC. The primary endpoint is rPFS and secondary endpoints include survival, symptomatic PFS, safety, and time to subsequent systemic therapy for prostate cancer.[52]

CDK4/6i

The use of cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) is well established in hormone-receptor positive, Her-2 not amplified breast cancer. Palbociclib, ribociclib, and abemaciclib are among the CDK4/6i currently approved for use in certain cases of breast cancer.[53] Similar to the estrogen signaling pathway in breast cancer pathogenesis, the AR axis activates CDK4 and 6, resulting in prostate cancer cell proliferation. Activation of the MAPK, AKT, and mTOR pathways leads to the upregulation of cyclin D1, which in turn increases the activation of the CDK4/6 pathway. This is one of several purported mechanisms of hormone resistance in prostate cancer.[54] Preclinical studies of palbociclib have shown that CDK4/6 inhibition limits castration-sensitive and castration-resistant prostate cancer cell lines in vitro, as well as ex vivo in primary human tumors.[55] Similar findings have been reported in preclinical models using abemaciclib.[56] The results of a phase II trial of palbociclib plus ADT versus ADT alone in 72 mCSPC patients were published in 2018. The primary endpoint was the rate of PSA reduction to less than or equal to 4 ng/mL after 28 weeks of therapy. Eighty percent of patients in both arms achieved a PSA of less than or equal to 4 ng/mL at 28 weeks of therapy. Data on clinical PFS were not mature at the time of this report.[57] CYCLONE-3 is a phase 3, double-blinded, randomized placebo-controlled trial of abemaciclib plus AA and prednisone versus placebo plus AA and prednisone in men with high-risk mCSPC. The primary endpoint is investigator-assessed rPFS and key secondary endpoints include rPFS assessed by blinded independent central review, CRPC-free survival, OS, time to pain progression, safety, and pharmacokinetics. Patients will be stratified based on the presence of visceral metastases and de novo presentation.[58]

AKT Inhibitors

Phosphatidylinositol 3-kinase (PI3K) alterations occur in almost 50% and loss of function of PTEN tumor suppressor occurs in around 40% of patients with mCRPC.[59] Loss of PTEN results in the activation of the PI3K/AKT pathway and promotes prostate cancer growth without AR signaling.[60] To date, trials of single-agent PI3K inhibitors, mTOR inhibitors, and AKT inhibitors in prostate cancer have not been successful due to dose-limiting toxicities and lack of efficacy, thought to be, in part, due to the presence of multiple compensatory pathways resulting in treatment resistance.[60-62] In a phase II study of 253 mCRPC patients, the combination of ipatasertib, an AKT inhibitor, plus AA showed promising efficacy with improvement in rPFS, OS, and time to PSA progression in those who received both drugs compared with AA alone. A greater rPFS improvement was observed in mCRPC patients with PTEN loss.[63] A phase III trial of another AKT inhibitor, capivasertib, is underway in mCSPC patients (CAPItello-281). In this trial, de novo PTEN deficient mCSPC patients will be randomized to receive capivasertib plus AA or placebo plus AA in addition to primary ADT. The primary endpoint of this study is rPFS and secondary endpoints include OS, time to start of first subsequent therapy or death, symptomatic-skeletal event–free survival, time to pain progression, and safety.[64]

Immunotherapy in Prostate Cancer

While immunotherapy has been well integrated into standard treatment regimens for virtually every other metastatic solid tumor, multiple studies conducted in advanced prostate cancer to date have not shown robust responses with the use of immunotherapy or immune checkpoint inhibitors. Efforts to add on pembrolizumab to standard-of-care treatments like DOC and enzalutamide have failed to meet its primary endpoints.[65,66]

Future Directions

Metastatic castration-sensitive prostate cancer is a heterogeneous disease entity characterized by a wide range of clinical behavior and presentation among patients. Much progress has been undoubtedly made in terms of genomic analysis, prognostication, and the identification of specific pathways involved in the pathogenesis of prostate cancer, including the development of castration-resistance. However, patients receiving treatment for mCSPC inevitably develop castration-resistance

and disease progression and available therapies for mCRPC generally do not offer a durable, sustained response. Ultimately, progression from mCSPC to mCRPC results in a dramatic reduction in life expectancy and patients are often limited in their ability to tolerate conventional systemic therapies as their disease progresses. Therefore, current clinical trials building on existing regimens and assessing the role of treatment intensification in first-line mCSPC are extremely valuable and worthwhile. The ARASENS and PEACE-1 triplet therapy protocols serve as proof of concept that upfront systemic treatment intensification in the castration-sensitive setting helps metastatic prostate cancer patients live longer by delaying the development of castration-resistance. The use of RLT and PARPi is better established in the mCRPC setting currently, but ongoing studies will help to determine whether treatment with these agents earlier on in when patients are still castration-sensitive will help to improve long-term outcomes. On the contrary, the improvement in treatment efficacy comes at the cost of increased risk of toxicity. Patients who are exposed earlier to marrow-toxic agents like PARPi or RLT or drugs in succession could have higher risks of myelosuppression as well. For instance, one instance (<1%) of myelodysplasia and another instance of acute myeloid leukemia were reported in the safety reporting and follow-up period, respectively, in the TALAPRO-2 study in the talazoparib with enzalutamide arm. Therefore, we must be cognizant of potential long-term toxicity from these agents in patients who have projected prolonged survival. In addition, we hope to gain a better understanding of targeted therapies and their potential, especially in combination with currently approved drugs, in the treatment of advanced prostate cancer.

Conclusion

Treatment of mHSPC has rapidly evolved through the years, with initial ADT monotherapy as the cornerstone of treatment, now with standard doublet or triplet therapy whenever appropriate. There are remaining questions with regard to the candidates for triplet therapy, and considerations include toxicity, impact on sequencing, and financial costs. In addition, as men survive longer, the potential impact of late toxicity becomes all the more important. Regardless, improvement in OS over the years with available therapies remains one of the most important goals. How to best incorporate novel therapies in the frontline setting would be one way to move forward.

Author Contributions

JBA-C conceptualized the article; E-MY, IP, FP, MWH, and JBA-C wrote original draft, provided materials, reviewed, edited, and drafted final manuscript.

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