The Treatment Landscape of Metastatic Prostate Cancer

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Abstract

The treatment landscape of metastatic prostate cancer has evolved significantly over the past two decades. Several landmark phase 3 trials led to new drug approvals and rapid changes in therapy options for patients, including drugs with distinct mechanisms of action (e.g., hormonal, chemotherapy, radionuclide, immunotherapy, and targeted therapies). Therapies initially developed in later stages of the disease (metastatic castration resistant prostate cancer) have started to move earlier in the prostate cancer continuum, with new standards of care for metastatic hormone naive prostate cancer and non-metastatic castration resistant prostate cancer. Overall, patients are living longer with a better quality of life. However, despite these significant advances, prostate cancer remains a leading cause of cancer death globally. Disease heterogeneity and the emergence of therapy resistance remain significant barriers, and the identification and application of molecular biomarkers to guide the choice and sequencing of systemic agents are still in early stages. Here we discuss the current treatment landscape of metastatic prostate cancer, clinical challenges, and the emerging role of molecular biomarkers for targeting biologic subsets of advanced disease and co-targeting heterogenous resistance patterns.

Keywords (5)

metastatic prostate cancer, castration resistance, androgen receptor pathway inhibitor, treatment sequencing, precision medicine

Introduction

Prostate cancer is a major cause of morbidity and mortality for men worldwide. In the United States, over 190,000 men were diagnosed with prostate cancer in 2020 and approximately 33,000 men died from prostate cancer (1). While localized prostate cancer is generally associated with more favorable outcomes, metastatic prostate cancer is currently considered incurable. Over the last twenty years, there have been significant advances in the field's biologic understanding and treatment of metastatic prostate cancer with nine new drugs approved in the United States for metastatic castration resistant prostate cancer (mCRPC) since 2004 (Table 1). Several of these drugs have now been tested and approved in earlier disease settings, including non-metastatic CRPC (nmCRPC) and metastatic hormone sensitive prostate cancer (mHSPC). Men are living longer with a better quality of life. Despite these significant advances in systemic therapy, tumor heterogeneity and acquired resistance remain significant barriers limiting durable remissions and precluding cures for individuals with metastatic disease (2-4). To overcome these challenges, biomarker-based precision medicine approaches are needed (4, 5).

With more drugs to now choose from, therapy selection and the optimal sequencing of treatments are current clinical challenges. For men with mCRPC, advances in genetics and genomics have identified predictive biomarkers for immune checkpoint inhibitor therapy (e.g., microsatellite instability (MSI), mismatch repair deficiency) and for poly (ADP-ribose) polymerase (PARP) inhibitor therapy (e.g., homologous recombination DNA repair deficiency), yet responses are heterogenous and there is still much to learn about the impact of specific genes, co-occurring alterations, and acquired resistance to these agents. Molecular imaging is emerging as a non-invasive biomarker to identify patients suitable for drugs targeting prostate cancer specific antigen (PSMA), which can be detected in tumors through the use of positron emission tomography (PET)-imaging (6). Potent androgen receptor (AR)-targeted drugs, initially developed for men with mCRPC to target androgen deprivation therapy (ADT)-resistance, have moved into earlier disease states including for nmCRPC and mHSPC. With earlier, longer, and more potent inhibition of the AR, resistance patterns after potent AR-targeted drugs are evolving, pointing to new therapeutic vulnerabilities. Chemotherapy continues to play an important role in metastatic prostate cancer, both in mCRPC and mHSPC, and determining who should receive chemotherapy early on to combat or prevent AR-resistant clones from emerging or to target the emergence of aggressive variants remain an unmet need. While certain clinical features prognosticate at different stages of prostate cancer progression (7-9), the implementation of predictive biomarkers to guide systemic therapy is still evolving.

Androgen Deprivation Therapy and the Development of Castration Resistance

Prostate cancer arises as androgen-driven disease, and ADT has been the standard backbone of therapy for men with advanced prostate cancer since the 1940s. ADT typically refers to lowering testosterone production through surgical or medical castration. This can be achieved through orchiectomy or medically through gonadotropin-releasing hormone (GnRH) agonists (goserelin, histrelin, leuprorelin or triptorelin) or GnRH antagonists (degarelix, relugolix). In addition to treating metastatic prostate cancer, ADT is also given in earlier disease settings as neoadjuvant and adjuvant treatment combined with radiotherapy for newly diagnosed intermediate and high-risk prostate cancer or in the salvage setting, adjuvantly for patients with nodal disease after radical prostatectomy, or for patients that develop biochemical recurrence with short doubling times. While testosterone-lowering approaches have generally been considered equivalent in overall efficacy, the new oral AR-antagonist relugolix has been associated with decreased cardiovascular events compared with leuprolide (10). Shore et al. conducted a phase 3 trial to investigate the efficacy and safety of relugolix as compared to leuprolide in men with advanced prostate cancer. This study showed superiority of relugolix in achieving rapid and sustained testosterone suppression and relugolix was also associated with lower risk of cardiovascular events versus leuprolide (2.9% vs 6.2%, hazard ration (HR); 0.46, 95% confidence interval (CI); 0.24-0.88) (10).

Historically, for locally advanced and metastatic prostate cancer, ADT with or without early-generation AR antagonists (e.g., bicalutamide) was commonly used (11, 12) until more recent data established ADT plus potent AR targeted therapies as a new standard of care (see mHSPC section). ADT, even when combined with potent AR drugs, is initially effective for the vast majority of men with metastatic prostate cancer but is not considered curative unless combined with local or focal therapy (i.e., radiation or surgery). Monitoring on ADT includes serial serum prostate specific antigen (PSA) testing, imaging, and clinical assessments. PSA is an androgen-regulated protein secreted from prostate tumor cells and detectable in serum with high sensitivity and specificity. In mHSPC, the degree of PSA response correlates with longer term outcomes (13) but resistance to ADT (i.e., castration resistance) generally occurs after approximately 10-15 months (14). Prior to 2004, there were no systemic therapies with a proven survival benefit for patients with mCRPC (15, 16). There are now nine drugs approved, based on landmark phase 3 trials and include drugs with varied mechanism of action (Figure1, Table 1).

Treatment of Metastatic Castration Resistant Prostate Cancer

-Taxane chemotherapy-

Docetaxel, a taxane chemotherapy, was the first drug to get approved for mCRPC in 2004 based on an overall survival (OS) benefit seen in the Phase 3 TAX327 and SWOG9916 trials (15-17). In TAX327, patients were randomized to receive docetaxel every 3 weeks (75mg/m^2), docetaxel weekly (30mg/m^2), or mitoxantrone every 3 weeks (12mg/m^2) with prednisone (10mg daily). The median OS was significantly prolonged with docetaxel every 3 weeks compared with the mitoxantrone group (18.9 vs. 16.5 months, P = 0.009, HR; 0.76, 95%CI; 0.62-0.94). This was not seen with weekly docetaxel (17.4 months, P = 0.36, HR; 0.91, 95%CI; 0.75-1.11) (16). PSA responses were also higher with docetaxel compared with mitoxantrone (45% vs. 32%, respectively *(*P < 0.001). There was a significant improvement in quality of life (QOL) with docetaxel (22% vs. 13%, P = 0.009) (16). In SWOG9916, docetaxel plus estramustine showed significantly improved OS versus mitoxantrone plus prednisone (median; 17.5 vs. 15.6 months, P = 0.02) (15). On the basis of these landmark phase 3 trials, every 3-week docetaxel treatment was approved by the Food and Drug Administration (FDA) for men with mCRPC.

Cabazitaxel was the second chemotherapy to be approved for patients with mCRPC. Also a taxane chemotherapy, cabazitaxel (25mg/m^2, intravenously, every 3 weeks) demonstrated an OS benefit compared with mitoxantrone in patients with mCRPC previously treated with docetaxel in the phase 3 TROPIC trial (median, 15.1 vs. 12.7 months, P < 0.0001, HR; 0.70, 95%CI; 0.59-0.83) (18). In a subsequent non-inferiority trial, the PROSELICA phase 3 trial compared cabazitaxel (25mg/m^2) with a reduced dose of cabazitaxel (20mg/m^2) (19). The noninferiority of the reduced dose was confirmed with the median OS was 13.4 months for 20mg/m^2 group and 14.5 months for 25mg/m^2 group (HR; 1.024). On the other hand, more favorable PSA response (29.5% vs. 42.9%, P < 0.001) and time to PSA progression (median, 5.7 months vs. 6.8 months) were observed with 25mg/m^2 (19). The incidence of grade 3/4 adverse events was lower with 20mg/m^2 as compared to 25mg/m^2 (39.7% vs. 54.5%). Based on these findings, both 20mg/m^2 and 25mg/m^2 are reasonable options, and the risks and benefits should be weighed based on the individual patient balancing potential need for deeper response with patient risk for chemotherapy toxicity. Supportive care measures and growth factor support has made cabazitaxel a manageable therapy for most patients. While cabazitaxel demonstrated benefit after docetaxel, it should not replace docetaxel as first line chemotherapy based on the phase 3 FIRSTANA trial (20).

-Sipuleucel-T-

Sipuleucel-T is a vaccine therapy targeting prostatic acid phosphatase (PAP) that was FDA-approved in the United States in 2010 for the treatment of asymptomatic and minimally symptomatic men with mCRPC based on the IMPACT trial (21). This phase 3 trial randomized patients to sipuleucel-T (intravenously, every 2 weeks, total of three infusions) or placebo; 15.5% of patients received docetaxel before enrollment and all patients were asymptomatic or minimally symptomatic. Sipuleucel-T administration decreased the risk for death by 22% compared with placebo (median OS, 25.8 vs. 21.7 months, 95%CI; 0.61-0.98, P = 0.03). Frequently observed adverse events with sipeleucel-T included chills (54.1%), pyrexia (29.3%), and headache (16%), and these were generally transient symptoms (21). Despite this positive trial and FDA approval in the United States, the logistic of administration, cost considerations, and approval of competing drugs at around the same time have limited its widespread adoption worldwide. Interestingly, in a recent world-wide registry (PROCEED) of over 1900 patients receiving sipuleucel-T, the OS of African Americans (AA, n = 221) was 35.3 months compared with 25.8 months in Caucasians (n = 1649) (HR 0.70, 95% CI 0.57–0.86; P < 0.001) (22). Along with other known prognostic factors, AA race was independently associated with prolonged OS on multivariable analyses (HR; 0.60, 95%CI; 0.48–0.74; P < 0.001). These data suggest racial differences in mCRPC tumors that may be leveraged therapeutically.

-AR pathway inhibitors-

It is now well established that most CRPC tumors are not hormone independent and that re-activation of AR signaling is a key driver of resistance and progression (23). This led to the rational development and FDA approval of potent AR pathway inhibitors (ARPIs) for mCRPC. Abiraterone is an inhibitor of CYP17 (17a-hydroxylase/C17, 20-lyase), which inhibits extragonadal androgen synthesis by the adrenal glands and by tumor cells (24, 25). Steroids such as prednisone is administered concurrently with abiraterone to replace cortisol and prevent side effects (e.g., hypertension, hypokalemia, edema). In the randomized phase 3 COU-AA-301 trial, patients with mCRPC previously treated with docetaxel were randomized to receive abiraterone plus prednisone versus placebo plus prednisone. There was a significant OS benefit favoring abiraterone/prednisone (14.8 vs. 10.9 months, P < 0.001, HR; 0.65), as well as improvements in time to PSA progression (10.2 vs. 6.6 months, P < 0.001) (26, 27), pain control (pain palliation ratio 45% with abiraterone/prednisone vs 28.8% in placebo/prednisone group (P = 0.0005) (28). The randomized phase 3 COU-AA-302 trial subsequently established an OS benefit for abiraterone/prednisone in patients with mCRPC not previously been exposed to docetaxel (34.7 vs. 30.3 months, P = 0.003, HR; 0.81). The main adverse reactions observed with abiraterone/prednisone were fatigue (39%), hypokalemia (17%), hypertension (22%), and hepatotoxicity (18%) (29). On the basis of these practice-changing clinical trials,

abiraterone/prednisone was added to the treatment sequence for mCRPC patients regardless of prior chemotherapy exposure.

Enzalutamide is a potent AR-antagonist that acts through three independent mechanisms: inhibition of binding of androgens to the AR, prevention of translocation of the AR to the nucleus, and inhibition of AR binding to DNA (30). In 2012, the FDA approved enzalutamide for the treatment of mCRPC after docetaxel treatment based on the AFFIRM trial (31, 32). This phase 3, double-blind, placebo-controlled trial randomized 1199 men with mCRPC, previously treated one or two chemotherapy regimens including docetaxel, to receive enzalutamide (160 mg per day) or placebo. The median OS was significantly prolonged with enzalutamide (18.4 months enzalutamide vs. 13.6 months with placebo ($P < 0.001$, HR; 0.63, 95%CI; 0.53-0.75) (31). PSA response rate (54% vs. 2%, $P < 0.001$), soft-tissue response (29% vs. 4%, $P < 0.001$), quality of life (43% vs. 18%, $P < 0.001$), time to PSA progression (8.3 vs. 3.0 months, $P < 0.001$), rPFS (8.3 vs. 2.9 months, $P < 0.001$), and time to first skeletal-related event (16.7 vs. 13.3 months, $P < 0.001$) all favored enzalutamide (31). The subsequent phase 3 PREVAIL study established the role for enzalutamide for chemotherapy-naive patients (33) with significantly prolonged rPFS (20.0 vs. 5.4 months, $P < 0.0001$, HR; 0.32) and OS (35.3 vs. 31.3 months, $P = 0.0002$, HR; 0.77) (34). Thus, enzalutamide became another important treatment option for patients with mCRPC, both in docetaxel-treated and docetaxel-naive disease settings.

-Radiopharmaceutical and bone targeted agents-

The majority of patients with mCRPC have bone metastases, and bone-only disease is seen in approximately 40-50% (29, 33, 35, 36). Radium-223 is a targeted alpha emitter radionuclide therapy that preferentially incorporates into newly formed bone matrix within osteoblastic metastatic lesions. The alpha particles induce double strand DNA breaks in exposed tumor cells. Radium-223 was approved by FDA in 2013 for patients with mCRPC with symptomatic bone metastases and without visceral metastasis, based on results from the ALSYMPCA trial (37). 921 patients were randomized to receive radium-223 intravenously once per month for 6 months (at a dose of 50kBq per kilogram of body weight) or placebo. Radium-223 significantly improved OS (median, 14.9 vs. 11.3 months, $P < 0.001$, HR; 0.70, 95%CI; 0.58-0.83) and time to first symptomatic skeletal event (median, 15.6 vs. 9.8 months, $P < 0.001$, HR; 0.66, 95%CI; 0.52-0.83) (37, 38). The survival benefit was observed irrespective of previous docetaxel use (39). The measurements of QOL showed significant improvement with radium-223 ($P = 0.02$) (40). The approval of radium-223 led to subsequent combination trials, many of which are still ongoing (41, 42) (Table 2). Notably the Phase 3 ERA-223 trial of abiraterone plus radium-223

or placebo was negative for its primary endpoint of symptomatic skeletal event-free survival, and the study was unblinded early due to increase fractures and deaths in the combination arm (29% with abiraterone plus radium-223 vs. 11% abiraterone plus placebo) (42). In patients receiving bone health agents (denosumab or zometa), fractures were less common (15% vs. 37% in the combination arm; 7% vs 15% with abiraterone alone), emphasizing the importance of bone targeting agents for men with mCRPC and bone metastases. Both zoledronic acid (43, 44) and denosumab (45) at every four week dosing have shown clinical benefit in decreasing skeletal-related events for men with mCRPC and bone metastases (but not in mHSPC (46-48)) and should be considered in the treatment paradigm as standard of care for patients with mCRPC and bone metastases.

-Immune checkpoint inhibition-

In 2017, the anti-PD1 immune checkpoint inhibitor pembrolizumab was approved by the FDA for patients with unresectable or metastatic solid tumors that have progressed after standard therapies and whose tumors harbor microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) (49). This represented the first pan-cancer drug approval based on biomarker-selection, and the first molecular-driven therapy for mCRPC. This pan-cancer approval was based on five clinical trials (KEYNOTE-016/164/012/028/158), though mCRPC was significantly underrepresented in these studies. The FDA label was recently updated to also include solid tumors with tumor mutational burden (TMB) $\geq$10 mutations/megabase, based on efficacy data of ten refractory solid tumors (50). MSI, high-TMB, and/or mismatch repair deficiency occurs in approximately 3-5% of mCRPC, and significant and even exceptional responses to pembrolizumab have been reported (as opposed to minimal responses in biomarker-unselected patients), justifying routine testing. However, responses in mCRPC in this setting are not universal (51, 52) and there still much to learn regarding the optimal assay to detect immunogenic prostate cancers most amenable to single agent checkpoint inhibition. To this end, the immune checkpoint inhibitor ipilimumab that targets CTLA-4 did not demonstrate benefit in two phase 3 studies for biomarker unselected mCRPC but has been associated with long term and exceptional responses in some individuals (53, 54). Underlying mismatch repair deficiency, high TMB, abundance of tumor infiltrating lymphocytes and/or other mechanisms may also have explained more favorable outcomes in these individuals. The combination of ipilimumab and nivolumab has also shown promising activity in some individuals (55). Combining immunotherapy with other agents to increase immune infiltration is also an area of active investigation. Recently the combination of the anti-PD-L1 antibody atezoluzimab with cabozantinib has shown encouraging clinical activity (56) and a phase 3 trial is ongoing (NCT 04446117) (Table 2).

-PARP inhibitors-

In 2020, two drugs targeting PARP-- olaparib and rucaparib-- were FDA-approved for the treatment of patients with mCRPC harboring distinct genomic alterations involving homologous recombination (HR) DNA repair genes. The biologic rationale for targeting HR defects with PARP inhibition has been well established in other tumor types elucidating synthetic lethality. In mCRPC, HR deficiency occurs in up to 20% of patients—with mutations occurring either at the somatic or germline level. While *BRCA2* is the most common HR gene alteration in prostate cancer, with loss of function occurring through mutation or deletion, other less common HR gene alterations are also observed. The phase 3 PROfound trial enrolled men with mCRPC and HR --gene deficiency (centrally tested for pathogenic alterations involving 15 genes). All patients were previously treated with enzalutamide or abiraterone, and they were randomized to receive the PARP inhibitor olaparib (300mg orally twice daily) or the other ARPI (abiraterone or enzalutamide, whichever drug they had not previously received) (57). Patients were divided into two cohorts (A and B); cohort A had at least one alteration in *BRCA1*, *BRCA2*, or *ATM,* and cohort B had alterations in any of 12 other HR pathway-related genes (*BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B/C/D, RAD54L*). Olaparib was associated with a significantly longer radiographic PFS and OS compared with the other ARPI in cohort A (median PFS 7.4 vs. 3.6 months, $P < 0.001$, HR; 0.34, 95%CI; 0.25-0.47; median OS, 18.5 vs. 15.1 months, $P = 0.02$, HR; 0.64, 95%CI; 0.43-0.97) and in the overall population (cohorts A and B) (median PFS, 5.8 vs. 3.5 months, $P < 0.001$, HR; 0.49, 95%CI; 0.38-0.63; median OS, 17.5 vs. 14.3 months, $P = 0.0063$, HR; 0.67, 95%CI; 0.49-0.93). Based on PROfound trial, olaparib was FDA approved for men harboring germline or somatic aberrations in any of the 12 genes used as inclusion criteria. The PARP inhibitor rucaparib was also FDA approved in 2020 for men with mCRPC harboring *BRCA* alterations based on the TRITON2 trial. In this open label phase 2 trial, patients with mCRPC who progressed after one or two lines of next generation ARPI and one taxane and harbored a mutation in a DNA repair gene were treated with rucaparib 600 mg twice daily (58, 59). The primary endpoint was overall response rate (objective response rate (ORR), PSA or radiographic). Rucaparib was approved based on 115 enrolled patients with *BRCA* alterations (germline or somatic) with or without measurable disease. In this cohort, ORR per independent radiology review and investigator assessment were 43.5% (95% CI, 31.0% to 56.7%; 27 of 62 patients) and 50.8% (95% CI, 38.1% to 63.4%; 33 of 65 patients), respectively. PSA response rate 54.8% (95% CI, 45.2%, 64.1%; 63 of 115 patients). ORRs were similar for patients with a germline or somatic *BRCA* alteration and for *BRCA1* or *BRCA2*. A phase 3 trial (TRITON3) of rucaparib vs. physician choice therapy is ongoing (NCT02975934) (Table 2). Response to PARP inhibition is influenced by the specific HR gene

alteration present (e.g., for instance, higher responses observed with BRCA and PALB2 compared with CDK12 or ATM) and the presence of biallelic loss of function (which is not always reported on commercial assays); other potential readouts of functional HR deficiency (e.g., RAD51 foci) may also be helpful (60). Collectively, these data support the use of PARP inhibitor therapy for mCRPC with homologous recombination gene alterations, especially *BRCA*. Larger cohort data for the other less common genes is still accumulating. Emerging data suggests that *ATM* mutated prostate cancer may be less responsive to PARP inhibitor monotherapy and may be more amenable to ATR inhibition or combined ATR and PARP inhibition (61). CDK12 alterations may also be less responsive to PARP inhibition and have been associated with immunotherapy responses (62). Beyond those HR gene aberrations, PARP inhibitors are also being tested in combination with ARPI for biomarker- unselected patients with mCRPC (NCT03395197, 04691804, 03732820) (Table 2). In situations where PARP inhibitors are not available or not desired, platinum chemotherapy can also be considered with activity seen in patients with HR gene deficiency (63).

-Targeting PTEN loss-

The approval of pembrolizumab and then PARP inhibitors for biomarker-positive subgroups of prostate cancer has expanded the role of genetic and genomic testing. Both tissue-based and circulating tumor DNA assays are now routinely applied for somatic testing and supported by NCCN guidelines. Germline testing is also recommended for all patients as inherited mutations are seen in up to 12% of men with advanced prostate cancer, which carries additional considerations for family members (64). Somatic and germline alterations are most commonly tested using targeted panels and therefore not only identify patients amenable to PARP inhibition or immune checkpoint therapy but can also identify other potential targets and biomarkers. Somatic PTEN loss is observed in 40-60% of mCRPC tumors, most commonly through homozygous deletion, resulting in hyperactivation of the PI3K-Akt-mTOR signaling pathway (65, 66). Crosstalk between the PI3K-Akt-mTOR pathway and AR signaling led to rational testing of the combination of abiraterone and the Akt inhibitor ipatasertib. The Phase 3 IPATential150 trial randomized patients with mCRPC in the first line setting to abiraterone in combination with ipatasertib 400 mg daily versus placebo (67). Patients were stratified by PTEN loss by immunohistochemistry. There was a significant radiographic PFS benefit for patients receiving abiraterone plus ipatasertib for those with PTEN loss (HR; 0.77), but not in the overall population. The OS data is still maturing. On the other hand, serious adverse events were observed in 40% of patients in the ipatasertib group, which caused 21% of patients to discontinue the treatment. Further consideration of risks and benefits of ipatasertib plus abiraterone should be examined as more mature trial data emerges. Biomarker analysis of PTEN loss by IHC

versus next generation sequencing (NGS) showed relatively high concordance (85.5%.), yet a more robust PFS difference was observed with NGS. We await more data regarding this combination and biomarker analyses.

-Targeting PSMA-

Prostate specific membrane antigen (PSMA) is a cell surface marker expressed on prostate cancer cells that can be imaged with PET-imaging as well as targeted therapeutically (68, 69). While PSMA PET-imaging was recently approved by the FDA for disease localization for high risk localized and biochemical recurrent prostate cancer, PET-imaging in mCRPC has been performed mainly in the context of clinical trials. The vast majority of mCRPC tumors express PSMA, though express can become heterogeneous or even lost in late stages of the disease (70). There are a number of therapeutic approaches in development to target PSMA, with the most advanced being the radionuclide ^{177}Lu -PSMA-617 (6, 71). ^{177}Lu is conjugated to the ligand PSMA-617, which has high affinity for PSMA (72), and the DOTA/DOTAGA chelator emits ɤ radiation and its β^- particle to attack cancer cells (73, 74). In a single-arm phase 2 study of ^{177}Lu -PSMA-617, 57% of heavily pretreated patients with mCRPC achieved ≥50% decline in PSA and 82% showed objective responses in nodal or visceral disease (6). Treatment was administered intravenously at six weekly intervals, with a maximum of 4 cycles. The most common side effect was grade 1 dry mouth reported in 87% of patients. Grade 3 or 4 thrombocytopenia was observed in 13% (6). In a subsequent randomized phase 2 trial (TheraP), patients with mCRPC previously treated with docetaxel were randomized to receive ^{177}Lu-PSMA-617 or cabazitaxel (75, 76). The key eligibility for TheraP included PSMA expression by ^{68}Ga-PSMA-11 PET/CT imaging and no FDG-positive/PSMA-negative discordant sites of disease. ^{177}Lu-PSMA-617 significantly improved PSA-PFS as compared to cabazitaxel (HR; 0.69) and achieved higher PSA response rates (66% vs. 37%). Fewer grade 3-4 adverse events were observed in ^{177}Lu-PSMA-617 group as compared to cabazitaxel (33% vs. 53%) (76). The international prospective open-label phase 3 study (the VISION trial) was recently reported as positive for its primary endpoints of overall survival and progression free survival (press release, March 2021). VISION enrolled patients with mCRPC previously treated with at least one ARPI and at least one but no more than two taxanes. All patients had positive PSMA-expression on PET/CT imaging. Patients were randomized to ^{177}Lu-PSMA-617 plus best supportive/standard of care versus best supportive/standard of care (2:1) (77). We await the full data release, nonetheless the development of ^{177}Lu-PSMA-617 and positive phase 2 and phase 3 results represents a significant advance and a potential paradigm shift for patients that may support the future use of PSMA imaging and PSMA-targeted radioligand therapy for mCRPC. Trials investigating ^{177}Lu-PSMA-617 combination approaches and in earlier disease settings, as

well as novel drugs with alternative PSMA-targeting approaches (actinium, CAR-T, BiTE) are areas of active investigation (78-80).

-Treatment of aggressive variants-

With the approval of new drugs for mCRPC, resistance patterns are also evolving. Up to 20% of patients with mCRPC can develop aggressive clinical features and/or transformation to small cell carcinoma that manifests as rapidly progressive disease and refractoriness to standard drugs. These patients may be considered for platinum-based chemotherapy. The combination of cabazitaxel and carboplatin was investigated in a phase 2 trial compared with cabazitaxel alone for men with mCRPC (81). The combination therapy showed significant improvement of PFS from 4.5 to 7.3 months (HR; 0.69, 95% CI; 0.50-0.95, P = 0.018), which was especially pronounced in those with aggressive variant clinical or molecular features (median PFS (7.5 vs. 1.7 months, P = 0.017, median OS 20.2 vs. 8.5 months, P = 0.0002). These features include: the presence of exclusive visceral metastases, low PSA and bulky disease, high lactose dehydrogenase levels, elevated CEA, lytic bone metastases, small cell/neuroendocrine histology, and/or loss of 2/3 tumor suppressors PTEN/RB1/TP53). Based on these data, NCCN guidelines now include the option of cabazitaxel and carboplatin for mCRPC and aggressive clinical or molecular features.

For patients with small cell neuroendocrine prostate cancer (NEPC), either those that arise *de novo* or are acquired during CRPC therapy resistance, other small cell carcinoma systemic therapy regimens may also be considered based on data in small cell lung cancer (SCLC) (82). This may include carboplatin plus etoposide with or without checkpoint inhibitor immunotherapy in the first line, and next line SCLC regimens such as topotecan, lubrinectidin, ipilumimab/nivolumab, or others. Clinical trials focused on targeting NEPC are currently underway and should be considered. In patients with mixed adenocarcinoma-NEPC features, therapy considerations are often individualized based on the presence of aggressive clinical features and the dominant histology. Refinement of molecular biomarkers may ultimately improve the detection and treatment of aggressive variants including NEPC.

Non-Metastatic Castration Resistant Prostate Cancer

Based on treatment advances in mCRPC, potent ARPI have moved their way earlier into the disease for nmCRPC and mHSPC. nmCRPC was defined in trials as the development of rising PSA despite castrate levels of testosterone, PSA doubling time $\leq$10 months, without evidence of metastases on standard imaging (i.e., CT and bone scan). Notably, PSMA PET-CT imaging was not included. We now know that most men with nmCRPC meeting these eligibility criteria do

have evidence of metastases on more sensitive imaging (i.e., pelvic or M1 disease) (83). Therefore, with more routine use of PSMA-PET imaging, the identification of non-metastatic disease is less frequent compared with prior nmCRPC trials. Enzalutamide, darolutamide, and apalutamide are three potent AR-antagonists with similar mechanisms **o**f action that each demonstrated significant clinical benefit in three phase 3 trials for nmCRPC (based on standard imaging) when compared with placebo (PROSPER, ARAMIS, SPARTAN, respectively) (84-86). While there were some differences the study designs, all three studies enriched for patients most likely to develop metastases defined by a PSA doubling time of $\leq$10 months and had a primary endpoint of metastasis-free survival (MFS) (84-87). These strongly positive trials were not only positive for their primary endpoint of MFS with an improvement of over 20 months seen (HR; 0.29, HR; 0.41, HR; 0.28, respectively) (Table 1), but they also demonstrated improvements in OS, time to pain progression, time to chemotherapy, and time to skeletal events. Overall, these data support the earlier use of life prolonging ARPI therapy for patients with CRPC.

Bringing Drugs Earlier: Metastatic Hormone Sensitive Prostate Cancer

-Docetaxel-

With significant benefits of systemic therapies observed in CRPC, trials investigating their use in metastatic hormone naive prostate cancer were also pursued, with positive phase 3 trials now reported that favor ADT in combination with docetaxel, abiraterone, enzalutamide, or apalutamide. The approval of docetaxel in combination with ADT for mHSPC was established by the Phase 3 CHAARTED and STAMPEDE trials (14, 88). In CHAARTED, patients with mHSPC were randomly assigned to ADT plus docetaxel (75mg/m^2 intravenously every 3 weeks for 6 cycles) or ADT-alone. Combination chemohormonal therapy significantly extended OS, and this was most predominant in patients with high-volume disease (HR; 0.63, 95%CI; 0.5-0.79, $P < 0.001$). In CHAARTED, high volume metastatic disease was defined as greater than or equal to four bone metastases with at least one outside of the vertebral column and pelvis and/or the presence of visceral metastases (14). The STAMPEDE trial evaluated the additional effect of docetaxel to standard of care (ADT +/- radiation therapy) in patients with M0 and M1 HSPC (88). As with CHAARTED, the STAMPEDE trial (arm C) showed a survival benefit supporting the combination of ADT plus docetaxel (the median OS 5,4 vs. 3.6 years) for newly diagnosed mHSPC (88).

-Abiraterone acetate-

The STAMPEDE trial also investigated the combination of abiraterone acetate (1000mg daily) plus prednisolone (5mg daily) and ADT versus ADT alone in patients with mHSPC (89). This

study also included non-metastatic disease. There was a significant OS benefit with ADT plus abiraterone versus ADT alone for mHSPC (HR; 0.61, 95% CI; 0.49-0.75) (89). Similarly, the LATITUDE trial also supported the combination of abiraterone with ADT for high-risk mHSPC (90). In this study, high-risk prostate cancer was defined as the presence of two of the three following features: Gleason score ≥8, ≥ 3 bone lesions, or measurable visceral metastasis. Median OS in patients who received ADT plus abiraterone was significantly longer compared with ADT alone (not reached vs. 34.7 months, $P < 0.001$, HR; 0.62. 95%CI; 0.51-0.76). Radiographic PFS also favored the combination (33.0 vs. 14.8 months placebo, $P < 0.001$) (90). Of note, STAMPEDE data showed that abiraterone benefits both high and low volume disease (based on CHAARTED criteria) and high and low risk disease (based on LATITUDE criteria) (91).

While docetaxel and abiraterone have not been directly compared head-to-head, a comparative analysis of patients on STAMPEDE demonstrated that there were no significant differences in OS, prostate cancer-specific survival and other clinical outcomes between the two agents (92). These accumulated evidence suggests that either ADT plus docetaxel or abiraterone are reasonable choices and decisions should be made based on other factors such as side effect profiles, volume of disease, patient comorbidities, preferences, and cost considerations.

-Enzalutamide and Apalutamide-

The potent AR antagonists enzalutamide and apalutamide are also approved for mHSPC (85, 93-95). The ENZAMET trial randomized 1125 men with mHSPC to ADT plus enzalutamide or ADT plus a nonsteroidal antiandrogen (e.g., bicalutamide). 17% of patients previously received docetaxel, 42.3% presented with relapsed disease, and 61% presented de novo with metastatic disease. ENZAMET showed a significant OS benefit for enzalutamide for both low and high volume disease, with 80% 3-year survival in the enzalutamide plus ADT group compared with 72% in the control group ($P = 0.002$, HR; 0.67) (95). PSA PFS ($P < 0.001$, HR; 0.39) and clinical PFS ($P < 0.001$, HR; 0.40) were also improved in the enzalutamide group (95). The approval of apalutamide was based on TITAN, a phase 3 trial of ADT plus apalutamide (240mg per day) or placebo. The majority of patients (80%) in TITAN presented de novo with metastatic disease. Patients receiving apalutamide with ADT had an improved rPFS (68.2 vs. 47.5%, $P < 0.001$) and OS (82.4% vs. 73.5%, $P = 0.005$) compared with the control group (93). Overall, these trials have expanded the number of choices of systemic therapy options in mHSPC and have changed the standard of care.

-Radiation therapy to primary prostate tumor for low volume metastatic disease-

In addition to advances in systemic therapy for mHSPC, recent data has also established a role of radiation to the primary prostate tumor for men with low volume metastatic disease (96-98). The STAMPEDE trial (arm H) enrolled 2061 newly diagnosed patients with de novo metastatic disease to standard care alone or standard care plus radiation therapy (RT) (daily: 55Gy in 20 fractions over 4weeks or weekly: 36Gy in 6 fractions over 6 weeks). 18% received ADT plus docetaxel as standard of care. RT to the primary tumor conferred a clinical benefit (OS, prostate cancer-specific survival, and PFS) for patients with low metastatic burden but not for those with high volume disease (97). The HORRAD trial showed a similar trend in the RT group, although it was not statistically significant (98). In addition to treating the primary tumor for low volume disease, focal therapy to oligometastatic lesions (detected by standard imaging or PET imaging) is commonly performed and current trials are investigating this prospectively.

Based on these mHSPC studies, it has become clear that patients with newly diagnosed metastatic prostate cancer should not be treated with ADT alone if they are candidates for adding these other life prolonging modalities. Clinical factors, including de novo vs. relapsed metastatic disease and high vs. low volume disease, are not only prognostic but also may be predictive. Other drugs approved in mCRPC are also being tested in the mHSPC disease setting, and several are moving even earlier in the neoadjuvant and adjuvant setting, which is beyond the scope of this review but highlights how earlier intervention may be of benefit for some individuals (Table 2).

How do we sequence therapies for metastatic prostate cancer?

With a growing armamentarium of drugs for metastatic prostate cancer, open questions exist regarding the optimal sequence of therapies. While every possible sequence cannot be tested prospectively, both biologic and clinical data have started to support practice patterns. For patients previously treated with docetaxel and ARPI therapy, there is level one evidence from the CARD trial to support the use of cabazitaxel (99). In CARD, a total of 255 patients who had progressed after docetaxel and ARPI therapy (abiraterone or enzalutamide) were randomly assigned to receive cabazitaxel (25 mg/m^2) or the other ARPI (that one they had not previously received). Cabazitaxel demonstrated a significant improvement in median PFS (4.4 vs. 2.7 months, HR; 0.52, $P < 0.001$) and OS (13.6 vs. 11 months, HR; 0.64, $P = 0.008$). The poor outcomes in the control group suggests cross resistance between ARPIs (99), with similar observations seen in the control arm of the PROfound trial (57). Molecular biomarkers such as AR-V7 splice variant expression in circulating tumor cells or AR amplification in circulating tumor DNA have been developed to help guide sequencing of APRI versus taxane therapy (100), and there may still be some patients that benefit when abiraterone is followed by enzalutamide

(vs. vice versa) (101), but the clinical data to date does not support routine sequential use of ARPIs especially if other life prolonging therapies are available. As discussed above, the earlier use and longer exposure to ARPIs in mHSPC and nmCRPC settings may also impact downstream resistance patterns including the development of AR-independent variants.

Conclusions

The treatment landscape of advanced prostate cancer has evolved dramatically in recent years, with drugs with distinct mechanisms of action improving outcomes for castration resistant prostate cancer and now moving to earlier disease settings. Furthermore, novel biomarker-driven therapeutic strategies based on biological features have made precision medicine a reality for patients. With these advances, a number of new opportunities and unmet needs arise to better refine biomarkers, conquer intra- and inter- patient heterogeneity, and combat emerging mechanisms of resistance.

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Table and Figure Legends

Table 1. Approved therapies for advanced prostate cancer.

Table 2. Ongoing phase 3 clinical trials for metastatic prostate cancer.

Figure 1. The current landscape of systemic therapies in prostate cancer

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Figure 1.

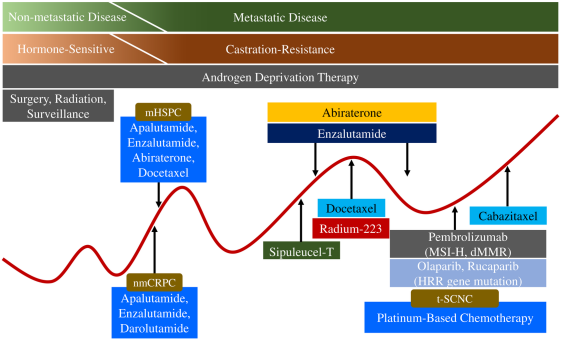
Non-metastatic Disease
Metastatic Disease
Hormone-Sensitive
Castration-Resistance
Androgen Deprivation Therapy
Surgery, Radiation, Surveillance
mHSPC
Apalutamide, Enzalutamide, Abiraterone, Docetaxel
nmCRPC
Apalutamide, Enzalutamide, Darolutamide
Abiraterone
Enzalutamide
Docetaxel
Radium-223
Sipuleucel-T
Cabazitaxel
Pembrolizumab (MSI-H, dMMR)
Olaparib, Rucaparib (HRR gene mutation)
t-SCNC
Platinum-Based Chemotherapy

Table 1

Disease Status	Agent	Clinical Trial	Control Arm	Outcome	FDA approved year	reference
(i) mHSPC	ADT + Docetaxel	CHAARTED	ADT + placebo	HR was 0.63 for OS in high-volume patients	2015	[11]
		STAMPEDE	ADT + SOC	HR was 0.78 for OS		[80]
	ADT + Abiraterone Acetate + Prednisolo	LATITUDE	ADT + placebo	HR was 0.62 for OS	2018	[82]
		STAMPEDE	ADT + placebo	HR was 0.61 for OS		[81]
	ADT + Apalutamide	TITAN	ADT + placebo	HR was 0.67 for OS	2019	[85]
	ADT + Enzalutamide	ARCHES	ADT + placebo	HR was 0.39 for rPFS	2019	[86]
		ENZAMET	ADT + standard care	HR was 0.67 for OS		[87]
(□) nmCRPC	Apalutamide	SPARTAN	plcacebo	HR was 0.28 for metastasis or death	2018	[78]
	Enzalutamide	PROSPER	placebo placebo	HR was 0.29 for metastasis or death	2018	[76]
	Darolutamide	ARAMIS		HR was 0.41 for MFS	2019	[77]
(□) mCRPC	Docetaxel	TAX327	mitoxantrone mitoxantrone	HR was 0.76 for OS	2004	[13]
		SWOG9916	plus prednisone placebo	HR was 0.80 for OS		[12]
	Sipuleucel-T	IMPACT	mitoxantrone placebo plus	HR was 0.78 for OS	2010	[18]
	Cabazitaxel	TROPIC	prednisone placebo plus	HR was 0.70 for OS and 0.74 for PFS	2010	[15]
	Abiraterone Acetate + Prednisolone	COU-AA-301	prednisone placebo placebo	HR was 0.65 for OS	2011	[23]
		COU-AA-302	placebo	HR was 0.81 for OS and 0.53 for rPFS		[26]
	Enzalutamide	AFFIRM	-	HR was 0.63 for OS	2012	[27]
		PREVAIL	abiraterone acetate or enzalutamide	HR was 0.77 for OS and 0.32 for rPFS		[29]
	Radium-223	ALSYMPCA	-	HR was 0.70 for OS and 0.66 for time to first skeletal event	2013	[33]
	Pembrolizumab	KEYNOTE-016/164/012/028/158		17.4% had PR and 34.8% had SD	2017	[45]
	Olaparib	PROfound		HR was 0.34 for imaging-based PFS and 0.64 for OS	2020	[53]
	Rucaparib	TRITON2		43.5% had ORR and 54.8% had PSA response (≥50%)	2020	[54]

mHSPC; metastatic hormone-sensitive prostate cancer, nmCRPC; non-metastatic castration-resistant prostate canecr, mCRPC; metastatic castration-resistant prostate canecr, FDA; Food and Drug Administration, HR was hazard ratio,
OS; overall survival, SOC; standard of care, rPFS; radiographic progression-free survival, MFS; metastasis-free survival, PR; partial response, SD; stable disease, ORR; objective response rate, PSA; prostate-specific antigen

Table 2

Therapeutic Target	Clinical Trials.gov Identifier (status)	Intervention/ Treatment Arm	Control Arm	Condition/Disease Status
local treatment	NCT03678025 (recruiting)	Definitive Treatment (Surgery or Radiation) plus Standard Systemic Therapy	Standard Systemic Therapy	mPCa
	NCT01949337 (Active, not recruiting)	Enzalutamide plus Abiraterone and Prednisone	Enzalutamide alone	mCRPC
	NCT04736199 (not yet recruiting)	Darolutamide plus plus ADT	Placebo plus ADT	mHSPC
	NCT02799602 (Active, not recruiting)	Darolutamide plus ADT and docetaxel	Placebo plus ADT	mHSPC
ARPI	NCT02257736 (Active, not recruiting)	Apalutamide plus Abiraterone Acetate and Prednisone	Abiraterone Acetate and Prednisone	mCRPC (chemotherapy-naïve)
	NCT02489318 (Active, not recruiting)	Apalutamide plus ADT	ADT	mHSPC
	NCT03850795 (recruiting)	HC-1119	Enzalutamide	mCRPC
	NCT03851640 (recruiting)	HC-1119	Placebo	mCRPC
AKT inhibitor	NCT03072238 (Active, not recruiting)	Ipatasertib plus Abiraterone and Prednisone/Prednisolone	Placebo plus abiraterone and prednisone/prednisolone	mCRPC
	NCT04493853 (recruiting)	Capivasertib plus Abiraterone (+Prednisone/Prednisolone) plus ADT	Placebo plus Abiraterone (+ Prednisone/Prednisolone) plus ADT	mHSPC with PTEN deficiency
	NCT03395197 (recruiting)	Talazoparib plus Enzalutamide	Enzalutamide	mCRPC
	NCT03748641 (recruiting)	Niraparib plus Abiraterone Acetate and Prednisone	Abiraterone Acetate and Prednisone	mPCa
	NCT04497844 (recruiting)	Niraparib plus Abiraterone Acetate and Prednisone	Abiraterone Acetate and Prednisone	mHSPC with deleterious germline or somatic HRR gene mutation
PARP inhibitor	NCT04691804 (not yet recruiting)	Fuzuloparib plus Abiraterone Acetate and Prednisone	Placebo plus Abiraterone Acetate and Prednisone	mCRPC
	NCT04455750 (not yet recruiting)	Rucaparib and Enzalutamide	Enzalutamide alone	mPCa
	NCT02975934 (recruiting)	Rucaparib	Physician's Choice of Therapy	mCRPC and HR gene deficiency
	NCT03732820 (Active, not recruiting)	Olaparib plus Abiraterone	Placebo plus abiraterone	mCRPC
PARP inhibitor/ anti-PD1 antibody	NCT03834519 (recruiting)	Pembrolizumab plus Olaparib	Abiraterone Acetate or Enzalutamide	mCRPC
	NCT04191096 (recruiting)	Pembrolizumab plus Enzalutamide plus ADT	Placebo plus Enzalutamide plus ADT	mHSPC
	NCT03834493 (recruiting)	Pembrolizumab plus Enzalutamide	Placebo plus Enzalutamide	mCRPC
anti-PD1 antibody	NCT03834506 (recruiting)	Pembrolizumab plus Docetaxel	Placebo plus Docetaxel	mCRPC (chemotherapy-naïve)
	NCT04100018 (recruiting)	Nivolmab plus docetaxel	Placebo plus docetaxel	mCRPC
	NCT04100018 (recruiting)	Nivolumab plus Docetaxel	Placebo plus Docetaxel	mCRPC
anti-PD-L1 antibody anti-PD-L1 antibody/ MET and VEGF inhibitor	NCT03016312 (Active, not recruiting)	Atezolizumab plus Enzalutamide	Enzalutamide second novel	mCRPC
	NCT04446117 (recruiting)	Cabozantinib plus Atezolizumab	hormonal therapy Placebo plus	mCRPC
TKI	NCT03761225 (Active, not recruiting)	Masitinib plus Docetaxel	Docetaxel	mCRPC
	NCT04647526 (recruiting)	[Lu-177]-PNT2002 ([Lu-177]-PSMA-I&T)	Abiraterone or Enzalutamide	mCRPC
	NCT04689828 (not yet recruiting)	177Lu-PSMA-617	Androgen Receptor-directed Therapy	mCRPC
PSMA	NCT03511664 (Active, not recruiting)	177Lu-PSMA-617 plus Best supportive/ Best SOC	Best supportive/ Best SOC	mCRPC with PSMA positive
	NCT04720157 (not yet recruiting)	177Lu-PSMA-617 plus SOC	SOC	mHSPC
	NCT04237584 (recruiting)	Radium-223 plus Enzalutamide or Darolutamide	Placebo plus Enzalutamide or Darolutamide	mCRPC
	NCT02194842 (recruiting)	Radium-223 plus Enzalutamide	Enzalutamide	mCRPC (asymptomatic or mildly symptomatic)
radiopharmaceutical	NCT03574571 (recruiting)	Radium-223 plus Docetaxel	Docetaxel	mCRPC
	NCT02043678 (Active, not recruiting)	Radium-223 plus Abiraterone Acetate	Placebo plus Abiraterone Acetate	mCRPC
	NCT03458559 (Active, not recruiting)	Rhenium-188-HEDP	Radium-223 chloride	prostate cancer with bone metastasis mPCa/ recurrent PCa
statin	NCT04026230 (recruiting)	Atorvastatin	Placebo	

ARPI; androgen receptor pathway inhibitor, PARP; poly(ADP-ribose) polymerase, VEGF; vascular endothelial growth factor, TKI; tyrosine kinase inhibitor, PSMA; prostate-specific membrane antigen, ADT; androgen deprivation therapy, HEDP; hydroxyethylidine diphosphonate, SOC; standard of care, mCRPC; metastatic castration-resistant prostate cancer, HSPC; hormone-sensitive prostate cancer, HRR; homologous recombination repair