American Journal of Men's Health
July-August 1–11
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15579883221115593
journals.sagepub.com/home/jmh
SAGE

Prostate Cancer Drug Therapy: What Have Clinicians Missed During the COVID-19 Pandemic

M. S. Rahnama'i[1,2]

Abstract

Due to the COVID-19 pandemic, major congresses and many teaching opportunities as well as the usual visits from medical advisors of pharmaceutical firms have been postponed and canceled. The major trials of prostate cancer in the last 5 years in each state are shortly discussed providing a panoramic overview of the available evidence and data on prostate cancer treatment. Apalutamide, enzalutamide, and darolutamide have proven to have clinical benefits when added to androgen deprivation therapy for patients with nonmetastatic castration-resistant prostate cancer. In patients in the metastatic hormone-sensitive setting, next to docetaxel, abiraterone, enzalutamide, and apalutamide have been shown to significantly improve overall survival and progression-free survival in comparison to standard hormone therapy. In addition, docetaxel abiraterone and enzalutamide are widely used in the metastatic setting. For second-line therapy of metastasized prostate cancer patients who have received either docetaxel or abiraterone or enzalutamide, olaparib, cabazitaxel, radium, and lutetium therapy have been shown to be beneficial in selected patient groups.

Keywords

abiraterone, enzalutamide, prostate cancer, oncology/cancer, darolutamide, cabazitaxel

Received April 19, 2022; revised July 5, 2022; accepted July 7, 2022

Introduction

In the last 5 years, treatment strategies for patients with advanced prostate cancer, hormone-sensitive prostate cancer (HSPC), and recurrent prostate cancer after curative intent therapy as well as castration-resistant prostate cancer (CRPC) have tremendously evolved leading to the introduction and approval of several new drugs. The appropriate use of these drugs and their proper sequencing are still a matter of debate.

In addition, due to the COVID-19 pandemic, major congresses and many teaching opportunities as well as the usual visits from medical advisors of pharmaceutical firms have been postponed and canceled.

The American Board of Medical Specialties (ABMS) and the Accreditation Council for Graduate Medical Education (ACGME) have released a joint statement with concerns regarding physician training during the coronavirus pandemic ("ABMS and ACGME Joint Principles: Physician Training During the COVID-2019 Accessed April 30, 2020.," 2020).

Hence, it is becoming more and more difficult for clinicians to stay up to date on the stand of knowledge and developments in the field of prostate cancer treatment.

This short overview article aims to help clinicians to get a clear picture of the current state of knowledge on prostate cancer drug therapy and will hopefully fill in the gap that has developed during the COVID-19 pandemic.

[1]Department of Urology, Maastricht University, Maastricht, The Netherlands
[2]Department of Urology, University Hospital RWTH Aachen, Aachen, Germany

*M. S. Rahnama'i is now affiliated with Department of Urology, St. Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands; Society of Urological Research and Education (SURE), Heerlen, The Netherlands

Corresponding Author:
M. S. Rahnama'i, Department of Urology, St. Elisabeth-Tweesteden Hospital, Dr. Deelenlaan 5, 5042 AD Tilburg, The Netherlands.
Email: sajjad_r@yahoo.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

The major trials of the recent years in each state of the disease are shortly discussed providing a panoramic overview of the available evidence and data on prostate cancer treatment.

Nonmetastatic Castration-Resistant Prostate Cancer

Radical prostatectomy or radiotherapy is the most applied treatments in patients diagnosed with localized prostate cancer. At times, many of these patients experience recurrence and elevated serum level of prostate-specific antigen (PSA) which is called biochemical recurrence. These patients are then commonly treated with androgen deprivation therapy (ADT). After an initial drop, the PSA levels of most of these patients rise eventually, despite the continuation of ADT and the absence of any sign of metastatic disease on traditional computed tomography and radionuclide bone scans. This state is known as nonmetastatic CRPC (Swami & Agarwal, 2020) The definition of nmCRPC is the CRPC state in the absence of metastases on conventional imaging with a bone scan and computed tomography scan. A study in 2019 has reported that most of these patients show lesions in prostate-specific membrane antigen-positron emission tomography (PSMA-PET) scan leading to debate on whether or not nmCRPC patients truly exist (Fendler et al., 2019).

The results of three major trials, SPARTAN (apalutamide), PROSPER (enzalutamide), and ARAMIS (darolutamide), have proven that in nmCRPC patients there is a clinical benefit of combining an androgen signaling inhibitor with ADT (Fenner, 2020). Unfortunately, there are no studies that have directly compared these three drugs in terms of safety or efficacy.

Apalutamide. Apalutamide is an inhibitor of the ligand-binding domain of the androgen receptor. In a study that included 1,207 men with nmCRPC (diagnosed by conventional imaging) and randomized them in a 2:1 ratio to apalutamide (240 mg/d) or placebo plus ongoing ADT (SPARTAN trial), it was reported that apalutamide improved median metastasis-free survival by 2 years (Small et al., 2019). More recently, a publication reported the mature data from the SPARTAN study and showed a significant overall survival (OS) benefit in this patient group.

In short, apalutamide improved median metastasis-free survival by 2 years over placebo plus ADT and was reported to decrease the hazard of initiating cytotoxic chemotherapy by 37% versus placebo, HR 0.63 (95% CI 0.49–0.81); $p = .0002$ (Fenner, 2020).

Enzalutamide. Androgen receptor overexpression is an adaptive mechanism that is involved in the development of metastatic CRPC. Enzalutamide is a potent androgen receptor inhibitor that can overcome this androgen receptor overexpression (Hussain et al., 2018).

In a randomized, double-blind, placebo-controlled, Phase 3 trial, conducted at 254 international study sites, 1,401 patients with nmCRPC and a PSA doubling time of up to 10 months were randomly assigned to receive oral enzalutamide or placebo (PROSPER trial).

At a median follow-up of 18·5 months, the time to increased pain severity, and worsening of urinary symptoms was longer with enzalutamide than with placebo. Time to clinically meaningful deterioration in EORTC QLQ-PR25 hormonal treatment-related symptoms was shorter with enzalutamide than with placebo (Hussain et al., 2018; Tombal et al., 2019).

The survival data of this trial were published in 2020. A total of 31% had died in the enzalutamide group compared with 38% in the placebo group. Median OS was 67.0 months in the enzalutamide group and 56.3 months in the placebo group (Sternberg et al., 2020). Fatigue and musculoskeletal events were the most commonly reported adverse events in the enzalutamide group (Sternberg et al., 2020).

Darolutamide. In 2017, a pivotal Phase 3 clinical study reported the benefit of another novel oral androgen receptor antagonist called darolutamide in nmCRPC (Fizazi et al., 2018; Shore, 2017). This drug has a unique chemical structure, exists as two pharmacologically active diastereomers, (S,R)- and (S,S)-darolutamide 12, and forms keto-darolutamide as the main metabolite in patients (Fizazi et al., 2014; Matsubara et al., 2017). In a double-blind, placebo-controlled trial, 1,509 men were randomized to receive darolutamide (955 patients) or placebo (554 patients) while they continued to receive ADT (ARAMIS trial). At a median follow-up time of 29.0 months, the risk of death was significantly lower, by 31%, in the darolutamide group than in the placebo group (HR for death, 0.69; 95% confidence interval [CI]: [0.53, 0.88]; $p = .003$). In the darolutamide arm, a significant improvement in all other secondary end points, including the time to first symptomatic skeletal event and the time to first use of chemotherapy, was observed. The occurrence of adverse events was comparable in both study arms (Fizazi et al., 2020).

Metastatic Hormone-Sensitive Prostate Cancer

Patients with metastatic prostate cancer and PSA levels that still respond to ADT are categorized as metastatic hormone-sensitive prostate cancer (mHSPC). Several studies have compared the use of ADT alone versus adding chemotherapy or new oral hormonal drugs to ADT in mHSPC patients.

In patients with mHSPC, in addition to docetaxel (CHAARTED trial) the following trials, TITAN (apalutamide), LATITUDE (abiraterone) and ARCHES and ENZAMET (enzalutamide), have led to the listing of the aforementioned drugs as first-line treatment choices in the European association of urology (EAU) guidelines of 2021. These three drugs all have been reported to significantly improve OS and PFS in comparison to standard ADT (Chi et al., 2019; Davis et al., 2019; Fizazi et al., 2017).

Apalutamide. A total of 1,052 patients with mHSPC (defined as not receiving ADT at the time of metastatic disease progression), receiving continuous ADT, were randomized to receive apalutamide or a matching placebo (TITAN trial). This double-blind study revealed that the time to deterioration as determined by FACT-P total score was 8·87 months in the apalutamide group and 9·23 months in the placebo group (Agarwal et al., 2019). A study published in 2021, reporting the final analysis of TITAN after a median follow-up of approximately 4 years, confirmed that, despite crossover, apalutamide plus ADT improved OS, delayed castration resistance, maintained health-related quality of life, and had a consistent safety profile in a broad population of patients with mHSPC (Chi et al., 2021).

Abiraterone. CYP17A1 is an essential enzyme in the process of androgen synthesis, which can be upregulated in mCRPC patients. Abiraterone is an inhibitor of CYP17A1 enzyme. In a double-blind, placebo-controlled, Phase 3 trial, 1,199 patients were randomized to receive either ADT plus abiraterone acetate plus prednisone (the abiraterone group) or ADT plus dual placebos (the placebo group). Inclusion criteria were newly diagnosed ($\leq$3 months) adult men with high-risk metastatic hormone treatment naive prostate cancer patients who met at least two of the three high-risk criteria: Gleason score of $\geq$8, presence of $\geq$3 lesions on bone scan, or presence of a visceral lesion. The two primary endpoints were OS and radiographic PFS (LATITUDE trial). This trial revealed that the median length of radiographic PFS of abiraterone-treated patients was 33.0 months and 14.8 months in patients who received placebo (HR for disease progression or death, 0.47; 95% CI, [0.39, 0.55]; $p < .001$). In addition, patients receiving abiraterone had better outcomes in all secondary end points ($p < .001$ for all comparisons). These results led to unblinding the study and allowing crossover. In patients receiving abiraterone, Grade 3 hypertension and hypokalemia were detected more frequently compared with the placebo group (Fizazi et al., 2017).

Enzalutamide. Enzalutamide, which is reported to have significant benefits in both metastatic and nonmetastatic castration-resistant prostate cancer was also evaluated in the mHSPC setting. Radiographic PFS was investigated as the primary end point of this multinational, double-blind, Phase III trial (ARCHES trial) among 1,150 men with mHSPC. The trial identified that the risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (HR, 0.39; 95% CI, 0.30 to 0.50; $p < .001$; median not reached vs. 19.0 months). Enzalutamide plus ADT significantly reduced the risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and reduced risk of pain progression (Armstrong et al., 2019).

In an open-label, randomized, Phase 3 trial (ENZAMET trial), 1,125 patients were assigned to either open-label enzalutamide with ADT or a nonsteroidal androgen receptor blocker (standard-care group). The primary endpoint was OS. Secondary endpoints included PFS as determined by the PSA level, clinical progression-free survival, and adverse events (Davis et al., 2019).

With a median follow-up of 34 months, this trial revealed showed 102 deaths in the enzalutamide group and 143 deaths in the standard care. Kaplan-Meier estimates of overall survival at 3 years were 80% (based on 94 events) in the enzalutamide group and 72% (based on 130 events) in the standard care group. Better results with enzalutamide were also seen in PSA PFS (174 and 333 events, respectively; hazard ratio [HR] 0.39; $p < .001$) and in clinical progression-free survival (167 and 320 events, respectively; HR, 0.40; $p < .001$). In the enzalutamide group, significantly longer PFS and OS were detected.

Docetaxel. Chemotherapy with docetaxel has been proven to improve OS in patients with mHSPC, especially those with high-volume metastatic disease, according to three Phase III studies (CHAARTED, STAMPEDE, and GETUG-AFU 15; Gravis et al., 2013; James et al., 2016; Sweeney et al., 2015) which was confirmed in a meta-analysis involving the data of these three trials (Sathianathen et al., 2018).

Metastatic Castration-Resistant Prostate Cancer

Metastatic castration-resistant prostate cancer is characterized by disease progression despite suppression of gonadal androgens with ADT and results in an increased symptom burden and ultimately death (Penson & Litwin, 2003).

The discovery of androgen receptor-mediated signaling as a principal mechanism of mCRPC progression led to the development of novel androgen receptor pathway inhibitors of which abiraterone (COU-AA-302 trial) and

enzalutamide (PREVAIL trail) are now widely used (Watson et al., 2015).

Abiraterone. In a placebo-controlled, double-blind, randomized Phase 3 study, in 1,088 asymptomatic or mildly symptomatic patients with chemotherapy-naive prostate cancer, abiraterone acetate plus prednisone significantly improved radiographic PFS compared with placebo plus prednisone (COU-AA-302 trial).

In this trial stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1) was randomly assigned with a permuted block allocation scheme via a web response system in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone. Co-primary endpoints were radiographic PFS and OS analyzed in the intention-to-treat population. Median OS at a median follow-up of more than 4 years, was significantly longer in the abiraterone acetate group than in the placebo group (34.7 months 95% CI [32.7, 36.8] vs. 30.3 months [28.7, 33.3]; HR0.81 95% CI: [0.70, 0.93]; $p = .0033$). The most common Grade 3–4 adverse events of special interest were cardiac disorders (41 [8%] of 542 patients in the abiraterone acetate group vs. 20 [4%] of 540 patients in the placebo group), increased alanine aminotransferase (32 [6%] vs. four [<1%]), and hypertension (25 [5%] vs. 17 [3%]; Ryan et al., 2015).

Enzalutamide. In another Phase 3 trial with enzalutamide, 1,717 chemotherapy-naive men with mCRPC were randomized to enzalutamide 160 mg or placebo until confirmed radiographic disease progression or a skeletal-related event and initiation of either cytotoxic chemotherapy or an investigational agent for prostate cancer treatment (PREVAIL trail; Beer et al., 2014) The study results showed that enzalutamide significantly reduced the risk of radiographic progression or death in all serious adverse events, with HR of 0.22 ($p < .001$; Beer et al., 2014; Rathkopf et al., 2018).

Second-Line mCRPC

Patients with progressing disease and mCRPC who have already had an failed chemotherapy with decetaxel or a treatment with enzalutamide or abiraterone are categorized into second-line mCRPC.

The efficacy of cabazitaxel compared with mitoxantrone after failure on docetaxel was initially demonstrated in a randomized trial (J. S. de Bono et al., 2010). Enzalutamide (AFFIRM trial) and abiraterone (COU-AA-301) have been studied in patients who had undergone chemotherapy with docetaxel.

Moreover, poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib (PROfound trial), was studied in second-line mCRPC patients who had disease progression while receiving either enzalutamide or abiraterone.

In addition, in the second-line mCRPC patients with exclusively bone metastasis, radium-223 (ALSYMPCA trial) was studied as the last therapy option. Lutetium-177 prostate-specific membrane antigen 617 (LuPSMA-617) therapy has been suggested although robust Phase III data are still lacking.

Enzalutamide. In a double-blind, placebo-controlled study that stratified 1199 men with CRPC after chemotherapy (AFFIRM trial), according to the ECOG performance status score and pain intensity, patients were randomized to receive oral enzalutamide or placebo. The primary end point of this study was OS. The median OS was 18.4 months (95% CI, 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI [11.3, 15.8]) in the placebo group (HR for death in the enzalutamide group, 0.63; 95% CI, [0.53, 0.75]; $p < .001$). In addition, the superiority of enzalutamide over placebo was shown with respect to all secondary endpoints: The proportion of patients with a reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs. 2%, $p < .001$), the soft-tissue response rate (29% vs. 4%, $p < .001$), the quality-of-life response rate (43% vs. 18%, $p < .001$), the time to PSA progression (8.3 vs. 3.0 months; HR 0.25; $p < .001$), radiographic PFS (8.3 vs. 2.9 months; HR, 0.40; $p < .001$), and the time to the first skeletal-related event (16.7 vs. 13.3 months; HR, 0.69; $p < .001$). Rates of fatigue, diarrhea, and hot flashes were higher in the enzalutamide group. This study confirmed that enzalutamide significantly prolongs the survival of men with mCRPC after chemotherapy (Loriot et al., 2017).

Abiraterone. A total of 1,195 patients who had previously received docetaxel were randomized to receive prednisone with either abiraterone acetate or placebo (COU-AA-301 trial). The primary end point was OS. The secondary endpoints included time to PSA progression (elevation in the PSA level according to prespecified criteria), PFS according to radiologic findings based on prespecified criteria, and the PSA response rate.

After a median follow-up of 12.8 months, OS was longer in the abiraterone acetate-prednisone group than in the placebo-prednisone group (14.8 months vs. 10.9 months; HR, 0.65; 95% CI [0.54, 0.77]; $p < .001$). Data were unblinded in the interim analysis, as these results exceeded the preplanned criteria for study termination. All secondary end points, including time to PSA progression (10.2 vs. 6.6 months; $p < .001$), PFS (5.6 months vs. 3.6 months; $p < .001$), and PSA response rate (29% vs. 6%, $p < .001$), favored the treatment group (J. S. de Bono et al., 2011).

Cabazitaxel. Chemotherapy with cabazitaxel in the second-line CRPC has been reported to be successful (J. S. de Bono et al., 2010). Last year, a multicenter randomized open-label Phase II trial was published that had randomly assigned patients to receive cabazitaxel plus prednisone (group A) or physician's choice of enzalutamide or abiraterone plus prednisone (group B) at standard doses. Patients could cross over at progression. The primary endpoint was clinical benefit rate for first-line treatment (defined as prostate-specific antigen response ≥50%, radiographic response, or stable disease ≥12 weeks). Although only 95 patients were included (median follow-up 21.9 months), the first-line clinical benefit rate was reported to be greater in the cabazitaxel group (80% vs. 62%, $p = .039$). OS was not different between the cabazitaxel and other treatments (median 37.0 vs. 15.5 months, HR = .58, $p = .073$) nor was time to progression (median 5.3 versus 2.8 months, HR = .87, $p = .52$; Annala et al., 2021).

Radium-223. A Phase 3, double-blind, randomized trial (ALSYMPCA trial) enrolled 921 men who had symptomatic CRPC with two or more bone metastases and no known visceral metastases, who were receiving the best standard of care, and had previously either received or were unsuitable for docetaxel.

Patients were stratified by previous docetaxel use, baseline total alkaline phosphatase level, and current bisphosphonate use, then randomly assigned (2:1) to receive either six intravenous injections of radium-223 (50 kBq/kg) or a matching placebo. Radium-223 prolonged median OS with placebo, irrespective of previous docetaxel use (previous docetaxel use, HR 0·70, 95% CI [0.56, 0.88]; $p = 0{\cdot}002$; no previous docetaxel use, HR 0.69, 95% CI [0.52, 0.92]; $p = .01$). The benefit of radium-223 compared with placebo was seen in both docetaxel subgroups for most main secondary efficacy endpoints; risk for time to time to first symptomatic skeletal event was reduced with radium-223 versus placebo in patients with previous docetaxel use, but the difference was not significant in those with no previous docetaxel use. In all, 322 (62%) of 518 patients previously treated with docetaxel had grade 3 to 4 adverse events, compared with 205 (54%) of 383 patients without docetaxel (Hoskin et al., 2014).

Olaparib. Multiple loss-of-function alterations in genes that are involved in DNA repair, including homologous recombination repair, are associated with response to poly (adenosine diphosphate-ribose) polymerase (PARP) inhibition in patients with prostate and other cancers. Olaparib is the first PARP inhibitor that has been introduced for prostate cancer treatment.

A randomized, open-label, Phase 3 trial evaluated olaparib in men with mCRPC who had disease progression while receiving either enzalutamide or abiraterone (PROfound trial). All included patients had a qualifying alteration in prespecified genes with a direct or indirect role in homologous recombination repair. Cohort A (245 patients) had at least one alteration in *BRCA1, BRCA2*, or *ATM*; cohort B (142 patients) had alterations in any of 12 other prespecified genes, prospectively and centrally determined from tumor tissue. Patients were randomly assigned (in a 2:1 ratio) to receive olaparib or the physician's choice of enzalutamide or abiraterone (control). The primary endpoint was imaging-based PFS in Cohort A according to a blinded independent central review. In cohort A, imaging-based PFS was significantly longer in the olaparib group than in the control group (median, 7.4 months vs. 3.6 months; hazard ratio for progression or death, 0.34; 95% CI [0.25, 0.47]; $p < .001$); a significant benefit was also observed with respect to the confirmed objective response rate and the time to pain progression. The median OS in Cohort A was 18.5 months in the olaparib group and 15.1 months in the control group; 81% of the patients in the control group who had progression crossed over to receive olaparib. A significant benefit for olaparib was also seen for imaging-based PFS in the overall population (Cohorts A and B). Anemia and nausea were the main toxic effects in patients who received olaparib (J. de Bono et al., 2020).

Lutetium. Lutetium-177 prostate-specific membrane antigen 617 (LuPSMA-617) is a radiolabeled small-molecule peptide that targets the prostate-specific membrane antigen (PSMA) receptor, which is highly expressed on prostate cancer (PCa) cells, to deliver targeted beta-particle therapy. Single-center studies of LuPSMA-617 have demonstrated good safety and efficacy (Emmett et al., 2019; Hofman et al., 2018; Violet et al., 2020).

An open-label, Phase 3 trial evaluating ^{177}Lu-PSMA-617 (VISION trial) included 831 patients who had mCRPC and were previously treated with at least one androgen-receptor–pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 (^{68}Ga)–labeled PSMA-11 PET-CT scans (Sartor et al., 2021).

Patients were randomly assigned in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus protocol-permitted standard care or standard care alone. Protocol-permitted standard care excluded chemotherapy, immunotherapy, radium-223 (^{223}Ra), and investigational drugs. The study reported that as compared with standard care, both imaging-based PFS (median, 8.7 vs. 3.4 months) and OS (median, 15.3 vs. 11.3 months) were prolonged in the ^{177}Lu-PSMA-617 plus standard care group. All the key secondary endpoints

significantly favored ^{177}Lu-PSMA-617. The incidence of adverse events of Grade 3 or above was higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but the quality of life was not adversely affected (Sartor et al., 2021).

Discussion

The emergence of new data on new treatment modalities for prostate cancer in the COVID-19 era has been partially undetected by clinicians who are not particularly active in research on this topic.

Prostate cancer treatment is patient-tailored but can roughly be categorized as localized prostate cancer, nmCRPC, mHSPC, mCRPC, and second-line mCRPC (Figure 1).

Abiraterone and enzalutamide have never been compared head to head and have shown similar activity and can both be used in HSPC as well as first-line treatment for mCRPC.

In chemotherapy-naive patients with prostate cancer, abiraterone plus prednisone has shown to bring an OS benefit when compared with placebo plus prednisone (Ryan et al., 2015). A separate Phase 3 trial has demonstrated the same results in the same group of patients for enzalutamide (Beer et al., 2017) that also improved OS compared with placebo. In addition, both drugs have also shown improvements in time to PSA as well as time to radiographic progression, frequency of skeletal-related events, and quality of life (Khalaf et al., 2019). The major unanswered question is the proper sequencing of the available treatment modalities.

Awareness of nmCRPC has risen due to increased use of ADT and its eventual failure to prevent rapid progression to the metastatic state of the disease (Lokeshwar et al., 2021). In this setting, three trials (PROSPER, SPARTAN, and ARAMIS) have shown a beneficial effect of novel nonsteroidal antiandrogen agents for treating high-risk nmCRPC (Lokeshwar et al., 2021). The data from the SPARTAN study, which evaluated the outcomes of apalutamide treatment versus placebo in patients with nmCRPC, have shown a significant OS benefit (Fenner, 2020). As apalutamide has only been approved for nmCRPC and mHSPC, it cannot be prescribed in the later stages of the disease such as mCRPC or second-line mCRPC. In addition, darolutamide, another agent that is only approved for the setting of nmCRPC, has been shown to reduce the risk of death significantly in comparison to placebo in prostate cancer patients treated with ADT (ARAMIS; Fizazi et al., 2020) Enzalutamide is the third agent that has been approved for the nmCRPC setting with beneficial effects (PROSPER) in terms of time to clinically meaningful pain progression, time to clinically meaningful symptom worsening and time to clinically meaningful deterioration in hormonal treatment-related symptoms (5). It seems practical to offer patients in the nmCRPC, apalutamide, or darolutamide before enzalutamide treatment is given as apalutamide and darolutamide are not approved for the later stages of the disease (mCRPC and second line mCRPC). There have been no studies comparing darolutamide, enzalutamide, and apalutamide so that no recommendation can be made about the choices between these two drugs.

In the setting of mHSPC, apalutamide should be considered the first choice next to the ADT as the agent has not been approved for the later stages of the disease.

As the next step, in mHSPC, enzalutamide or abiraterone must be considered. However, the sequencing of these two drugs has been a matter of debate. To date, there has been one multicenter, randomized, open-label, Phase 2, crossover trial conducted in six cancer centers in British Columbia and Canada, which looked into the question of sequencing abiraterone and enzalutamide. This study enrolled 202 patients were enrolled and randomly assigned them to either (Group A) who receive abiraterone plus prednisone until PSA progression followed by crossover to enzalutamide (Group A), or the opposite sequence (Group B). Time to second PSA progression was longer in Group A than in Group B (median 19.3 vs. 15.2 months). Moreover, this study showed enzalutamide benefit as a second-line novel androgen receptor pathway inhibitor, whereas abiraterone did not show any benefit in the setting given after enzalutamide. Hence, these data suggest that using a sequencing strategy of abiraterone acetate followed by enzalutamide provides the greatest clinical benefit (Khalaf et al., 2019).

In the setting of mCRPC, abiraterone and enzalutamide should both be considered in asymptomatic or mildly symptomatic patients. In addition, in men with mCRPC who had disease progression while receiving enzalutamide or abiraterone and who had alterations in genes with a role in homologous recombination repair, olaparib has been shown to be associated with longer PFS and better measures of response and patient-reported endpoints than either enzalutamide or abiraterone (28). Hence, in this setting, rather than a switch between abiraterone and enzalutamide or vice versa olaparib should be the first choice.

In the setting of second-line mCRPC and patients progressing after an androgen receptor axis–targeted therapy and/or docetaxel, two different alternatives have been identified to be beneficial in Phase 3 clinical trials. First, a targeted strategy using PARP inhibitors, and second, a nontargeted chemotherapy strategy using cabazitaxel. Until today, there is no direct randomized evidence to compare PARP inhibitors with cabazitaxel.

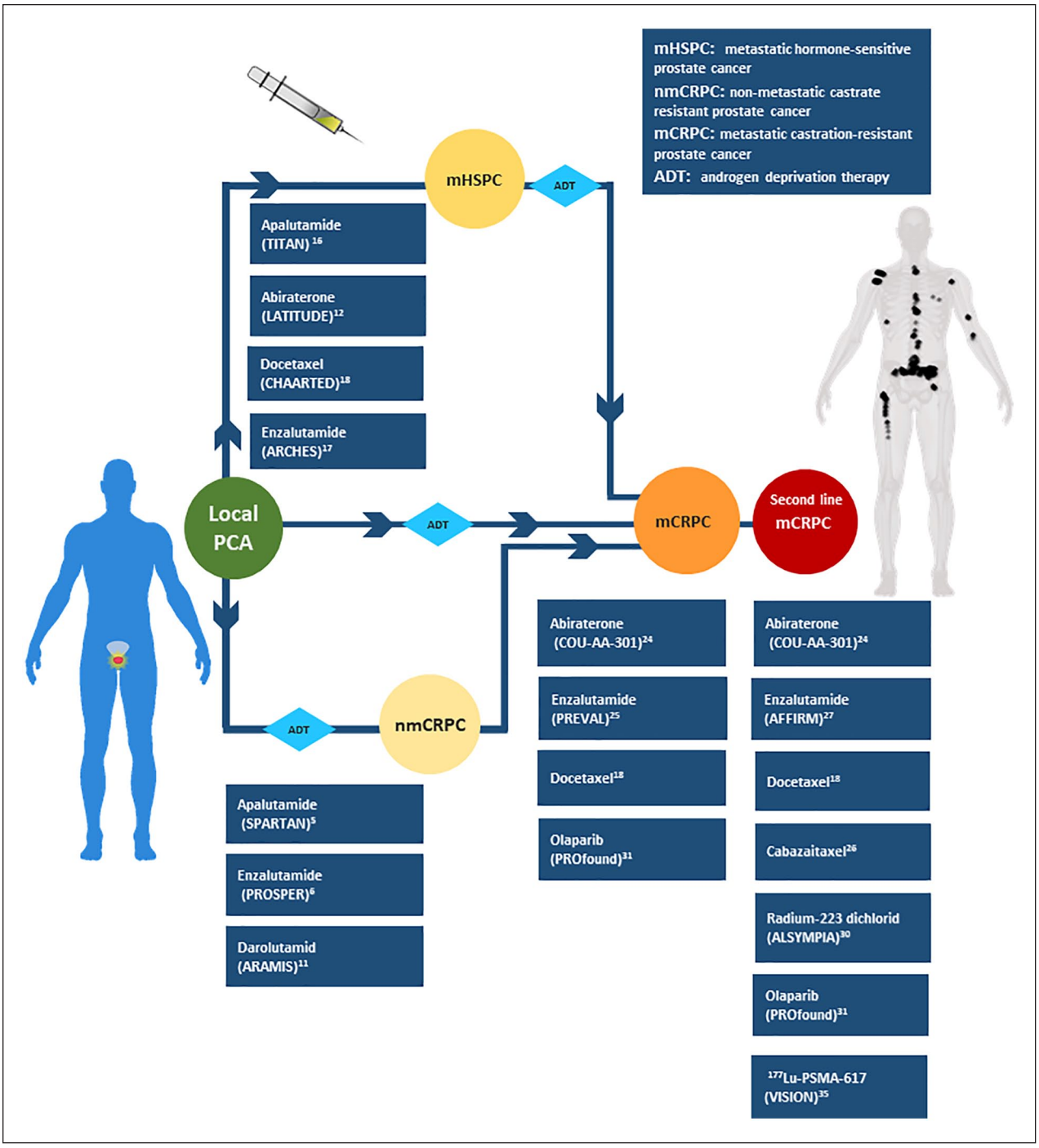

Figure 1. An Overview of Approved Drugs for Each State of Prostate Cancer Disease.

A study that investigated whether cabazitaxel still provided a benefit as a third-line agent after progression on docetaxel and one ARAT. Compared with the ARAT agent not previously used (CARD trial), this showed significant improvement in radiographic PFS of 8.0 versus 3.7 months favoring cabazitaxel (HR 0.54; $p < .001$). OS was also statistically higher with cabazitaxel (13.6 vs. 11.0 months, HR 0.64; $p = .008$; de Wit et al., 2019).

In contrast to cabazitaxel, PARP inhibition represents a targeted approach to mCRPC treatment. Two PARP inhibitors, olaparib and rupacarib, have been approved for patients who have progressed on docetaxel and whose

tumors harbor deleterious aberrations in DNA repair genes. It has been reported that these deleterious aberrations are present in up to 30% of patients with mCRPC (Mateo et al., 2015). Among the most common genes altered are BRCA1 and BRCA2. It is believed that such gene alterations confer sensitivity to PARP inhibition (Mateo et al., 2020).

Chemotherapy with docetaxel has been proven to improve OS in patients with mHSPC, especially those with high-volume metastatic disease, in symptomatic mCRPC patients as well second-line mCRPC (Gravis et al., 2013; James et al., 2016; Sathianathen et al., 2018; Sweeney et al., 2015). Robust data are lacking regarding the optimal sequencing of docetaxel versus abiraterone or enzalutamide. Therefore, the sequencing of prostate cancer therapy in these settings remains up to the patient's wish and performance score as well as the physician's preference.

When all other therapy options are used, Radium-223 and Lutetium therapy must be considered as last resort therapy in patients who still desire further therapy and are fit enough to withstand the side effect of these treatments.

In conclusion, the choice of drug therapy for prostate cancer must be patient-tailored through shared decision-making between patients and physicians based on differing adverse effect profiles and other differing parameters between the available therapeutic modalities.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

M.S. Rahnama'i https://orcid.org/0000-0003-1953-7441

References

ABMS and ACGME Joint Principles: Physician Training During the COVID-2019 Accessed April 30, 2020. (2020)

Agarwal, N., McQuarrie, K., Bjartell, A., Chowdhury, S., Pereira de Santana Gomes, A. J., Chung, B. H., Özgüroğlu, M., Soto, A. J., Merseburger, A. S., Uemura, H., Ye, D., Given, R., Cella, D., Basch, E., Miladinovic, B., Dearden, L., Deprince, K., Naini, V., Lopez-Gitlitz, A., Chi, K. N., & on behalf of the TITAN investigators. (2019). Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): A randomised, placebo-controlled, phase 3 study. *The Lancet Oncology*, *20*(11), 1518–1530. https://doi.org/10.1016/S1470-2045(19)30620-5

Annala, M., Fu, S., Bacon, J. V. W., Sipola, J., Iqbal, N., Ferrario, C., Ong, M., Wadhwa, D., Hotte, S. J., Lo, G., Tran, B., Wood, L. A., Gingerich, J. R., North, S. A., Pezaro, C. J., Ruether, J. D., Sridhar, S. S., Kallio, H. M. L., Khalaf, D. J., Wong, A., . . . Chi, K. N. (2021). Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: A multicentre, randomised, open-label, phase II trial. *Annals of Oncology*, *32*(7), 896–905. https://doi.org/10.1016/j.annonc.2021.03.205

Armstrong, A. J., Szmulewitz, R. Z., Petrylak, D. P., Holzbeierlein, J., Villers, A., Azad, A., Alcaraz, A., Alekseev, B., Iguchi, T., Shore, N. D., Rosbrook, B., Sugg, J., Baron, B., Chen, L., & Stenzl, A. (2019). ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *Journal of Clinical Oncology*, *37*(32), 2974–2986. https://doi.org/10.1200/JCO.19.00799

Beer, T. M., Armstrong, A. J., Rathkopf, D. E., Loriot, Y., Sternberg, C. N., Higano, C. S., Iversen, P., Bhattacharya, S., Carles, J., Chowdhury, S., Davis, I. D., de Bono, J. S., Evans, C. P., Fizazi, K., Joshua, A. M., Kim, C., Kimura, G., Mainwaring, P., Mansbach, H., Miller, K., . . . for the PREVAIL Investigators. (2014). Enzalutamide in metastatic prostate cancer before chemotherapy. *New England Journal of Medicine*, *371*(5), 424–433. https://doi.org/10.1056/NEJMoa1405095

Beer, T. M., Armstrong, A. J., Rathkopf, D., Loriot, Y., Sternberg, C. N., Higano, C. S., Iversen, P., Evans, C. P., Kim, C., Kimura, G., Miller, K., Saad, F., Bjartell, A. S., Borre, M., Mulders, P., Tammela, T. L., Parli, T., Sari, S., Os, S., Theeuwes, A., & Tombal, B. (2017). Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: Extended analysis of the phase 3 PREVAIL study. *European Urology*, *71*(2), 151–154. https://doi.org/10.1016/j.eururo.2016.07.032

Chi, K. N., Agarwal, N., Bjartell, A., Chung, B. H., Pereira de Santana Gomes, A. J., Given, R., Soto, J., Merseburger, A. S., Özgüroğlu, M., Uemura, H., Ye, D., Deprince, K., Naini, V., Li, J., Cheng, S., Yu, M. K., Zhang, K., Larsen, J. S., McCarthy, S., Chowdhury, S., & for the TITAN Investigators. (2019). Apalutamide for metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine*, *381*(1), 13–24. https://doi.org/10.1056/NEJMoa1903307

Chi, K. N., Chowdhury, S., Bjartell, A., Chung, B. H., Pereira de Santana Gomes, A. J., Given, R., Soto, A. J., Merseburger, A. S., Özgüroğlu, M., Uemura, H., Ye, D., Brookman-May, S., Mundle, S. D., McCarthy, S. A., Larsen, J. S., Sun, W., Bevans, K. B., Zhang, K., Bandyopadhyay, N., & Agarwal, N. (2021). Apalutamide in patients with metastatic castration-sensitive prostate cancer: Final survival analysis of the randomized, double-blind, phase III TITAN study. *Journal of Clinical Oncology*, *39*(20), 2294–2303. https://doi.org/10.1200/JCO.20.03488

Davis, I. D., Martin, A. J., Stockler, M. R., Begbie, S., Chi, K. N., Chowdhury, S., Coskinas, X., Frydenberg, M., Hague, W. E., Horvath, L. G., Joshua, A. M., Lawrence, N. J., Marx, G., McCaffrey, J., McDermott, R., McJannett, M., North, S. A., Parnis, F., Parulekar, W., Pook, D. W., . . . Prostate Cancer Trials, G. (2019). Enzalutamide with standard first-line therapy in metastatic prostate cancer. *New England Journal of Medicine*, *381*(2), 121–131. https://doi.org/10.1056/NEJMoa1903835

de Bono, J., Mateo, J., Fizazi, K., Saad, F., Shore, N., Sandhu, S., Chi, K. N., Sartor, O., Agarwal, N., Olmos, D., Thiery-Vuillemin, A., Twardowski, P., Mehra, N., Goessl, C., Kang, J., Burgents, J., Wu, W., Kohlmann, A., Adelman, C. A., & Hussain, M. (2020). Olaparib for metastatic castration-resistant prostate cancer. *New England Journal of Medicine*, *382*(22), 2091–2102. https://doi.org/10.1056/NEJMoa1911440

de Bono, J. S., Logothetis, C. J., Molina, A., Fizazi, K., North, S., Chu, L., Chi, K. N., Jones, R. J., Goodman, O. S., Saad, F., Staffurth, J. N., Mainwaring, P., Harland, S., Flaig, T. W., Hutson, T. E., Cheng, T., Patterson, H., Hainsworth, J. D., Ryan, C. J., & Sternberg, C. N., . . . for the COU-AA-301 Investigators. (2011). Abiraterone and increased survival in metastatic prostate cancer. *New England Journal of Medicine*, *364*(21), 1995–2005. https://doi.org/10.1056/NEJMoa1014618

de Bono, J. S., Oudard, S., Ozguroglu, M., Hansen, S., Machiels, J. P., Kocak, I., Gravis, G., Bodrogi, I., Mackenzie, M. J., Shen, L., Roessner, M., Gupta, S., Sartor, A. O., & for the TROPIC Investigators. (2010). Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*, *376*(9747), 1147–1154. https://doi.org/10.1016/S0140-6736(10)61389-X

de Wit, R., de Bono, J., Sternberg, C. N., Fizazi, K., Tombal, B., Wulfing, C., Kramer, G., Eymard, J., Bamias, A., Carles, J., Iacovelli, R., Melichar, B., Sverrisdóttir, A., Theodore, C., Feyerabend, S., Helissey, C., Ozatilgan, A., Geffriaud-Ricouard, C.,Castellano, D., & for the CARD Investigators. (2019). Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *New England Journal of Medicine*, *381*(26), 2506–2518. https://doi.org/10.1056/NEJMoa1911206

Emmett, L., Crumbaker, M., Ho, B., Willowson, K., Eu, P., Ratnayake, L., Epstein, R., Blanksby, A., Horvath, L., Guminski, A., Mahon, A., Gedye, C., Yin, C., Stricker, P., & Joshua, A. M. (2019). Results of a prospective phase 2 pilot trial of (177)Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer including imaging predictors of treatment response and patterns of progression. *Clinical Genitourinary Cancer*, *17*(1), 15–22. https://doi.org/10.1016/j.clgc.2018.09.014

Fendler, W. P., Weber, M., Iravani, A., Hofman, M. S., Calais, J., Czernin, J., Iihan, H., Saad, F., Small, E. J., Smith, M. R., Perez, P. M., Hope, T. A., Rauscher, I., Londhe, A., Lopez-Gitlitz, A., Cheng, S., Maurer, T., Herrmann, K., Eiber, M., & Hadaschik, B. (2019). Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer. *Clinical Cancer Research*, *25*(24), 7448–7454. https://doi.org/10.1158/1078-0432.CCR-19-1050

Fenner, A. (2020). Final SPARTAN data show OS benefit. *Nature Reviews Urology*, *17*(11), 602. https://doi.org/10.1038/s41585-020-00381-w

Fizazi, K., Massard, C., Bono, P., Jones, R., Kataja, V., James, N., Garcia, J. A., Protheroe, A., Tammela, T. L., Elliott, T., Mattila, L., Aspegren, J., Vuorela, A., Langmuir, P., Mustonen, M., & for the ARADES study group. (2014). Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): An open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. *The Lancet Oncology*, *15*(9), 975–985. https://doi.org/10.1016/S1470-2045(14)70240-2

Fizazi, K., Shore, N., Tammela, T. L., Ulys, A., Vjaters, E., Polyakov, S., Jievaltas, M., Luz, M., Alekseev, B., Kuss, I., Le Berre, M., Petrenciuc, O., Snapir, A., Sarapohja, T., Smith, M. R., & for the ARAMIS Investigators. (2020). Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *New England Journal of Medicine*, *383*(11), 1040–1049. https://doi.org/10.1056/NEJMoa2001342

Fizazi, K., Smith, M. R., & Tombal, B. (2018). Clinical development of darolutamide: A novel androgen receptor antagonist for the treatment of prostate cancer. *Clinical Genitourinary Cancer*, *16*(5), 332–340. https://doi.org/10.1016/j.clgc.2018.07.017

Fizazi, K., Tran, N., Fein, L., Matsubara, N., Rodriguez-Antolin, A., Alekseev, B. Y., Özgüroğlu, M., Ye, D., Feyerabend, S., Protheroe, A., De Porre, P., Kheoh, T., Park, Y. C., Todd, M. B., Chi, K. N., & for the LATITUDE Investigators. (2017). Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine*, *377*(4), 352–360. https://doi.org/10.1056/NEJMoa1704174

Gravis, G., Fizazi, K., Joly, F., Oudard, S., Priou, F., Esterni, B., Latorzeff, I., Delva, R., Krakowski, I., Laguerre, B., Rolland, F., Théodore, C., Deplanque, G., Ferrero, J. M., Pouessel, D., Mourey, L., Beuzeboc, P., Zanetta, S., Habibian, M., Berdah, J. F., . . . Soulie, M. (2013). Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): A randomised, open-label, phase 3 trial. *The Lancet Oncology*, *14*(2), 149–158. https://doi.org/10.1016/S1470-2045(12)70560-0

Hofman, M. S., Violet, J., Hicks, R. J., Ferdinandus, J., Thang, S. P., Akhurst, T., Iravani, A., Kong, G., Kumar, A. R., Murphy, D. G., Eu, P., Jackson, P., Scalzo, M., Williams, S. G., & Sandhu, S. (2018). [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, phase 2 study. *The Lancet Oncology*, *19*(6), 825–833. https://doi.org/10.1016/S1470-2045(18)30198-0

Hoskin, P., Sartor, O., O'Sullivan, J. M., Johannessen, D. C., Helle, S. I., Logue, J., Bottomley, D., Nilsson, S., Vogelzang, N. J., Fang, F., Wahba, M., Aksnes, A., &

Parker, C. (2014). Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: A prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *The Lancet Oncology*, *15*(12), 1397–1406. https://doi.org/10.1016/S1470-2045(14)70474-7

Hussain, M., Fizazi, K., Saad, F., Rathenborg, P., Shore, N., Ferreira, U., Ivashchenko, P., Demirhan, E., Modelska, K., Phung, D., Krivoshik, A., & Sternberg, C. N. (2018). Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine*, *378*(26), 2465–2474. https://doi.org/10.1056/NEJMoa1800536

James, N. D., Sydes, M. R., Clarke, N. W., Mason, M. D., Dearnaley, D. P., Spears, M. R., Ritchie, A. W. S., Parker, C. C., Russell, J. M., Attard, G., de Bono, J., Cross, W., Jones, R. J., Thalmann, G., Amos, C., Matheson, D., Alzouebi, R. M. M., Beesley, S., Birtle, A. J., Brock, S., . . . investigators, S. (2016). Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*, *387*(10024), 1163–1177. https://doi.org/10.1016/S0140-6736(15)01037-5

Khalaf, D. J., Annala, M., Taavitsainen, S., Finch, D. L., Oja, C., Vergidis, J., Zulfiqar, M., Sunderland, K., Azad, A. A., Kollmannsberger, C. K., Eigl, B. J., Noonan, K., Wadhwa, D., Attwell, A., Keith, B., Ellard, S. L., Le, L., Gleave, M. E., Wyatt, A. W., & Chi, K. N. (2019). Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: A multicentre, randomised, open-label, phase 2, crossover trial. *The Lancet Oncology*, *20*(12), 1730–1739. https://doi.org/10.1016/S1470-2045(19)30688-6

Lokeshwar, S. D., Klaassen, Z., & Saad, F. (2021). Treatment and trials in non-metastatic castration-resistant prostate cancer. *Nature Reviews Urology*, *18*, 433–442. https://doi.org/10.1038/s41585-021-00470-4

Loriot, Y., Fizazi, K., de Bono, J. S., Forer, D., Hirmand, M., & Scher, H. I. (2017). Enzalutamide in castration-resistant prostate cancer patients with visceral disease in the liver and/or lung: Outcomes from the randomized controlled phase 3 AFFIRM trial. *Cancer*, *123*(2), 253–262. https://doi.org/10.1002/cncr.30336

Mateo, J., Carreira, S., Sandhu, S., Miranda, S., Mossop, H., Perez-Lopez, R., Rodrigues, D. N., Robinson, D., Omlin, A., Tunariu, N., Boysen, G., Porta, N., Flohr, P., Gillman, A., Figueiredo, I., Paulding, C., Seed, G., Jain, S., Ralph, C., Protheroe, A., . . . de Bono, J. S. (2015). DNA-repair defects and olaparib in metastatic prostate cancer. *New England Journal of Medicine*, *373*(18), 1697–1708. https://doi.org/10.1056/NEJMoa1506859

Mateo, J., Porta, N., Bianchini, D., McGovern, U., Elliott, T., Jones, R., Syndikus, I., Ralph, C., Jain, S., Varughese, M., Parikh, O., Crabb, S., Robinson, A., McLaren, D., Birtle, A., Tanguay, J., Miranda, S., Figueiredo, I., Seed, G., Bertan, C., Flohr, P., . . . de Bono, J. S. (2020). Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): A multicentre, open-label, randomised, phase 2 trial. *The Lancet Oncology*, *21*(1), 162–174. https://doi.org/10.1016/S1470-2045(19)30684-9

Matsubara, N., Mukai, H., Hosono, A., Onomura, M., Sasaki, M., Yajima, Y., Hashizume, K., Yasuda, M., Uemura, M., & Zurth, C. (2017). Phase 1 study of darolutamide (ODM-201): A new-generation androgen receptor antagonist, in Japanese patients with metastatic castration-resistant prostate cancer. *Cancer Chemotherapy and Pharmacology*, *80*(6), 1063–1072. https://doi.org/10.1007/s00280-017-3417-3

Penson, D. F., & Litwin, M. S. (2003). The physical burden of prostate cancer. *Urologic Clinics of North America*, *30*(2), 305–313. https://doi.org/10.1016/s0094-0143(02)00187-8

Rathkopf, D. E., Beer, T. M., Loriot, Y., Higano, C. S., Armstrong, A. J., Sternberg, C. N., de Bono, J. S., Tombal, B., Parli, T., Bhattacharya, S., Phung, D., Krivoshik, A., Scher, H. I., & Morris, M. J. (2018). Radiographic progression-free survival as a clinically meaningful end point in metastatic castration-resistant prostate cancer: The PREVAIL randomized clinical trial. *JAMA Oncology*, *4*(5), 694–701. https://doi.org/10.1001/jamaoncol.2017.5808

Ryan, C. J., Smith, M. R., Fizazi, K., Saad, F., Mulders, P. F., Sternberg, C. N., Miller, K., Logothetis, C. J., Shore, N. D., Small, E. J., Carles, J., Flaig, T. W., Taplin, M., Higano, C. S., de Souza, P., de Bono, J. S., Griffin, T. W., De Porre, P., Yu, M. K., Park, Y. C., Li, J., . . . for the COU-AA-302 Investigators. (2015). Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *The Lancet Oncology*, *16*(2), 152–160. https://doi.org/10.1016/S1470-2045(14)71205-7

Sartor, O., de Bono, J., Chi, K. N., Fizazi, K., Herrmann, K., Rahbar, K., Tagawa, S. T., Nordquist, L. T., Vaishampayan, N., El-Haddad, G., Park, C. H., Beer, T. M., Armour, A., Pérez-Contreras, W. J., DeSilvio, M., Kpamegan, E., Gericke, G., Messmann, R. A., Morris, M. J., Krause, B. J., & for the VISION Investigators. (2021). Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *New England Journal of Medicine*, *385*, 1091–1103. https://doi.org/10.1056/NEJMoa2107322

Sathianathen, N. J., Philippou, Y. A., Kuntz, G. M., Konety, B. R., Gupta, S., Lamb, A. D., & Dahm, P. (2018). Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. *Cochrane Database of Systematic Reviews*, *10*, CD012816. https://doi.org/10.1002/14651858.CD012816.pub2

Shore, N. D. (2017). Darolutamide (ODM-201) for the treatment of prostate cancer. *Expert Opinion on Pharmacotherapy*, *18*(9), 945–952. https://doi.org/10.1080/14656566.2017.1329820

Small, E. J., Saad, F., Chowdhury, S., Oudard, S., Hadaschik, B. A., Graff, J. N., Olmos, D., Mainwaring, P. N., Lee, J. Y., Uemura, H., De Porre, P., Smith, A. A., Zhang, K.,

Lopez-Gitlitz, A., & Smith, M. R. (2019). Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. *Annals of Oncology*, *30*(11), 1813–1820. https://doi.org/10.1093/annonc/mdz397

Sternberg, C. N., Fizazi, K., Saad, F., Shore, N. D., De Giorgi, U., Penson, D. F., Ferreira, U., Efstathiou, E., Madziarska, K., Kolinsky, M. P., Cubero, D. I. G., Noerby, B., Zohren, F., Lin, X., Modelska, K., Sugg, J., Steinberg, J., & Hussain, M., & for the PROSPER Investigators. (2020). Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *New England Journal of Medicine*, *382*(23), 2197–2206. https://doi.org/10.1056/NEJMoa2003892

Swami, U., & Agarwal, N. (2020). Improvement in overall survival with apalutamide, darolutamide and enzalutamide in patients with non-metastatic castration-resistant prostate cancer. *Cancer Treatment and Research Communications*, *25*, 100205. https://doi.org/10.1016/j.ctarc.2020.100205

Sweeney, C. J., Chen, Y. H., Carducci, M., Liu, G., Jarrard, D. F., Eisenberger, M., Wong, Y., Hahn, N., Kohli, M., Cooney, M. M., Dreicer, R., Vogelzang, N. J., Picus, J., Shevrin, D., Hussain, M., Garcia, J. A., & DiPaola, R. S. (2015). Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *New England Journal of Medicine*, *373*(8), 737–746. https://doi.org/10.1056/NEJMoa1503747

Tombal, B., Saad, F., Penson, D., Hussain, M., Sternberg, C. N., Morlock, R., Ramaswamy, K., Ivanescu, C., & Attard, G. (2019). Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): A multicentre, randomised, double-blind, phase 3 trial. *The Lancet Oncology*, *20*(4), 556–569. https://doi.org/10.1016/S1470-2045(18)30898-2

Violet, J., Sandhu, S., Iravani, A., Ferdinandus, J., Thang, S. P., Kong, G., Kumar, A. R., Akhurst, T., Pattison, D., Beaulieu, A., Mooi, J., Tran, B., Guo, C., Kalff, V., Murphy, D. G., Jackson, P., Eu, P., Scalzo, M., Williams, S., Hicks, R. J., & Hofman, M. S. (2020). Long-term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of (177)Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. *Journal of Nuclear Medicine*, *61*(6), 857–865. https://doi.org/10.2967/jnumed.119.236414

Watson, P. A., Arora, V. K., & Sawyers, C. L. (2015). Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nature Reviews Cancer*, *15*(12), 701–711. https://doi.org/10.1038/nrc4016