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Review Article

Castration resistant prostate cancer: from existing therapies to compounds under investigation

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ABSTRACT

Prostate carcinoma is a highly prevalent biologically and clinically heterogeneous disease. Unfortunately, within 5 years of diagnosis, 10-20% of patients acquire a castration-resistant prostate cancer (CRPC) in spite of multiple surgical and non-surgical therapy choices. The clinical context of CRPC is heterogeneous, encompassing patients with asymptomatic prostate-specific antigen (PSA) elevation following ADT failure and good performance status, as well as those experiencing severe, incapacitating symptoms and a rapidly progressing disease that ultimately results in death. Non-metastatic CRPC (nmCRPC) is a stage of the disease that is transient and is defined by certain criteria that are set within a certain time frame. Most patients with nmCRPC will eventually develop metastatic lesions, which are linked to morbidity and death specific to prostate cancer. Until 2010, the only treatments for patients with metastatic prostate cancer were androgen deprivation therapy and docetaxel. The advent of several hormonal and non-hormonal therapies such as abiraterone acetate, enzalutamide, apalutamide, cabazitaxel, darolutamide, the immunotherapeutic sipuleucel-T has brought about a paradigm shift in management of CRPC patients. These molecules have demonstrated a survival benefit in mCRPC & nmCRPC. For patients with advanced PSMA-positive mCRPC, 177Lu-PSMA-617 radioligand therapy offers a novel and efficacious therapeutic approach. PARPi are sensitive to tumors with gene mutations that impact homologous recombination repair, such as BRCA1 and BRCA2 abnormalities in mCRPC. The goal of this study was to highlight recent developments in CRPC clinical trials as well as guidelines recommendations for CRPC.

Keywords: Metastatic, Advanced prostate cancer, CRPC, Guidelines

INTRODUCTION

According to the Global Cancer Observatory, prostate cancer was the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men in 2020.[1] Almost 1.4 million new cases and 375,000 deaths have been reported worldwide in that year alone, representing a substantial health burden.[1] It accounts for 7.3% of all cancer cases worldwide and approximately 7% of patients are in metastatic stage when the disease first manifests.[2] Generally, active surveillance or local therapy (surgery, and radiation therapy) with or without ADT can achieve very high disease control rates for localized Prostate Cancer. However, systemic treatment is necessary for locally advanced and metastatic cancer. Androgen receptor (AR) signalling is crucial for the development and progression of prostate cancer. In this context, the key to managing the prostate cancer progression is to target the androgen receptor signalling axis, whose activation is mediated by androgens.[3] Thus, androgen deprivation therapy (ADT) with medical castration, antiandrogens, or surgical castration is initially recommended which usually results in a 90-95% reduction in circulating testosterone levels and prevents tumor cell survival.[3] Overtime, cells inevitably become

resistant to this androgen deprivation & becomes castration resistant.[3] Despite several surgical and non-surgical therapeutic options, unfortunately, 10–20% of all patients develop a CRPC within 5 years from diagnosis. CRPC is characterised by tumor progression despite blood testosterone levels below 50 ng/dl.[3] The landscape of CRPC treatment has deeply transformed, with the emergence of several new compounds in the recent years. We aimed to perform a comprehensive literature review on CRPC treatment landscape, with insights into currently available drugs and upcoming innovative treatment options.

Approach to initial treatment of CRPC

Castration-resistant disease is a fatal manifestation of prostate cancer. Approach to initial treatment of CRPC is determined by a number of parameters, including the patient's clinical status, metastatic sites, medication history of prostate cancer, and other tumor characteristics.

Continuation of ADT

CRPC was once also known as "androgen-independent" or "hormone-refractory." It is now known that being castration-resistant does not imply that tumor cells are not susceptible to hormone suppression. In fact, CRPC remains highly dependent on the AR signaling axis, so it is recommended to maintain ADT indefinitely as the mainstay of treatment.[4-7]

Patients with metastatic CRPC

Chemotherapy, hormone therapy, immunotherapy, and bone-targeting therapy are some of the treatments available for mCRPC. With the approval of an increasing number of innovative drugs for use in the treatment of mCRPC patients, significant advancements in the field have been accomplished in recent years. Efficacy of different systemic treatment options for mCRPC is outlined in the (Table 1).

The choice of treatment is dependent on prior therapy, and outlined in the sections below

Patients previously not exposed to an Androgen Receptor Signalling inhibitors (ARSI) or a taxane, For this group of patients, guidelines recommend adding an ARSI (Abiraterone acetate 1000 mg/day plus prednisone 5 mg/twice daily or Enzalutamide 160 mg/day) to ADT as first line therapy.[5-7]

Cytotoxic chemotherapy using docetaxel 75 mg/m2 every three weeks plus 5 mg oral prednisone twice daily can be considered for patients with relatively rapidly progressing symptomatic disease.[6] Sipuleucel-T is recommended for asymptomatic or minimally symptomatic males not requiring a rapid response.[5]

Patients previously exposed to an ARSI but not docetaxel

Treatment with a taxane is an option, for those who are appropriate candidates for a cytotoxic agent. Docetaxel over cabazitaxel as the initial chemotherapy regimen for chemotherapy-naïve patients is suggested.[4] Cabazitaxel may be preferred in older or frail patients and those at high risk for neutropenia, based on its lower toxicity and similar efficacy.[15]

Patients previously exposed to both an ARSI and docetaxel

For patients with progression despite prior ADT plus an ARSI and docetaxel, lutetium Lu-177 vipivotide tetraxetan, also known as 177Lu-PSMA-617 is a recommended option for those with Prostate Specific Membrane Antigen (PSMA)-positive disease.[6] Cabazitaxel (25 mg/m^2) plus prednisone (5 mg/day) is another option for those who are appropriate candidates for cytotoxic therapy.[4,5] The bone-targeted radiopharmaceutical Radium-223 is an option for males with symptomatic bone metastases and no visceral disease following progression with docetaxel.[4,6] Radium-223 significantly improved overall survival and reduced symptomatic skeletal-related events in patients with symptomatic mCRPC who had previously received docetaxel chemotherapy or were deemed unfit for docetaxel.[6] Selected patients may be eligible for a PARP*i* (homologous recombination repair deficiency) or an immune checkpoint inhibitor (eg, deficient mismatch repair, high levels of tumor mutational burden).[4,6]

Patients with non-metastatic CRPC (nmCRPC)

Short PSA doubling time: For males with nmCRPC and a PSA doubling time (PSADT) of 10 months or less progressing on ADT monotherapy, a second-generation androgen receptor blocker (enzalutamide, apalutamide, or darolutamide) plus ADT is recommended, rather than continued ADT alone or another form of therapy.[4-7] At least three placebo-controlled RCTs have demonstrated delayed disease progression and prolonged survival using ARSI drugs that interfere with androgenic stimulation of prostate cancer growth, including enzalutamide, apalutamide, and darolutamide, in conjunction with continued ADT for the treatment of males with nonmetastatic CRPC as shown in (Table 2).[16-18] These drugs are now US Food and Drug Administration (USFDA) approved for nmCRPC, all given in conjunction with continued ADT. These trials were all conducted in males with short PSA doubling times (≤10 months), and the control arm was placebo plus ongoing ADT. Abiraterone is an alternative, but does not have USFDA approval for this indication. Results from the uncontrolled phase II IMAAGEN trial, and a network meta-analysis comparing different treatments for nmCRPC supports the use of abiraterone acetate for the management of nmCRPC.[19,20]

Table 1: Efficacy of various systemic treatment options for mCRPC.

Compound	Study design	Patient population	Results
Abiraterone Acetate	COU-AA 302 study randomised, double-blind, placebo-controlled phase 3 study.[8]	1088 men with CRPC & chemotherapy-naive were randomised to receive abiraterone acetate 1 g daily or placebo	Abiraterone was associated with significantly prolonged overall survival (OS) (34.7 vs. 30.3 months) & increase in radiographic progression free survival (rPFS) (16.5 vs. 8.2 months)
Enzalutamide	PREVAIL study Phase III, double -blind, randomized study.[9]	1717 pre-chemotherapy mCRPC patients were randomised to enzalutamide 160 mg daily or placebo	Enzalutamide reduced the risk of radiographic progression or death by 68% (20 vs. 5. 4 months, p<0.0001) and the risk of death by 23% (OS 35.3 vs. 31.3).
Enzalutamide	AFFIRM trial, Phase III study.[10]	1199 patients post chemotherapy mCRPC patients were randomised to enzalutamide 160 mg daily vs. Placebo.	Enzalutamide treatment showed improved OS (18.4 vs. 13.6 mo).
Docetaxel	SWOG-9916 Trial.[11]	770 men with metastatic prostate cancer were randomised to docetaxel 60 mg/m^2 every 3 weeks vs. Mitoxantrone 12 mg/m^2 every 3 weeks	The improvement in median survival of nearly two months with docetaxel vs. Mitoxantrone (OS: 17.5 vs 15.6 months).
Cabazitaxel	TROPIC Trial, open-label, randomised, phase III trial.[12]	755 mCRPC men post chemotherapy and ARSI were randomised to either 12 mg/m^2 mitoxantrone IV over 15-30 mins or 25 mg/m^2 cabazitaxel IV over 1 h every 3 weeks.	Cabazitaxel improved OS (15.1 vs. 12.7 months). Median progression-free survival was 2.8 months in the cabazitaxel vs. 1.4 months in the mitoxantrone group (p<0·0001).
Sipuleucel-T	IMPACT Trial, double-blind, placebo-controlled, multicenter phase III trial.[13]	512 mCRPC men were randomised to sipuleucel-T 3 infusion IV every 3 weeks) vs. placebo	Sipuleucel-T resulted in a 4.1-month improvement in median survival (OS 25.8 vs. 21.7 months).
Radium-223	ALSYMPCA Phase III, randomized, double-blind, placebo-controlled study.[14]	921 men with CRPC & bone metastasis were randomised to receive 6 injections of radium-223 (50 kBq/kg IV) vs. placebo.	Radium 223 significantly improved OS (14 vs. 11.2 months).

Table 2: Efficacy of various systemic treatment options for nmCRPC.

Compound	Study design	Patient population	Results
Enzalutamide[16]	Double-blind, phase III trial	1401 nmCRPC men with PSADT≤10 months were randomised to receive enzalutamide 160 mg or placebo once daily.	The median metastasis-free survival was 36.6 months in the enzalutamide Vs. 14.7 months in the placebo (p<0.001).
Apalutamide[17]	Double-blind, placebo-controlled, phase III trial	1207 nmCRPC men with PSADT≤10 months were randomised to receive apalutamide 240 mg or placebo once daily.	Metastasis-free survival (40.5 vs. 16.2 months) and time to symptomatic progression were significantly longer with apalutamide.
Darolutamide[18]	Randomized, double-blind, placebo-controlled, phase III trial	1509 nmCRPC men with PSADT≤10 months were randomised to receive darolutamide 600 mg twice daily vs. placebo.	The median metastasis-free survival was 40.4 months vs. 18.4 with placebo. Darolutamide was also associated with benefits in OS, time to pain progression, time to chemotherapy, and time to a symptomatic skeletal event.

Longer PSA doubling times: The optimal approach for patients with nmCRPC and longer PSADT is not established. Guidelines recommend observation with continued ADT or treatment with a secondary hormonal therapy can be attempted.[4-7]

ALTERNATIVES FOR REFRACTORY DISEASE

PARPi for patients with deficiency in homologous recombination repair (HRR)[21]

Poly-ADP ribose polymerase inhibitors (PARP*i*) are an emerging therapeutic option for the treatment of prostate cancer and alterations in DNA damage response genes. Additionally, this has caused the mCRPC patients to undergo genomic testing on a large scale. The high frequency of genetic mutations found in Prostate Cancer serves as the primary justification for the use of PARP*i*. About 10-15% of individuals with metastatic Prostate Cancer have germline mutations in the homologous recombination DNA repair genes, whereas somatic mutations affect 20-25% of those patients.Genetic alterations in Prostate Cancer include breast cancer susceptibility gene (BRCA) 1, BRCA2, checkpoint kinase 2 (CHEK2), ataxia telangiectasia mutated (ATM), etc. PARP*i* has the ability to make tumor cells more sensitive to therapies that cause DNA damage, such as chemotherapy or radiotherapy.

Several PARP*i* have been studied in males with mCRPC and DNA repair mutations, and two of these (olaparib, rucaparib) are currently approved for treatment in CRPC with HRR deficiency. Rucaparib received an accelerated USFDA approval for patients with BRCA1/2 germline or somatic defects after failure of an ARSI and a chemotherapy. Olaparib is USFDA approved for those after an ARSI alone or an ARSI plus a chemothearpy for those with a broad spectrum of HRR deficiency mutations. Males with BRCA2 mutations appear to benefit the most with PARP*i*. It has been demonstrated that PARP*i* therapy produces objective tumor responses as well as improve progression free and overall survival.

Pembrolizumab for deficient mismatch repair[22]

Immunotherapy has come to be as a significant standard of care for a number of cancers in recent years. However, because prostate cancer is an immunologically "cold" tumor, the utility of immunotherapies has been limited. Immunotherapy may still be beneficial for a subgroup of Prostate Cancer patients, such as those with high microsatellite instability (MSI), and defective mismatch repair (dMMR). Currently, Pembrolizumab, a humanized, anti–programmed death-1 (anti–PD-1) monoclonal antibody is the only immune checkpoint inhibitor approved for the treatment of mCRPC patients that have MSI-H or dMMR.

Radioligand therapy for PSMA-positive tumors[23,24]

Theragnostic techniques, such as the use of Prostate Specific Membrane Antigen (PSMA)-Targeted Radioligands for Prostate Cancer has gained popularity in recent years. A therapy approach called "Theragnostic" blends medicine and diagnostics. It connects targeted pharmacological therapy based on test results with a diagnostic test that finds patients most likely to benefit or be damaged by a new drug.

Theragnostic also seeks to improve drug safety and efficacy and monitor the response to treatment. Because PSMA is extensively expressed in Prostate Cancer cells, it can be used as a reliable tissue biomarker for functional imaging of Prostate Cancer. Currently, a number of PSMA ligands are being investigated globally for PET imaging. 177Lu-PSMA-617 is a radioligand that delivers beta-particle radiation preferentially to PSMA-positive cells and the surrounding microenvironment. USFDA has approved 177Lu-PSMA-617, for the treatment of adult patients with mCRPC who have highly expressed PSMA and have at least one metastatic lesion. It is the first FDA-approved targeted radioligand therapy for eligible men with PSMA-positive mCRPC. As precision medicine advances, this is an exciting new chapter in the history of highly customised medical care.

BIPOLAR ANDROGEN THERAPY (BAT)

ADT remains the cornerstone of prostate cancer treatment. However, because the cancer cells reactivate androgen receptor signalling and adapt to the castrate state through androgen receptor autoregulation, the progression towards CRPC is unavoidable.[1] At this point of time, patients are treated with second generation ARSI or androgen biosynthesis inhibitor. However, few patients may also develop resistance to these agents which in turn is associated with poor prognosis.[25]

An emerging therapeutic approach for patients with mCRPC is bipolar androgen therapy. Every month, serum testosterone level is cycled from supraphysiologic (>1500 ng/dL) to near-castrate (<50 ng/dl) during BAT.[26] This rapid cycling is accomplished by ADT and concurrent monthly intramuscular testosterone injections. The goal is to target the spectrum of AR expression found in heterogeneous CRPC tumors while also interfering with the adaptive regulation of AR linked to long-term exposure to high or low testosterone levels.[24,25] The effectiveness of BAT and its ability to resensitize patients to androgen receptor (AR)-targeted treatments have been shown in numerous clinical trials:

Restore trial[27]

A phase II, multicohort, open label study of BAT included 59 males with asymptomatic mCRPC.

Table 3: Clinical trials of various drugs conducted for mCRPC in the year 2023.

Compound	Study design	Patient population	Result
Enzalutamide[29]	Alliance A031201 Trial Randomized Phase III	Men with untreated mCRPC randomised to Enzalutamide (n-657) vs. Enzalutamide + Abiraterone acetate plus progesterone (n-654) for 32-34 months	rPFS was longer in the combination arm (21.3 vs. 24.3 months)
Abiraterone Acetate[30]	Phase II, single-arm, open-label multicenter study	21 Naive mCRPC men received Abiraterone acetate plus progesterone for 4 weeks followed by 0.5 mg Dutasteride daily.	85.7% achieved ≥50% PSA reduction. Dutasteride was associated with shorter time to treatment failure.
Darolutamide[31]	*SAKK* trial Randomized phase II	92 mCRPC patients with prior ARSIs & chemotherapy randomised to Darolutamide 600 mg BD Vs. placebo	Improvement was seen with Darolutamide in rPFS at 12 weeks (64.7 vs. 52.2%), Median event-free survival (5.4 vs. 2.9 months, PSA 50% response rate (22 vs. 4%) & Median OS (24 vs. 21.3 months)
Proxalutamide[32]	Multicenter, randomized, open-label, phase II trial	108 mCRPC patients randomised to 100, 200 and 300mg dose in 1:1:1 ratio.	By week 16, there were 35.1, 36.4 and 42.9% patients with confirmed 50% or greater PSA decline in 100, 200 and 300 mg groups, respectively. The proxalutamide dose of 200 mg daily is suggested.
Cabazitaxel[33]	Multicenter phase II open-label, randomized, parallel-group study	73 mCRPC patients were randomized to 3-weekly Arm A (cabazitaxel at 25 mg/m^2) Vs. Arm B (individualized dosing of cabazitaxel).	Median PFS and OS was higher in arm B compared with arm A (OS- 16.2 vs. 7.3 months). Individualized dosing improves clinical outcome
Cabazitaxel[34]	CARD Trial, Retrospective and observational real world data	12,140 mCRPC patients with prior ARSIs/Chemotherapy	Results indicate the CARD population is reflective of routine clinical practice and duration of response to cabazitaxel was similar in a real-world population.
Olaparib[35]	TAPUR Study, Phase II	30 mCRPC patients with BRCA1/2 mutations were treated with olaparib	The disease control rate was 69%. Median rPFS and the median OS were 38.4 and 76.4 weeks, respectively.
Olaparib[36]	Randomized, open-label, phase II trial	90 patients with progressive mCRPC were randomised to cediranib 30 mg OD + olaparib 200 mg BD vs. olaparib 300 mg BD alone.	Median rPFS was 8.5 vs. 4 months. Cediranib/olaparib significantly improved rPFS especially in BRCA2-mutated subgroups
Olaparib[37]	COMRADE Trial, Multicenter phase	12 mCRPC patients with bone metastases & prior ARSIs/ Chemotherapy were given olaparib with radium-223	At the dose of 200 mg orally BD with radium-223, rPFS at 6 months was 58%
Niraparib[38]	MAGNITUDE Trial, Phase III, randomized, double-blinded	mCRPC patients with or without HRR-associated gene alterations received niraparib + Abiraterone acetate & prednisolone or placebo + Abiraterone acetate & prednisolone	Combination significantly increased median rPFS (16.5 vs. 13.7 months) even in patients with HRR-associated gene alterations.
Niraparib[39]	Phase I Study	30 men with progressive mCPRC and prior ARSIs/ Chemotherapy received Niraparib (100-300 mg) in combination with radium-223	Combining niraparib with Radium-223 in patients with mCRPC was safe. Anemia & neutropenia were the most common grade 3 adverse events.
Rucaparib[41]	TRITON2 Study, Phase II	277 mCRPC men who had progressed on prior ARSIs/	Almost half of TRITON2 patients with BRCA-mutated mCRPC had a

Continued.

Compound	Study design	Patient population	Result
		Chemotherapy & associated with a BRCA1 or BRCA2 or DNA damage response (DDR) gene alteration received rucaparib 600 mg BID	complete or partial tumor size reduction with rucaparib; clinical benefits were also observed with other DDR gene alterations.
Talazoparib[42]	TALAPRO-2 Study, Phase III, randomized, double-blind	805 mCRPC patients were randomly assigned to talazoparib 0·5 mg or placebo, plus enzalutamide 160 mg, administered orally OD	Talazoparib plus enzalutamide resulted in clinically meaningful and statistically significant improvement in rPFS versus enzalutamide as first-line treatment for patients with mCRPC.

Table 4: Clinical trials of various drugs conducted for mCRPC in the year 2023.

Compound	Study design	Patient population	Result
Darolutamide[42]	ARAMIS Trial, Multicenter, double-blind, randomized, Phase III trial	1509 nmCRPC men were randomized to oral darolutamide 600 mg BD or placebo. Group 1: PSADT 6-10 months; Group 2: PSADT ≤6 months	Darolutamide significantly prolonged Metastasis Free Survival (MFS) vs. placebo in both groups.
Flutamide[43]	Multicenter,randomized, phase II	Thirty-three nmCRPC patients randomized to flutamide(tid) and 31 to flutamide(tid) + Pox viral based therapeutic cancer vaccine (once in 28 days).	Combination of flutamide + vaccine did not improve PSA-specific T cells & thus outcomes in men with nmCRPC compared with flutamide alone.
Darolutamide[44]	ARAMIS subgroup analysis, Multicenter, double-blind, randomized, Phase III trial	117 high risk nmCRPC men were randomized to oral darolutamide 600 mg BD or placebo.	Darolutamide prolonged MFS versus placebo
Relugolix in combination with Apalutamide [45]	Open-label, phase 1, parallel cohort study, 52-week study	10 mCRPC or mCSPC were given Relugolix 240 mg od and apalutamide 240 mg od.	Relugolix and apalutamide was associated with a favorable safety and tolerability profile consistent with the known profiles of the individual medications.
Apalutamide[46]	SPARTAN study, Post-hoc analysis to study Clinical characteristics associated with falls	806 nmCRPC men who were randomized to apalutamide experienced falls more frequently vs. those receiving placebo (15.6% vs. 9.0%)	Older age, poor performance status, history of neuropathy, and α-blocker use remained significantly associated with fall.

This study evaluated whether BAT (400 mg testosterone cypionate intramuscularly every 28 days) restores sensitivity to abiraterone and/or enzalutamide in males with mCRPC who have previously failed one or both of these therapies by treating such patients with BAT followed by subsequent retreatment with abiraterone or enzalutamide. PSA50 response rates to BAT was 30% in post-enzalutamide cohort vs. 17% in post-abiraterone cohort. PSA50 responses to AR-targeted therapy rechallenge were 68% in post-enzalutamide cohort & 16% in post-abiraterone cohort. The median time from enrollment to progression following rechallenge with AR-targeted therapy (ie, progression-free survival 2; PFS2) was 12.8 vs 8.1 months in post-enzalutamide cohort and post-abiraterone cohort respectively. The study concludes BAT may be effective at resensitizing enzalutamide in mCRPC patients.

Meta-analysis[28]

A total of ten studies (353 patients with CRPC) were included. Participants who underwent BAT achieved a PSA50 response rate of 27%. Patients who completed BAT proceeded to AR-targeted therapy (Abiraterone or Enzalutamide) and achieved a PSA50 response rate of 57%. Patients with prior Enzalutamide resistance had a stronger impact on the PSA50 of AR-target therapy rechallenge. The results of this meta-analysis indicate that BAT is a safe and effective treatment for patients who have progressed after Abiraterone or Enzalutamide. BAT

can trigger the resensitization of patients with CRPC to subsequent endocrine therapy and improve the overall survival of patients and their quality of life.

UPDATES IN THE MANAGEMENT OF CRPC

The updates in management of CRPC is summarized in (Table 3,4).

CONCLUSION

CRPC is a lethal disease that imposes a enormous burden on patients. With the advent of novel medicines with diverse mechanisms, such as ARSIs, PARP*i*, and theragnostics, the landscape of mCRPC treatment has seen a significant transformation in the past few years. The therapeutic landscape may be further revolutionised by ongoing trials utilising medicines with novel mechanisms of action, such as targeted therapies and immunotherapies. Results of several trials over the next few years promise a new era in the field which will hopefully further improve the outcomes of men with advanced prostate cancer.

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