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Decoding Prostate Cancer Complexity: Insights into Classification, Molecular Therapies, and Immune Modulation Strategies

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A B S T R A C T

The prostate cancer is a little gland found only in men that produces the white fluid. These is one of the semen containing sperm prostate cancer occurs at age of 45. Prostate cancer is also called as the benign prostatic hyperplasia (BPH). Prostate cancer classification such as the adenocarcinoma of prostate cancer, transitional cell carcinoma of prostate, cell squamous carcinoma prostate cancer, small cell prostate cancer. Epidemiology, global condition, incidence, mortality, molecular targeted therapies for treatment of metastatic prostate cancer such as the PSMA-targeted radionuclide therapies used LU-177 PSMA-617) and Taxane chemotherapy, DNA repair inhibitors involved such as the PARP-1 and PARP-2 and olaparib, Rucaparib, Talazoparib, mechanism of action DNA repair inhibitors such as the olaparib, rucaparib, Talazoparib, involved in the poly (ADP-ribose) polymerase inhibitors. Therapies targeted prostate cancer neovascularization anti-angiogenic medicines primary targets are vascular endothelial signal pathway for prostate cancer such as the Receptors tyrosine kinase pathway, Androgen receptors mediated pathway, NF-Kb pathway, JAK/STAT pathway, Wnt pathway. Using anti-androgen compounds like abiraterone acetate and enzalutamide as well as particles emitting radionuclide (radium-223), immune check point pathway such as the cytotoxic T-Lymphocyte antigen (CTLA-4) and programmed death-1 (PD-1) immunomodulatory receptors and their associated ligands B7-1 and B7-2 and PDL-1 inhibit T-cell function physiologically, which is important for reducing tissue damage caused by inflammatory processes while maintaining self-tolerance.

Keywords: Prostate Cancer, PSMA- Radionuclide Targeted Therapies, DNA Repair Inhibitors, Immune Check Point Inhibitors

1. Introduction

The prostate is a small gland that only exists in men and generates a white fluid. This fluid, that includes sperm, is one element of sperm. Prostate is around the size of an almond after puberty. During puberty, the prostate gland doubles in size, reaching the size of a walnut. Then, around the age of 45, a man's prostate gets started to develop again and continue to expand for the rest of his life. This cancer speed is typical and has nothing to do with cancer. This cancer is also known as benign prostatic hyperplasia (BPH) prostate cancer and damages the prostate gland, which is situated just below the bladder and near the front of the rectum. Plenty of many men Prostate cancer is diagnosed with a prostate biopsy and investigation, a PSA test, a digital rectal exam, magnetic resonance imaging (MRI), or medical screening. Prostate cancer risk factors include heritage, culture, age, overweight and obesity, and other environmental variables (Dai et al., 2016). The prostate has two lobes, the right and left, and is separated into five zones, two of which are the transition zone and the periphery zone. The transition zone is placed on the centre portion of the prostate, and this area benign growth cancer occurs in many men, and these benign prostatic hyperplasia in men usually arise when they are 80 years old. The horseshoe-shaped peripheral zones exist in the rectums on both sides of the urethra and are where the majority of prostate cancers arise. Prostate cancer is the second most common disease in males (15.1%) and causes the fifth highest percentage of cancer deaths in men (6.83%) worldwide. Malignant tumours are the third leading cause of cancer-related death in men in Europe (22.2%), after lung and colorectal cancer (Aaron et al., 2016).

1.1 Classification of Prostate Cancer

1.1.1 Adenocarcinoma of Prostate Cancer

Adenocarcinoma is a form of cancer can affect various bodily parts because it starts in the glands that line the interior of the organs. In glandular epithelial cells that liberates mucus, digestive juices, or other fluids, adenocarcinoma develops. Adenocarcinoma can proliferate in other bodily regions in some circumstances; at this stage, it is known as metastatic adenocarcinoma.

1.1.2 Prostate Transitional Cell Carcinoma

Prostate transitional cell carcinoma begins in the cells that line the urethra, the tube that transports pee to the outside of the body. This form of cancer usually affects the prostate after it spreads from the bladder. Rarely, it can begin in the prostate and spread to the bladder opening and surrounding tissues. Another name for this is prostate urothelial carcinoma. This type of prostate cancer affects 2 to 4 out of every 100 cases (between 2 and 4%) (Ngninkeu et al., n.d.).

1.1.3 Cell Squamous Carcinoma of Prostate

Squamous cell carcinoma is a type of prostate cancer that is very aggressive and frequently metastasizes to the bone, liver, and lungs. Bone pain can develop as an outcome of metastasis. Squamous cell carcinoma is the most important carcinoma of malignancy they are very rare malignancy less than 1% of all prostate cancer. 68 the average age of the diagnosis of squamous cell carcinoma almost common symptoms occurs in the squamous cell carcinoma are obstructive urinary symptoms including straining (constipation doesn't affect prostate gland directly they make the BPH symptoms urinary urgency frequency or incontinence may result from the rectum pressing on the bladder when it is full (Lee, 2019).

1.1.4 Small Cell Prostate Cancer

The most prevalent type of cancer is squamous cell carcinoma, contributing to less than 1% of all prostate cancers. The most prevalent kind of prostate cancer is substantially different from small cell prostate cancers. They develop faster than other varieties. By time small cell prostate cancer is discovered, it has usually spread to other parts of body. This indicates that cancer has progressed to several body systems, including bones (Rawla, 2019a).

1.2 Global Condition

According to Farley et al. (2015), prostate cancer has a remarkable worldwide burden and it is among top five cancers in terms of prevalence and mortality. Geographic differences in prostate cancer incidence and mortality are considerable deaths rates (Rawla, 2019a). An examination of trends in prostate cancer prevalence and mortality worldwide populations and over time offers perceptions of the importance of both population and individual risk factors the epidemiology of this screening behaviors disease (Wang et al., 2022a).

1.3 Incidence

Prostate cancer is frequently diagnosed cancer in men worldwide with about 1.6 million incident cases in 2015 (Global Burden of Disease Cancer Collaboration) (Fitzmaurice & Global Burden of Disease Cancer Collaboration, 2018). In wealthy nations, prostate cancer is particularly prevalent (Taitt, 2018a). Prostate cancer diagnosis chances by the age of 79, one in 47 countries including index of low-middle socioeconomic status, compared to countries, one in six characterized by a high sociodemographic index (Global The 2016 Cancer Collaboration's Burden of Disease) (Hassanipour-Azgomi et al., 2016). Prostate cancer is almost common cancer among new cases in United States, with an estimated that in 201, 180,890 new cases were identified (claire h.pernar) prostate cancer is the leading incidence and mortality in men Black males in Europe, Caribbean men, and African American men (Rawla, 2019a),(Taitt, 2018b). It is unknown if black people experience the same high rates, men who call Africa home (Ogunsanya et al., 2017). Even though reports claim Although PCa is a rare disease among African black guys, it is one of the most frequent urological malignancies. Deaths and incidents Rates and rate ratios comparing AANHPIs and NHWs from 2008 to 2012 (Benedict et al., n.d.).

1.4 Mortality

Prostate cancer prevalence and death rate in 2020of major nations, and in 2020, more than 1.4 million new cases of prostate cancer were discovered worldwide (Sung et al., 2021). The most prevalent incidence rate per 100,000 males was 36.0, with the age standard incidence rate being 37.0 per 100,000 males (O'Brien et al., 2014). Northern America and Oceania had age standard incidence rate that were higher than 59 per 100,000 males in America and the Caribbean, males whereas ASIRs in Africa and Asia were fewer than 30 per 100,000 (Wang et al., 2022b). Regional diffusion ASMR was discovered, however, highly uneven. distinct, with Latin America and Africa having the greatest rates Europe, Oceania, Europe, North America, and the Caribbean both Asia ASIRs (Poerio et al., 2018). Among 174 nations, the greatest highest ASIR was 110.7 per 100,000 men in Northern Europe's Ireland, while the lowest was 0.9 per 100,000 men in South-Central Asia's Bhutan. Similarly, ASMRs varied more than 77-fold among 174 people nations, with Bhutan having the lowest ASMR of 0.54 per 100,000 men and Zimbabwe having guys with the highest ASMR of 41.7 per 100,000 ,while having a crude mortality rate of 12.2 per 100,000 people (prostate cancer incidence mortality-3). In the United States, an estimated 232,000 new instances of prostate cancer would be diagnosed in 2005, with 30,000 deaths (Wang et al., 2022c). Every year, over around the world, 200,000 people die, the vast majority of them are males over the age of 65 in developed countries. African American men have the highest incidence rates of prostate cancer in the United States world, for unknown causes that may be related to genetic variations in androgenic hormone synthesis and metabolism. Age, race, and heredity are the only well-established risk variables. Environmental influences are at work, as seen by changing incidence rates when populations relocate. For example, Japanese Americans [Nisei] born in the United States have a greater incidence of prostate cancer than Caucasian Americans. men's population [This higher risk also applies to colorectal and breast cancer] A high fat and red meat diet are dietary risk factors. Antioxidants in the diet, such as selenium and lycopene, minimize risk. The most consistent risk factor is a family history of prostate cancer, which accounts for up to 40% of prostate cancer patients. Serval

molecular genetic alterations associated with prostate carcinogenesis and development have been discovered, involving chromosomes 8,10,13,16, and 17. Loss of heterozygosity on chromosome 8p appears to be an inherited condition (Rawla, 2019b). Cancer is thought to begin with a single clone of changed cells that continue to proliferate and, through cellular development accompanied by genetic instability, evolve into a full-fledged malignant neoplasm. Using the same patients and four DNA microsatellite polymorphism markers, researchers discovered that different tumour foci in the same patient have a separate genesis. Phenotypically comparable tumor foci showed distinct genotypes, providing more support for tumour foci multifocality in the prostate. This discovery has crucial clinical consequences because these tumours differ in terms of invasiveness, estrogen dependency, and treatment responsiveness (Ferguson et al., 2015).

1.5 Molecular Targets on CRPC Treatment

Table 1. Molecularly targeted drugs for the treatment of mCRPC.

Therapeutic Agent	**Mechanism of action**	**References**
PSMA- Targeted Radionuclides		
177lu-PSMA-617	Beta-emitting radionuclides lutenium-177 conjugated with the PSMA ligand PSMA-617	(Ritawidya et al., 2023)
177lu-DOTA-Rosopatamab	Lutetium-177 conjugated, via the chelating agent dodecanetetraacetic acid (DOTA), with rosopatamab, a humanized monoclonal antibody against PSMA	(Abusalem et al., 2023)
225Ac-PSMA-617	Alpha-emitting radioisotope Actinium-225 conjugated with PSMA-617	(Ling et al., 2022)
225Ac-PSMA-I&T	Actinium-225 conjugated with the PSMA ligand PSMA-I&T	(Hooijman et al., 2021)
DNA Repair Inhibitors		
Olaparib	Inhibitor of PARP1 and PARP2	(Gunderson & Moore, 2015)
Rucaparib	Inhibitor of PARP1, PARP2 and PARP3	(Dal Molin et al., 2018)
Talazoparib	Inhibitor of PARP1 and PARP2	(McCann, 2019)
Therapies Targeting Tumor Neovascularization		
Bevacizumab	Monoclonal antibody specific for VEGF-A	(Ferrara et al., 2005)
Aflibercept	Inhibitor of VEGF-A and -B	(Schicht et al., 2017)
Cediranib	Inhibitor of VEGFR-1, -2 and -3	(Yamamoto et al., 2009)
Sunitinib	Inhibitor of VEGFR-1, -2, -3; PDGFR-A and -	(Delbaldo et al., 2012a)
Immune Checkpoint Inhibitors		
Ipilimumab	Monoclonal antibody specific for CTLA-4	(Savoia et al., 2016)
Pembrolizumab	Monoclonal antibody specific for PD-1	(Dang et al., 2016)
Atezolizumab	Monoclonal antibody specific for PD-L1	(Shah et al., 2018)

CTLA-cytotoxic T-lymphocyte antigen 4. PD-1- programmed cell death protein 1. PD-L1 programmed death-ligand 1.

1.6 Molecularly Targeted Treatments for Metastatic Prostate Cancer

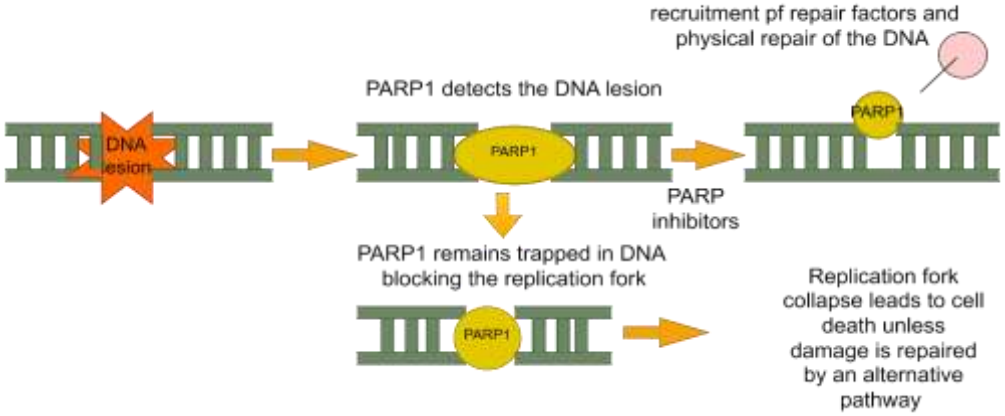
The prostate-specific membrane antigen (PSMA) is an excellent target for the treatment of metastatic castration-resistant prostate cancer (mCRPC). DOTA coupled ligand PSMA-617 is an excellent candidate for therapeutic use due to its minimal kidney absorption, high affinity, and prolonged tumor retention (Plichta et al., 2021).

2. PSMA-Targeted Radionuclide Therapies

PSMA is most important target for directing new therapies PSMA found majorly in prostate cancer and PSMA majorly used to treatment of metastatic prostate cancer (lu-177 PSMA-617). Prostate cancer is usually radiosensitive (lu-177PSMA-617). For that palliative administration of castration-resistant metastatic prostate cancer, radiotherapy is conventional treatment, and radiopharmaceuticals that target the surrounding bone matrix rather than the tumor itself can enhance outcomes. Treatment is prolonged metastatic prostate cancer retention in the cell PSMA-antibody auristatin conjugates have been considered one option A synthetic antineoplastic agent is called monomethyl auristatin E (MMAE). It must be combined with a monoclonal antibody (MAB) that targets cancer cells because it is too toxic to be used as a medication on its own (Jang et al., 2023). PSMA protein has been the subject of numerous prostate cancer studies because it is significantly expressed in prostate cells compared to normal epithelial cells and increases in the early stages of the illness. Based on that finding of phase III VISION study, a PSMA-based RLT drug (NCT03511664) was cleared for clinical use in patients with metastatic prostate cancer. 177Lu-PSMA-617, which combines the PSMA ligand PSMA-617 (also known as vipivotide tetraxetan) with that beta emitter lutetium-177 (Giraudet et al., 2021). In the vision research, 551 patients from 84 sites in North America and Europe with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) that had progressed despite treatment with androgen receptor inhibitors and taxane chemotherapy were given four to six cycles of 177-lu-PSMA-617 every 6 weeks, while 280 patients with the same clinical-pathological features were given standard-of-care medication, such as the contentious The four types of molecular targeted treatments approved for the treatment of metastatic prostate cancer are as follows: Radionuclide medicines that target PSMA, DNA repair inhibitors, cancer neovascularization therapies, and immune checkpoint inhibitors (figure 1) (Ferretti et al., 2023).

2.1 DNA Repair Inhibitors

Endogenous and exogenous stimuli, such as cell growth or exposure to chemotherapy and radiation therapy, can both induce DNA damage in malignant and normal cells. Depending on the kind of chromosomal rearrangement, a specific DNA damage response (DDR) can be activated during homologous recombination (HR) and non-homologous end joining (NHEL) repair single strand breaks (SSB) in DNA, mismatch repair (MMR), base excision repair (BER), and nucleotide excision repair (NER) processes. single nucleotide damage repair. Apoptosis is a response to genetic instability when repair mechanism fails. BRCA1 and BRCA2 genes, which are involved in DSB repair, are frequently altered in metastatic prostate cancer, and a higher frequency of mutations encourages tumor development. Somatic mutations are found in 20-25% of people with metastatic prostate cancer, while 10%–15% of these patients have germline mutations in the HR DNA repair genes. BRCA2 mutations are more common (12–18%) than ATM (3-6%), CHEK2 (2–5%), and BRCA1 (2%) mutations. Hyperactivation of alternative DNA repair mechanisms, driven by the polyenyne's ADP-ribose polymerase 1, PARP1, and PARP2, partially makes up for this faulty HR. PARP is enzymatically triggered and polymerizes after stopping DNA breaks that are either single-stranded or double-strand (Alhmoud et al., 2020). The long chains of poly (ADP)-ribose (PAR) on itself and other nuclear acceptor proteins drive the PARylation process. PAR chains recruit DNA repair machinery to DNA alteration sites. As a result, because PARPs frequently play a critical role in genomic integrity and cancer cell survival to DNA damage, PARP inhibitors (PARPi) can greatly influence cancer cell viability (synthetic lethality). Olaparib and rucaparib, two kinds of PARPi, have currently mCPRC has been approved for treatment. The Food and Drug Administration (FDA) approved olaparib in May 2020 for the treatment of mCRPC with progression. in patients who had mutations in any HR gene after receiving second-generation hormone therapy (abiraterone or enzalutamide). The data for its approval came from the PROFOUND study, a randomized phase III trial. It discovered that olaparib-treated patients had considerably greater response rates (33% vs. 2%), as well as OS (19.1 vs. 14.7 months). than control patients who only received hormone therapy (Gupte et al., 2017). Because there are still unanswered doubts about PARPi's efficacy in hormone-sensitive prostate cancer, olaparib is being investigated in current research on individuals with biochemically recurrent prostate cancer after surgery who did not get concomitant androgen deprivation therapy. According to preliminary findings, A PSA response is seen in 35% of olaparib-treated people. The FDA authorised rucaparib in 2020 after the TRITON2 research found Patients with BRCA1 or BRCA2 mutations who had previously received second-generation hormone therapy as well as taxane-based therapy before being treated with rucaparib had a PSA response rate of 54.8%.Rucaparib is the topic of two current studies, one of which looks at its effectiveness in men with metastatic hormone-sensitive prostate cancer and the other at its effectiveness in nonmetastatic prostate cancer males biochemically repeated recurrence of prostate cancer following surgery or radiation therapy. Most promising of the novel PARPi is talazoparib, which has shown increased effectiveness in trapping PARP1 to DNA mistakes in addition to severely reducing the function of catalytic enzymes (Congregado et al., 2022). The term "PARP trapping" refers to the increase in PARP1's affinity for damaged DNA caused by PARPi. Briefly stated, PARPi prevents PARylation, and PARP1 is still strongly linked to DNA that has been damaged. Because PARP trapping prevents DNA replication, the damage is not repaired, and cell death results. The clinical trial found that when veliparib was combined with abiraterone acetate and prednisone, patients improved, had a higher progression-free survival rate than those treated with olaparib or talazoparib. Veliparib is a novel PARPi that is also attracting a lot of attention. The encouraging results obtained when PARPi was combined with anti-androgen therapy have prompted the development of new clinical trials examining the combination of PARPi with other therapeutic strategies, such as immune checkpoint inhibitors, anti-VEGF therapies, AKT inhibitors/ATR inhibitors, and radionuclides.. In upcoming years, the study' conclusive findings will be released (Prokhorova et al., 2021).



2.1.1 Mechanism Action of the DNA Repair Inhibitors

2.1.1.1 Olaparib (LYNPARZA)

Olaparib is an orally accessible inhibitor of PARP1 and PARP2 catalytic activity. Its primary function is DNA damage response (DDR). Olaparib is approved for the Breast and ovarian cancer treatment connected to genetic abnormalities such as BRCA1 and BRCA2. And to assess Olaparib's anticancer effectiveness in metastatic castration-resistant prostate cancer in order to identify biomarkers for PARP suppression sensitivity in metastatic castration-resistant prostate cancer, TOPARP was created (Biegała et al., 2023). TOPARP is a serial phase 2 clinical trial adaptation programme. In 49 molecularly unselected individuals, we found a connection between responsiveness to olaparib and putatively harmful DDR gene aberrations in the first trial, TOPARP-A.12 In this article, discuss the TOPARP-B study's findings, which were intended to support the antitumor activity of olaparib that had been observed in patients with metastatic castration-resistant prostate cancer and DDR gene mutation) (Mateo et al., 2020).

2.1.1.2 Rucaparib

Rucaparib is the PARP inhibitors sold the brand name such as the Rebraca is the PARP inhibitor and also known as the anticancer agent rucaparib is the class of DNA repair enzyme poly-d-ribose most frequent side effects are weakness and exhaustion, nausea (feeling sick), elevated creatinine and Vomiting, anaemia (low red blood cell counts), decreased appetite, dysgeusia (taste problems), diarrhea, thrombocytopenia (low platelet levels), and abdominal pain (belly ache) are also symptoms of liver enzyme deficiency. Outlying vascular smooth muscle contraction, including that from cancer patients' tumours, is reluctant by rucaparib. Additionally, it slows down some cancer and healthy cell migration in vitro Rucaparib is anticipated to be more efficient as a PARP inhibitor in 9% of pancreatic tumours with BRCA mutations (BRCA1 or BRCA2) (Colombo et al., 2018).

2.1.1.3 Talazoparib

Several DNA damage response (DDR) genes, and the talazoparib a poly (ADP-ribose) polymerase reluctant which are direct route or indirect route associated with homologized related coalescence repair (HRR), have been found to have either germline or somatic changes in 23%–27% of men with mCRPC. Although these replace linked to lower clinical outcomes16–18, they may make patients more susceptible to targeted treatments such PARP inhibitors. Cancer cells that have mutations Talazoparib inhibits PARP1 and PARP2, two DDR-related point proteins, and efficiently traps PARP on single-stranded DNA breaks, leading in an accumulation of double-stranded DNA breaks that cannot be repaired (Jurkovicova et al., 2022).

2.2 Therapies Targeted Prostate Cancer (Tumor) Neovascularization

Tumors require the neovascularization and the neovascularization furnish the nutrition for the body cells for their instant growth and the rapid discharge such as the excretory system is composed of the lungs, gills, skin, and kidney, as well as their ducts, which are the primary full-time eliminative organs. tumor targeted therapy since 1970 one of the most important fields in oncology research (Katayama et al., 2019). The foundation of vascular targeted treatment is the targeting of specific molecules expressed by malignant endothelial cells. These chemicals can be targeted to stop tumor development and angiogenesis. Anti-angiogenic medicines' primary targets are VEGF and ET (vascular endothelial growth factor and endothelin), and most of these treatments have already begun clinical studies. The most significant regulating cytokine for tumor angiogenesis is VEGF. Although it is widely expressed in almost all cancer cells, it is also produced by fibroblasts, endothelial cells, and immune cells in the tumour microenvironment. VEGFR-1 (Flt-1) and VEGFR-2 are two receptor tyrosine kinases (RTKs) with distinct signalling properties that are activated by non-signaling co-receptors and mediate VEGF's biological impact on endothelial cells VEGF-A, one of the VEGF isoforms, is overexpressed in prostate cancer and has been linked to angiogenesis and tumor growth in tumor cells, endothelial cells, and epithelium fibroblasts (Lugano et al., 2020). A worse prognosis has been linked to distant metastases and high levels of VEGF-A. Aflibercept and sunitinib, two other medicines that target the VEGF-A pathway, have failed to treat mCRPC in big clinical studies. Anti-angiogenic agents have also been linked to enhanced toxicity rates and side effects, including fatigue, asthenia, pulmonary embolus, high blood pressure, peripheral blood cytopenia, intestinal cleft, and bleeding, which have forced end of treatment even when they

have marginally collectively implied that anti-angiogenic therapy in mCRPC does not improve when combined with chemotherapy or hormone therapy. Because targeting a single pathway may be counteracted by activating alternate pathways, angiogenic pathway redundancy may be one of likely explanations of lack of a therapeutic response. As a result, focusing on these alternative pathways may result in an effective anti-angiogenic therapy. Anti-angiogenic therapy can be safely combined with other therapeutic modalities, according to a phase II study involving 63 patients with mCRPC who received bevacizumab in combination with the immunomodulatory drug lenalidomide (a 4-amino-glutamyl analogue of thalidomide with potent anti-angiogenic, anti-inflammatory, and antineoplastic properties), docetaxel, prednisone, and hormonal therapy. collectively imply that antiangiogenic therapy in mCRPC does not improve when combined with chemotherapy or hormone therapy. Because targeting a single pathway can be countered by activating alternate pathways, the recurrence of angiogenic pathways is one of the most likely reasons for the lack of a therapeutic response. It is therefore possible that focusing on these alternative pathways could result in an efficient antiangiogenic therapy ET is a protein made up of 21 amino acids, and its major job is to control heart rate. Advanced prostate cancer with bone metastases has been identified to express ET and its receptors. discovered that the combination of androgen deprivation and ET receptor antagonists can dramatically lessen bone metastases. It is therefore widely hoped that ET targeted therapy, which is now in test phase, would be developed for treatment of advanced prostate cancer (Ebos & Kerbel, 2011).

2.2.1 Bevacizumab

There are numerous treatment approaches being developed to stop tumor angiogenesis. Pro-angiogenic factors can be directly inhibited, and their receptors can be targeted. Vascular endothelial cells associated with tumors that are signal-blocking small-molecule tyrosine kinase inhibitor cascades, and direct destruction of vascular endothelial cells associated with tumors .A number of medications have finished or are still in Phase III. studies using aflibercept for recently developed prostate cancer Sunitinib, a VEGF trap, and cabozantinib (a VEGF receptor) Tyrosine kinase inhibitors, as well as the endogenous anti-angiogenic factor inducer tasquinimod. Anti-VEGF monoclonal antibodies, specifically, directly block VEGF Bevacizumab, which has undergone the most rigorous testing, is the topic of this review Avastin; Genentech/Roche Pharmaceuticals; bevacizumab USA) is a humanized murine monoclonal antibody (Teleanu et al., 2019). VEGF-specific antibody that blocks VEGF. It is a protein. roughly 93 percent human and 7 percent murine, which help create specialized, focused antibodies with minimum have a suitably extended half-life and immunogenicity. In vitro endothelial cell growth was decreased by the antibody in preclinical trials, and it prevented rhabdomyosarcoma tumor angiogenesis in human cell lines in vivo mouse xenografts. A dose-dependent reduction of tumor cell proliferation was shown in further experiments.in several different tumor forms. prostatic cancer (Shibuya, 2011).

2.2.2 Aflibercept

The choriocapillaris, a layer of capillaries in the eye, develops aberrant blood vessels in wet macular degeneration, which causes blood and protein leaking below the macula. Aflibercept (Zaltrap) functions as a "VEGF trap" by binding to circulating VEGFs[82]. This prevents the function of the placental growth factor (PGF), VEGF two types VEGF-A and VEGF-B, and prevents formation of current blood vessels in choriocapillaris or tumor, respectively. To starve the tumor, so to speak, is the goal of the cancer treatment (Xu et al., 2022).

2.2.3 Cediranib

The bone is the almost common site for secondary colonization, and distant metastatic lesions are primary reason of death in PCa cases. Expected to unacceptable toxicities, the use of little molecule reluctant to cure bone metastasis PCa has had only limited effectiveness, whether as polytherapy or in conjunction with another chemotherapy. In the current study, we generated a clinically relevant intraosseous tumour model that overexpresses platelet-derived growth factor D to assess the efficacy of the recently discovered VEGFR/PDGFR enzyme cediranib (also known as AZD2171). An intratibial-injection model was constructed using DU145 cells with or without enhanced platelet-derived growth factor D (PDGF D) expression. For seven weeks, mice with tumors were given daily doses of cediranib via gavage and/or weekly doses of docetaxel via intraperitoneal injection. Tibiae were studied using in vivo/ex vivo x-rays to measure cancer volume and tumor-associated trabecular bone growth (Macedo et al., 2017).

2.2.4 Sunitinib

The oral RTK inhibitor sunitinib is a mini, multitargeted small molecule drug. Sunitinib has been shown in numerous clinical trials to have impressive uninvolved response rates (ORRs) and after imatinib, there were therapeutic advantages when administered as first-line therapy for metastatic renal cell carcinoma (mRCC) and as second-line therapy for malignant gastrointestinal stromal tumour (GIST) (Papaetis & Syrigos, 2009). Sunitinib has also showed promise in improving progression-free survival in patients with incurable, locally advanced, or metastatic well-differentiated pancreatic neuroendocrine tumours (pNETs). Sunitinib has demonstrated potential anticancer efficacy in a variety of different cancers, including gliomas, sarcoma, scarcinomas of the thyroid, lung, pancreas, oesophagus, and bladder. We evaluate progress made thus far, including medicine development, pharmacology, and mechanisms of action, and resistance, as well as execution of crucial studies that resulted in the FDA's (US Food and medication Administration) clearance. We also provide an overview of recent preclinical and clinical research targeted at increasing the efficacy of sunitinib by combining it with radiation therapy, chemotherapy, and immunotherapeutic approaches (Delbaldo et al., 2012b).

2.3.4.1 Mechanism Action of Sunitinib

In biochemical and cell-based studies, sunitinib inhibits a wide range of RTKs and has powerful anti-angiogenesis and anticancer effects in animal research. Sunitinib inhibits myeloid-derived suppressor cells (MDSC), which are hypothesized to have a role in anticancer activity. The inhibitor constant [Ki], which indicates how potent an inhibitor is, was 0.009 M for the 80 kinases evaluated in the first characterization. The best activity was against VEGFR-1, -2, and -3, PDGFR-, PDGFR- (Ki=0.008 M), and fibroblast growth factor receptor 1 (Ki=0.83 M). Furthermore, the cKIT (KIT) proto-oncogene, the FLT3 tyrosine kinase, the RET proto-oncogene, the colony stimulating factor 1 receptor, and the RET proto-oncogene were all inhibited (Hao & Sadek, 2016). There were no discernible actions against the MET, IGFR, or the EGFR, in contrast. Sunitinib also inhibited the proliferation of human endothelial cells and mouse fibroblasts in designated cell lines in response to vascular permeability factor (VPF), Basic fibroblast growth factor (bFGF), and PDGF stimulation (Naumov et al., 2009).

2.3 Signaling Pathway of Prostate Cancer

Wnt signalling pathway is found in the primary molecular signalling pathways of prostate cancer, including the Androgen receptor mediated signalling pathway, the NF-kB signalling pathway, the RTK signalling pathway, and the JAK/STAT signalling pathway (Saraon et al., n.d.).

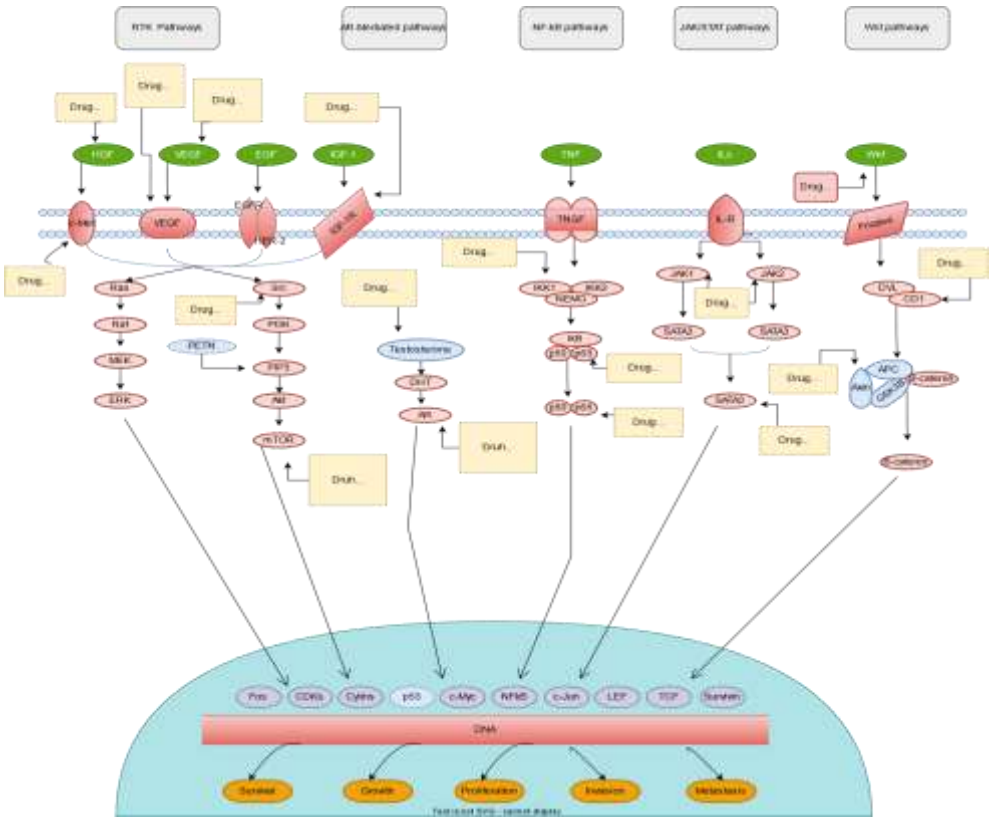


Figure 2. Prostate cancer signaling pathway

2.3.1 Androgen Receptor (AR) Mediated Signaling Pathway

Androgen receptor signaling is main role in simple functioning of prostate tumor and signaling cascades regulating the initiation of translation in prostate cancer and therapeutic agents. And the androgen receptor preservation of spermatogenesis androgen receptors (Culig & Santer, 2014). The steroid hormone receptor family is a subfamily of the ligand activated nuclear transcription factor family. And testosterone and dihydrotestosterone bind to Androgen receptor signaling and activate the Androgen receptor-signaling. When a ligand binds to Androgen receptor, it causes compliance replace in LBD that enable NTD also CTD to interact both intra- and intermolecularly. Leukemia reluctant factor receptor dimerization activity interfere by acetylation of extracellular lysine elevate prostate cancer progression through phosphorylation, and nuclear translocation, AR homo-dimerization, phosphorylation, and nuclear translocation are all mediated by the PDPK1/AKT/GCN5 axis. AR signalling is frequently disrupted during PCa and CRPC progression as a result of AR overexpression caused by amplification/mutations, co-activator and co-repressor modifications, aberrant activation/post-translational modification, altered steroidogenesis, and the production of AR splice variants. Alterations in steroidogenesis pathways caused by abnormal AR activation can also allow PCa cells to adopt the testosterone route. Adrenaline androgens produce functionally powerful DHT via the 5-dione route (Davey & Grossmann, n.d.). Some AR variations display solely cytoplasmic activity Furthermore, this is adequate for transcriptional effects to nucleus

localization. Additionally, ARVs can move freely via the Hsp90 chaperone complex and into the nucleus. Several transcription factors exist, including the protooncogenes c-Myc, c-Jun, Sp1, FOXO3a, lymphoid enhancer binding factor 1 (LEF1), NF-B, and twist-1., play significant gene regulation plays a role in increasing AR expression in addition to the mechanisms previously described that result in diversity in activity of AR (Calderwood & Neckers, 2016).

2.3.2 NF-kB Signaling Pathway

A protein mixture known as NF-B controls the impression of crucial genes needed in order to promote innate and adaptive immunity, cell inflammation and survival, the development of lymphoid organs. Five proteins make up the NF-B family in humans: NF-B1 (p100/p52), RelA (p65), RelB (p105/p50), and c-Rel. These proteins combine to generate transcriptionally active homo- or heterodimeric complexes. In the conventional mode of activation, the I-B kinase complex, this is made up of the catalytic subunits IKK and IKK, as well as the regulatory scaffolding protein NEMO, phosphorylates certain serine residues on the I-B inhibitory protein, causing its disintegration. When a free NF-B dimer reaches the nucleus and binds to B enhancer sites in DNA, it activates a slew of genes implicated in immune and inflammatory responses, cell proliferation, adhesion, metastasis, and apoptosis evasion (Claudio et al., n.d.). Due to elevated amounts of receptors like TNF that dramatically promote IB breakdown, NF-B is usually observed triggered in prostate tumour cells. The expression of interleukin 6 (IL-6) has increased. Signal transmission via NF-B inducing kinase (NIK) and IKK promotes constitutive NF-B activation, which raises NF-B expression at both the mRNA and protein levels in androgen-independent prostate tumours. A transcriptional regulator of PSA, a crucial marker for PCa development and progression, is another NF-B target. Furthermore, NF-B activation in PCa cells has been associated to cancer progression, chemoresistance, and PSA recurrence. Furthermore, data indicate that NF-B activation assists in the spread of prostate cancer to soft tissues or bones. Additionally, p65 of NF-B may boost the expression of endogenous AR and the downstream target genes linked to it, encouraging human PCa cell proliferation and survival (Da Silva et al., 2013).

2.3.3 RTK-Signaling Pathway

The two principal branches of the RTK signalling pathway are the PI3K/AKT and Ras/MAPK pathways. Important intracellular signalling route known as the PI3K/AKT pathway, which connects various classes of membrane receptors, is structurally important for cellular dormancy, cell growing, expansion, differentiation, mobility, survivance, and angiogenesis. PI3K triggers conscription and stimulation of the serine/threonine-specific protein kinase AKT after stimulation by tyrosine kinase growth factor receptors, culminating in membrane translocation and phosphorylation of AKT. When AKT is activated, it phosphorylates and galvanises multiple other proteins, including mTOR, therefore beginning and controlling a wide range of cellular processes. loss of the tumor suppressor PTEN frequently leads to an increase in the PI3K/AKT pathway. Erks' function is disrupted in PCa cells through an abnormal PI3K/AKT pathway, which promotes proliferation that is AR-independent. In line with this, AR target genes may block the PI3K/AKT signalling pathway to promote AR-reliant PCa cell proliferation, invasion, and metastases (Xie et al., 2018). The three distinct categories that make up ERKs, JNKs, and p38 isoforms are examples of mitogen-activated protein kinases (MAPKs). The mechanism that regulates essential cellular activities like growth, proliferation, differentiation, migration, death, and transformation is connected to external signals by MAPK signaling. In PCa, excessive EGF, FGF, IGF, and KGF production typically activates the endogenous Ras and MAPK pathways. Additionally, aquaporins, pore-forming proteins whose expression is increased by p38 signaling, which is mostly triggered at later stages of PCa, allow PCa cells to survive under hypoxia (Tikkanen & Nikolic-Paterson, 2019).

2.3.4 JAK/STAT Signaling Pathways

The JAK/STAT pathway is a critical and pleiotropic membrane-to-nucleus cascade that transmits numerous signals for healthy evaluation, cellular homeostasis, cell proliferation, differentiation, migration, and apoptosis in response to stimuli such as reactive oxygen species, cytokines, and growth factors (Hu et al., 2021). In a nutshell, the JAK/STAT pathway is activated when ligand interaction causes the receptor subunits to multimerize. This phosphorylates the JAK tyrosine kinases (JAK1, JAK2, JAK3, and Tyk2), which are receptor-associated tyrosine kinases, which propagates the signal. activated JAKs cause the phosphorylation of additional targets, including STAT proteins and receptors. In turn, phosphorylation causes STAT dimerization through the conserved SH2 domain, which then permits their nuclear import through The Ran nuclear import pathway and importin-5. Target genes can be stimulated or suppressed in their transcription by STATs, which attach to particular nucleoplasmic DNA sequences. In PCa cells, the DNA repair gene BRAC1 interacts concomitant phosphorylation of JAK1/2 and STAT3 to promote cell growth and prevent apoptotic cell death. Additionally, STAT3 activation in PCa cells promotes several other genes linked to tumor invasion, angiogenesis, anti-apoptosis, and cell cycle progression. STAT5a/b dimerization and subsequent nuclear translocation, in which the dimers link to specific response areas of target genes, all contribute in the growth, progression, and distant metastasis of prostate cancer (Seif et al., 2017). JAK-STAT pathway constituents, in particular pJAK-1 and pSTAT-3 are markers of poor prognosis in PCa. and biochemical relapse (Ramalingam et al., 2017).

2.3.5 Wnt Signaling Pathway

A critical part of tissue homeostasis, cell expansion, distinctness, moving, The Wnt/-catenin signalling pathway, which is made up of secreted glycoproteins, is involved in epithelial-mesenchymal communication, polarity, and asymmetric cell division. Wnt signaling is -catenin is mostly found in cytosol association APC, Axin, and CK1, and GSK-3, It is based on the multifunctional protein's capacity to be stabilised. Free -catenin accumulates in the perinuclear region and eventually interacts with lymphoid enhancer factor/T cell factor (LEF/TCF) in DNA to trigger transcription of numerous

target genes such as c-Myc, p300, Foxo, Bcl9-2, c-Jun, CtBP, and cyclin D1. Development, expansion, and metastasis of prostate cancer cells are all correlated with increased expression of -catenin, which is extremely frequent in PCa (MacDonald et al., 2009).

2.4 Immune Check-Point Inhibitors

Malignant tumours in males are a leading cause of death, accounting for 385,560 deaths in 2020. Several medications are utilised to treat metastatic castration prostate cancer, including anti-androgen drugs such as abiraterone acetate and enzalutamide, as well as radionuclide-emitting particles (radium-223). Tumour development and progression are caused by cancer-induced immunosuppression in the patient's immune system, which destroys neoplastic cell clones because cancer cells are capable of anti-tumor immune response (cancer-immunoediting) immune check-point pathway such as CTLA-4 and PD-1 immunomodulatory receptors and their associated ligands, B7-1/B7-2 and PD-1 (He et al., 2020).

2.4.1. Ipilimumab (CTLA-4) Is A Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitor

Activated T CD4+ and CD8+ lymphocytes express co-inhibitory receptor CTLA-4 is a protein that prevents T-cell activation by attaching to it. Ipilimumab is a monoclonal completely Anti-human immunoglobulin G1 (IgG1) antibody CTLA-4 function to improve immune response by activating T cells (Quirk et al., 2015). It is permissible for the treatment. It is now being studied in a variety of cancer types, including mCRPC and advanced melanoma. Ipilimumab has been studied in people with mCRPC at various doses, times, and combinations. Radiotherapy may result in immune-mediated tumor killing, according to preclinical and clinical research. This might cause tumor regression in places other than the original the abscopal effect), a location of radiation in an immune-mediated method. It's noteworthy that ipilimumab and standard anticancer treatments work together to attack tumours, providing support to the idea that tumour antigens produced during radiation-induced cell death could boost ipilimumab's anticancer efficacy. As a result of this, data, mCRPC patients who received external-beam irradiation A non-randomized phase I/II trial of the medication ipilimumab (CA184-107) was conducted. No more than one prior treatment, which resulted in a 15% reduction in prostate-specific antigen (PSA). 43 Comparable outcomes from a small, randomized phase II study comparing ipilimumab to androgen deprivation therapy (ADT) alone in people with advanced PC (undetectable PSA levels rate at 3 months of 55% versus 38%, respectively)44 motivate additional research in this situation. Combining ipilimumab with granulocyte-macrophage colony-stimulating factor (GM-CSF) or PD-L1 improves biochemical tumour response. rate by 25–50%. without getting worse, vaccinations adverse effects brought on by ipilimumab (Slovin et al., 2013).

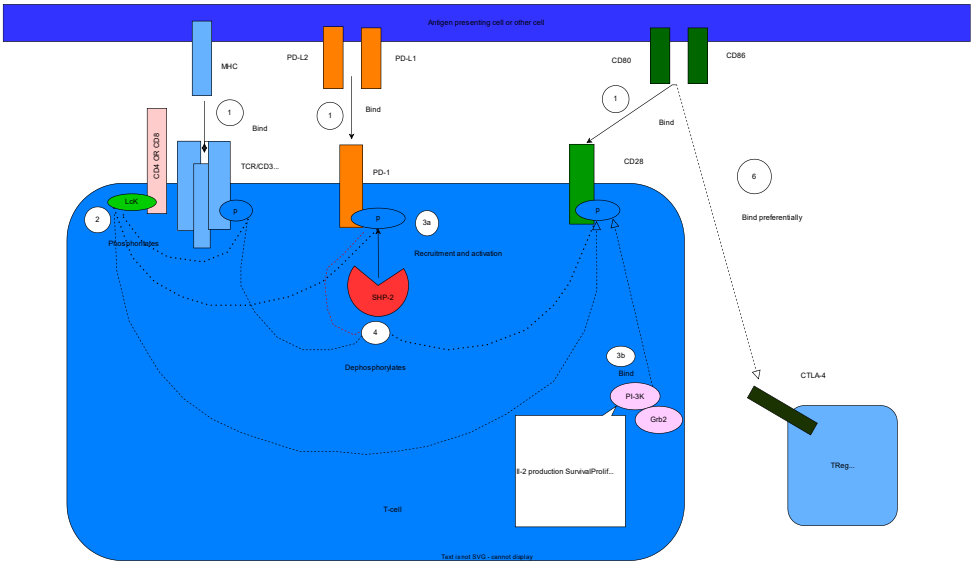


Figure 3. Immune Check Point Inhibitors

Tremelimumab

Tremelimumab, a completely human IgG2 monoclonal antibody specific for CTLA-4, is also being examined in PC, neoadjuvant therapy, and recurring disease. Tremelimumab in combination with short-term ADT produced dose-limiting toxicities such as grade G3 diarrhoea and skin rash in 3 of 11 patients many months after the completion of treatment in a phase I trial of dose-escalation in PSA-recurrent PC (Ribas, 2010).

2.4.2 Death-1/Programmed Pathway of Programmed Death Ligand 1

Control of T-cell activity during inflammatory processes is greatly influenced by PD-1/PD-L1 pathway. T-cells, B lymphocytes, NK cells, and monocytes that have been activated express the transmembrane glycoprotein T-cell co-inhibitory receptor known as PD-1 within 24 hours. from cytokine-induced immune system activation, including IL-2 Limiting the production of Immunosuppression immunological mediators (IL-7, IL-15, and IL-21) system cell

lysis. 54 Unlike CTLA-4, which blocks T-cell activation during the priming stage of T-cell activation. The PD-1/PD-L1 axis is a pathway that permits tumours to avoid detection by the immune system of the host and contributes significantly to growth and progression of cancers (Ghosh et al., 2021). Overexpressed Cancer cells contain PD-L1. The tumor microenvironment's stromal cells and TILs, supporting immune evasion by a tumor.57 Addiction often expresses PD-1 at increased tumor-infiltrating Treg levels that promote their proliferation after ligand binding and promoting tumour development by lowering the system of defense Inhibiting the PD-1/PD-L1 pathway (by mAbs against PD-1 or PD-L1) may thus boost the immune response by increasing the activity of effector T-cells against cancer cells and tumour against tumors. Microenvironment and reducing intratumoral Treg's suppressive activity.10,58 The excellent outcomes obtained in the clinical context have validated the viability of this biological explanation. utilising monoclonal antibodies that inhibit the interaction of PD-1/PD-L1 (for example, Nivolumab, Pembrolizumab, and Atezolizumab). Significant survival extension, exceptional long-term effects, and critical Clinical outcomes with PD-1/PD-L1 treatments have improved. a number of solid tumours, including renal-cell carcinoma, melanoma, and non-small-cell lung cancer. The one factor thought to be most strongly anti-PD-1 pathway and tumour PD-L1 expression are linked to aggressive tumour behavior and response to anti-PD1 suppression., which is commonly coupled with lymphocytes PD-1 expression (Yi et al., 2021). In a cohort of various cancers, immunohistochemistry The presence of PD-L1 and the likelihood of responding to PD-1 inhibition. However, the limited subset of CRPC samples with negative PD-L1 staining (only 2 patients) included in this investigation prevented drawing firm conclusions. Rare primary prostate carcinoma PD-L1 expression has lately been reported. Curiously, PC PD-L1 expression appears may not depend on PTEN loss, despite the fact that some researches have demonstrated that PTEN deficiency may result in PD-L1 upregulation as an innate immune response), taking on an adaptive role. immune suppression of anticancer immune responses. High levels PD-1 expression has been observed in CD8+ T cells that have infiltrated the prostate but are unable to establish a functional immunological response (Han et al., n.d.).72 Additionally, Gevensleben as well as for the first time, researchers examined the expression of PD-L1 in tissues from individuals undergoing primary radical prostatectomy (n = 8 samples) who have never received hormone therapy utilizing a recently validated mAb using a semi-quantitative grading system in comparison to PD-L1 (clone EPR1161(2) staining intensity rating system. This analysis revealed a raised PD-L1 level. expression (52.2 and 61.7% in the two cohorts studied, respectively) There is a link between PD-L1 expression and Ki-67 expression. in PC samples expression of the androgen receptor, a proliferation marker, and considerably shorter (tumor-independent) biochemical-recurrence-free survival surgical margins, Gleason score, stage, and PSA levels). the underprivileged predictive role of PD-L1 expression supports PD-L1's ability to promote (Calagua et al., 2017).

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