

Clinical Implications in Understanding Prostate Cancer Biology: From Androgen Receptor to Molecular Target Therapy in Metastatic Castration Resistant Prostate Cancer

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Abstract

Prostate cancer is one of the most common malignancies in the world. For a long time, the cornerstone of treatment for advanced disease has been the manipulation of hormonal pathway of testosterone since is well established that androgen receptor regulates prostate growth, differentiation and apoptosis in regular and cancer cells. However, during the treatment of metastatic disease with androgen deprivation therapy resistance mechanisms appear, which led to the development of new treatments, such as second-generation anti-androgens-like (such as enzalutamide, apalutamide and darolutamide), and abiraterone acetate. In addition to the development of this new antiandrogens the deeper knowledge about DNA damage repair and their pathways such as direct reversal, mismatch repair, base excision repair, homologous recombination and the non-homologous end joining, resulted in new opportunities of treatment. Recently, PARP inhibitors have showed their efficacy in the treatment of advanced prostate cancer. Therefore, the aim of this article is to review the current knowledge about cancer prostate biology and its clinical implications.

Keywords: Prostate Cancer; Biology; Androgen-receptor; Molecular Therapy; DNA Damage Repair; PARP Inhibitor

Abbreviations

PCa: Prostate Cancer; DHT: Dihydrotestosterone; ADT: Androgen Deprivation Therapy; AR: Androgen Receptor; T: Testosterone; GnRH: Gonadotropin-releasing Hormone; GnRH-R: Gonadotropin-releasing Hormone Receptor; LH: Lutinizing Hormone; FSH: Follicle Stimulating Hormone; DHEA: Dehydroepiandrosterone; 3 β -HSD: 3 β -Hydroxysteroid Dehydrogenase; CRPC: Castration Resistant PC; PARP: (polyADP-ribose) Polymerase; DDR: DNA Damage Repair; DSB: Double Strand Breaks; HRD: HR Deficiency; LOH: Loss of Heterozygosity; DDRe: DNA Damage Response; mCRPC: Metastatic Castration-resistant PC; PTEN: Phosphatase and Tensin Homolog; RAC-alpha serine/threonine-protein Kinase AKT; mTOR: Mammalian Target of Rapamycin; PARP: Inhibitor iPARP

Introduction

Prostate cancer is one of the 5 most common malignancy and according to GLOBOCAN is expected that 1,414,259 new cases of

prostate cancer will occur in the world in 2020, corresponding to 7.3% of all neoplasms diagnoses and 375,304 deaths [1]. It is known that most patients present at diagnosis as localized or regional disease (89%) and in general the 5-year survival rate is 97.8%. However, when disease is metastatic, the 5-year survival rate is only 30% [2]. The most important risk factor for the development of prostate cancer is aging. Epidemiologic studies have shown that the risk of prostate cancer is higher in African American compared with other ethnic groups and that it occurs at an earlier age [3]. Genetic factors, especially germline mutations in DNA repair genes appear to play a role in the development of certain prostate cancer and maybe associated with more aggressive disease [4]. Other factors, such as diet, hormone levels and obesity have been studied, but their role appears limited [3].

For a long time, the main systemic treatment for advanced disease has been the manipulation of hormonal pathway of testoster-

one. Since seminal Huggins's study, understanding the testosterone pathway as primarily responsible for the progression of prostate cancer has led researching and treatment of prostate cancer [5]. Only in 2004 with the publication of the TAX 327 trial, cytotoxic chemotherapy became an option in the therapeutic arsenal. In this trial of patients with castration-resistant metastatic prostate cancer, the use of docetaxel resulted in 24% reduction in the risk of death, but eventually chemotherapy fails, and therapeutic options are needed [6].

Fortunately, in the last decade the better understanding of the testosterone pathway and its relationship with the androgen receptor as well the steroidogenesis in the adrenal gland has promoted the development of new therapies, the so-called novel antiandrogen therapy, like abiraterone, enzalutamide, apalutamide and darolutamide [7-10]. In addition to that, the knowledge that molecular routes like DNA repair pathway are also responsible for tumor growth has led to the emergence of new horizon of therapeutic options [4]. Deficiency in the DNA repair pathway is one of the hallmarks in the development of cancer as it causes genomic instability, and the development of molecular target therapies is currently a revolution in the treatment of prostate cancer. The purpose of this article is to review the biology of prostate cancer and its relationship with hormonal and molecular pathways.

Biology of prostate cancer Androgenic pathway

Prostate cancer (PCa) has been recognized as a hormone-dependent affection since early 1940s. Experimental demonstrations observed tumor regression after reducing serum androgen concentrations by orchiectomy or exogenous estrogen administration, and tumor activation by androgen injections [4]. Hormone modulation of PCa growth provides the basis for androgen deprivation therapy (ADT), which is the core treatment of advanced PCa [11]. Its primary objective is to reduce circulating levels of androgens. The two principal androgens in men are testosterone, produced by testicular Leydig cells, and dihydrotestosterone (DHT), produced from testosterone in peripheral tissues by 5- α reductase [12].

The prostate contains high affinity androgen receptor (AR) cells that regulate prostate growth, differentiation and apoptosis in regular and cancer cells by promoting and inhibiting secretion of various growth factors from stromal cells that act on the epithelial ones [13]. Androgens, such as testosterone (T) and dihydrotestosterone (DHT), are the most important agonists for AR. DHT has a 10-fold higher affinity for the androgen receptor and thus it is the primary ligand for the AR in the prostate [14]. When androgens bind to the

AR, it induces conformational change and subsequent translocation of the AR into the nucleus. Nuclear AR binds to androgen responsive elements in the DNA, resulting in transcriptional activity that can induce cellular proliferation and cellular differentiation [15].

Gonadal steroid hormone production is stimulated by the hypothalamic-pituitary-axis through synthesis and release of Gonadotropin-releasing hormone (GnRH), also referred to as LHRH. This peptide is produced by a small number of hypothalamic neurons, which are released in a pulsatile way into the hypophyseal circulation to reach the gonadotrophs in the anterior pituitary where it binds to its specific receptors (GnRH-R). By binding to these receptors, GnRH triggers the synthesis and release of the two gonadotropins LH (luteinizing hormone) and FSH (follicle stimulating hormone), which are responsible for inducing the production of testosterone in the testes [16] as seen in figure 1.

Another pathway to steroid biosynthesis happens through a complex mechanism that takes place in the cortex of the adrenal gland and in the genital tissue [17]. The process starts with the conversion of cholesterol to pregnenolone. This conversion is done by the mitochondrial cholesterol side-chain cleavage enzyme (cytochrome P450_{scc}) encoded by the cholesterol side-chain cleavage gene (CYP11A1) [18]. Then, pregnenolone is converted to progesterone by 3 β -hydroxysteroid dehydrogenase (3 β -HSD). These two metabolites are the precursors for others steroid hormones [19,20]. Pregnenolone and progesterone are hydroxylated by CYP17 (an enzyme with both 17 α -hydroxylase and 17,20-lyase activities) to form 17 α -hydroxysteroids [18]. From there on, the 17,20-lyase activity converts the two 17 α -hydroxylated steroids to dehydroepiandrosterone (DHEA) and androstenedione.

Finally, in the zona reticularis of the adrenal gland, 17 β HSD5 (encoded by AKR1C3) converts small amounts of androstenedione to testosterone, whereas in the testis this reaction is catalyzed by 17 β HSD [18] as seen in figure 1.

Chronic administration of LHRH agonists results in suppression of the hypothalamic-pituitary-gonadal axis by downregulation of the pituitary receptors for LHRH, leading to suppression of follicle-stimulating hormone (FSH) and LH. This reduces the production of testosterone in the testes resulting in castrate levels of testosterone [21,22]. Many synthetic LHRH agonists (such as goserelin, leuprolide, buserelin and triptorelin) are now used as first-line hormonal treatment in patients with advanced-stage prostate cancer. However, the use of LHRH agonists is associated to a 'testosterone flare'

phenomenon, an initial increase in testosterone production; this event can trigger exacerbation of pain, worsen obstructive urinary symptoms and in rare cases it can lead to ureteral obstruction or spinal cord compression. This 'testosterone flare' can be overcome by association with AR blocker-like [23], and it has also led to the development of LHRH antagonists that directly bind to the LHRH receptors without causing the initial testosterone surge. Currently, degarelix is an LHRH antagonist that is well established for clinical use [24]. In December 2020, the Food and Drug Administration approved the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist, relugolix. Based on HERO (NCT03085095), a phase 3 open label trial which showed that 96.7% men achieved sustained testosterone suppression to castrate levels through 48 weeks of treatment [25]. Relugolix is a new treatment perspective because it leads to a rapid testosterone suppression without an initial testosterone surge and its facility in administration.

Additionally, antiandrogens therapy is also used in metastatic or recurrent PCa. Antiandrogen molecules prevent binding of androgen to the AR in the cytoplasm. This inhibits the AR signaling pathway and thus prevents translocation of the AR into the nucleus and binding to DNA, decreasing cell proliferation and inducing cell death [26]. First generation antiandrogens (like flutamide, bicalutamide and nilutamide) can be used in association with LHRH agonist and antagonist in order to achieve "complete androgen blockade" [27].

In some cases, PCa cells develop alternative mechanisms of AR signaling, AR amplification, alternative splicing, intratumoral androgen production, or adrenal gland testosterone production. In these cases, the treatments aforementioned lose their efficacy and the disease is termed castration resistant PC (CRPC) [28]. Also, an adaptive response to androgen deprivation has been observed in CRPC where there were intratumoral testosterone production and 5 α -DHT biosynthesis, which lead to the understanding that ADT alone is insufficient to reduce androgens precursors [7]. The need to overcome these resistance mechanism has led to the development of new treatments, such as second-generation anti-androgens-like (such as enzalutamide, apalutamide and darolutamide), and abiraterone acetate, which is a CYP17A1 inhibitor that targets both 17 α -hydroxylase and 17,20-lyase activities and inhibits residual androgen biosynthesis [7]. These medications are currently largely used in the CRPC scenario in clinical practice.

Treatment response is often short-lived in metastatic CRPC because patients develop tumor resistance, and so novel improved therapeutic options are needed [29]. Studies have been exploring

immunotherapy and inhibition of poly(ADP-ribose) polymerase (PARP) in tumors with DNA repair defects inducing synthetic lethality [30]; more randomized trials are required to test the interplay between androgen receptor signaling and PARP functions [31].

DNA damage repair pathways

The field of PCa has benefited from the emergence of multiple new therapies over the past few years and the best understanding about DNA damage repair (DDR) provided the use of some drugs in PCa [4].

The genome is constantly under the action of external and internal agents that cause DNA damage. Mutagenesis has an important role in the maintenance of the genome and evolution of the species, but it can contribute to the appearance of cancer. So, deleterious mutations due to DNA lesions must be repaired. Cells respond to DNA damage by instigating robust DNA damage response pathways. These pathways include the direct reversal pathway, the mismatch repair (MMR) pathway, the nucleotide excision repair (NER) pathway, the base excision repair (BER) pathway, the homologous recombination (HR) pathway, and the non-homologous end joining (NHEJ) pathway. This way, mechanisms that can be deregulated such as repair DNA, DNA damage tolerance and DDR pathways, which increases mutagenesis and genomic instability, can lead to cancer progression [32-34].

Researchers realized that a variety of currently known proteins have critical functions in maintaining DNA integrity, particularly regarding the recognition and repair of DNA damage through multiple pathways. Then, they have an important role in maintaining the genomic integrity of the cell and ensures its ability to persist and proliferate [35,36]. DDR deficiency plays an important role in genome instability and mutations in tumors and has been recognized as one of the hallmarks of cancer, and provides a logical framework for understanding the diversity of neoplastic diseases [37,38]. Mutations that modify the function of genes involved in repairing DNA damage through homologous recombination have been shown to be associated with the aggressive clinical behavior of PCa and with cancer-specific mortality. In addition, they contribute to destabilizing PC cells, often making them more susceptible to cell death [36,39].

Homologous recombination (HR) has a fundamental role in carcinogenesis. HR pathway is essential for high-fidelity DNA double strand break repair. When defective HR occurs, it results in chromatid exchanges leading to genomic instability. Cells deficient in

HR are known to be sensitive to ionizing radiation and chemotherapeutic drugs. That affects both strands of DNA and acts in the S/G2-phases of the cell cycle where HR is the preferential pathway of double strand breaks (DSB) repair. HR pathway involves several genes, including BRCA1 and BRCA2. HR deficiency (HRD) due to inactivation of such genes leads to increased levels of genomic alterations. HRD causes loss of heterozygosity (LOH), telomeric allelic imbalance and large-scale state transitions. LOH results from one allele being lost from a cell that is then either homozygous or hemizygous for the remaining allele. In addition to that, the extent of genome wide LOH provides a single global assessment of HRD irrespective of causative lesion, and the potential for using it as a therapeutic target [40-42].

When compared to the general population, the risk of PC is estimated to be 1.8-3,75 fold higher for people with germline BRCA1 and 2,5-8,6 fold with germline BRCA2. Moreover, the data about the frequency of germline mutation of DDR in men (12%) is higher than that in the general population. Thus, DDR deficiency becomes a potential PCa driver [43]. When evaluating men with BRCA2 mutations, it was found that they can cause a higher risk of developing life-threatening prostate cancer, and these mutations may be associated with worse treatment outcomes within the setting of castration-resistant disease. It is known that BRCA2 mutations are involved in the repair of-DSB through homologous recombination and are also important in several other processes central to maintaining genome stability, including DNA replication, telomere homeostasis and cell cycle progression [39,44]. Dall Era, *et al.* evaluated 152 patients harvested from metastatic and localized tumors that presented with germline or somatic mutation in ≥ 1 DNA repair genes. The most prevalent mutations were BRCA2 (11.4%) and ATM (5.8%) and highest rates of DNA repair mutation were found in solid organ metastases including brain (36%), liver (34%), and lung (32%) [39]. The role of DNA gene mutations in localized PCa was analyzed by Marshall, *et al.* In this trial, patients with Gleason grade group 3 and higher were 2.2 times more likely to harbor any DNA repair mutation and 2,7 times more likely to have BRCA1/2 or ATM mutations compared to those in Gleason grade groups 1-2. Moreover, the data about patients with pathologic T3 e T4 were 2,6 times more likely to have any DNA repair mutations and were 3,2 times more likely to have BRCA1/2 or ATM mutations compared to those with pT2 disease [45]. The analyses about prevalence of DNA damage response (DDRe) gene mutation in PCa was carried out by Lang, *et al.* Median prevalence rates for DDRe germline mutation were; 18.6% in PCa, 11.6% in metastatic PCa and 8.3% in metastatic castration-resistant PC (mCRPC). Median prevalence rates for

DDRe somatic mutation were 10.7% in PCa, 13.2% in metastatic PCa and not reported in metastatic mCRPC [35].

Among the most commonly altered signaling pathways in prostate cancer we have the phosphatase and tensin homolog (PTEN) tumor suppressor on chromosome 10 and the phosphoinositide 3-kinase (PI3K), about 40% of cases of PCa localized and 70% of cases of advanced disease have alterations in this pathway [45]. Normally, PTEN acts as lipid phosphatase converting phosphatidylinositol 3,4,5-trisphosphate into phosphatidylinositol 4,5-bisphosphate. This lipid phosphatase activity of PTEN suppresses the activation of the downstream oncogenic RAC-alpha serine/threonine-protein kinase (AKT) and mechanistic mammalian target of rapamycin (mTOR) signalling cascades, which have a fundamental role in controlling apoptosis, cell cycle progression, cellular proliferation, metabolism, differentiation and invasion. PTEN also has several other noncanonical functions as regulating cell adhesion and promoting chromosome stability and DNA repair through PI3K-independent function in the nucleus [47]. AR and PTEN/PI3K/AKT pathways cross-regulate each other by reciprocal feedback. Models of human and murine tumors show that inhibition of the PI3K pathway in *PTEN*-negative prostate cancer results in feedback signaling to the receptor tyrosine kinase HER2/HER3 leading to activation of AR. Conversely, blockade of AR results in activation of AKT through reduced levels of FKBP5 (FK506-binding protein 51) [48] impairing the stability of phosphatase PHLPP (pH domain leucine-rich repeat protein phosphatase) [49]. This bidirectional crosstalk between two critical survival pathways in prostate cancer provides the molecular rationale for simultaneously targeting both pathways [46].

Clinical implications and perspectives

Defects in DNA repair are present in a significant proportion of patients with prostate cancer. These alterations are associated with developing PCa and with developing more aggressive forms of the disease mutations affecting DDR pathway genes. Then, the knowledge about this topic can change the treatment selection resulting in a potential prognostic impact [50].

TOPARP-A was a phase II trial where 50 patients with mCRPC were treated with Olaparib, a PARP inhibitor, 400 mg twice daily until disease progression. The primary endpoint was the composite response rate defined either as an objective response according to Response Evaluation Criteria in Solid Tumors criteria, or a $\geq 50\%$ reduction in prostate-specific antigen (PSA), or a reduction in the circulating tumor-cell count from ≥ 5 per 7.5 ml of blood to

< 5 per 7.5 ml. All patients had prior treatment with docetaxel and 49 (98%) with abiraterone or enzalutamide. Sixteen of 49 (33%) evaluable patients had a response. Remarkably, however, 14 of the 16 responders had homozygous deletions, deleterious mutations, or both in DNA-repair genes — including *BRCA1/2*, *ATM*, Fanconi's anemia genes, and *CHEK2* [51].

TOPARP-B, an open-label, phase II trial in which men with HRR-mutated mCRPC that had progressed on at least one taxane therapy were treated with olaparib 400 mg or 300 mg twice daily in a randomized fashion. The primary endpoint was identical to the TOPAPRP-A trial. A targetable HRR gene aberration was found in 161 of 592 (27.2%) patients who underwent a targeted next-generation tumor sequencing. However, sequencing could not be performed on 119 (17%) of consented patients because of insufficient or poor-quality tissue. The confirmed composite response rate was 54.3% (95% confidence interval [CI] 39.0-69.1) in the 400 mg cohort and 39.1% (95% CI 25.1-54.6) in the 300 mg cohort ($p=0.14$). Median radiographic progression-free survival (rPFS) was 5.5 months (95% CI 4.4-8.3) in the 400 mg cohort and 5.6 months (3.7-7.7) in the 300 mg cohort. The predefined criteria for success were met for the 400 mg regimen but not for the 300 mg regimen [52].

The PRO found trial was an open-label, phase III randomized (2:1) controlled trial of olaparib versus physician's choice of enzalutamide or abiraterone in men with metastatic castration resistant prostate cancer (mCRPC) with alterations in at least one of 15 homologous recombination repair genes who had disease progression on next-generation hormonal agent. Patients were randomized to olaparib (300 mg BID; $n=256$) or physician's choice of enzalutamide or abiraterone (control; $n = 131$). Cohort A included 245 patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM*, and cohort B included 142 patients with at least one alteration in any of the other 12 prespecified genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*). Crossover to olaparib was allowed after imaging-based disease progression. The trial met its primary endpoint of an improvement in radiographic progression-free survival with olaparib in mCRPC with alterations in *BRCA1*, *BRCA2*, or *ATM* (Cohort A). Key secondary endpoints, including improved overall survival in Cohort A, were also met - 19.1 months with olaparib versus 14.7 months with control therapy (HR for death, 0.69; 95% confidence interval [CI], 0.50 to 0.97; $P = 0.02$). In cohort B, the median duration of overall survival was 14.1 months with olaparib and 11.5 months with control therapy (HR for death, 0.96; 95% CI, 0.63 to 1.49). In the overall population (cohorts A and B), the corresponding durations were 17.3 months and 14.0 months (HR for death,

0.79; 95% CI, 0.61 to 1.03). Overall, 86 of 131 patients (66%) in the control group crossed over to receive olaparib (56 of 83 patients [67%] in cohort A). A sensitivity analysis that adjusted for crossover to olaparib showed hazard ratios for death of 0.42 (95% CI, 0.19 to 0.91) in cohort A, 0.83 (95% CI, 0.11 to 5.98) in cohort B, and 0.55 (95% CI, 0.29 to 1.06) in the overall population. The most common adverse events among the patients in the olaparib group and those who crossed over to receive olaparib were anemia, nausea, and fatigue or asthenia. These results led to the approval of olaparib treatment in patients with mCRPC who had progressed on prior enzalutamide or abiraterone with homologous recombination repair alterations. Patients who had tumors with a *BRCA1* or *BRCA2* alteration, appeared to derive the greatest benefit from olaparib with respect to overall survival. Assessment of olaparib in patients in Cohort B with rare homologous recombination repair gene alterations provides evidence of activity, which warrants further assessment. However, *PPP2R2A* does not show benefit (HR for death 5.11, 95% CI, 1.10-35.73) and preclinical studies do not support PARP inhibitor sensitivity [53].

Another PARP inhibitor that has been developed and FDA-approved for HRR-mutated (germline and/or somatic) mCRPC was rucaparib. TRITON2 [54] was a multicenter, single-arm, clinical trial of rucaparib in previously treated men with taxane-based chemotherapy and at least one novel antihormonal agent. The TRITON2 study showed an objective response rate for patients with a *BRCA1/2* alterations of 43.5% (27/62 patients) when assessed by independent radiology review and 50.8% (33 of 65 patients) when assessed by the investigators, and a similar proportion achieved PSA responses as well. When HRD alterations in non*BRCA1/2* genes were analyzed [55] (*ATM*, *CDK12*, *CHEK2* and other), minimal response was observed. Important toxicities that were reported include nausea, anemia, elevation in AST/ALT and gastrointestinal and hematological side effects. A confirmatory trial TRITON3 is currently ongoing. The design of this trial is like the PROfound trial, with 400 men with *BRCA1/2* or *ATM*-mutated mCRPC randomized to rucaparib or standard of care therapy in 2:1 fashion. The primary endpoint is rPFS and the results are expected by 2022.

Other two iPARP drugs are being tested for HRR-aberrant mCRPC: niraparib and talazoparib. GALAHAD [56] and TALAPRO-1 [57] are ongoing phase II trials of niraparib and talazoparib (respectively) in men with HRR-aberrant mCRPC that has progressed after at least one novel antihormonal agent and taxane-based chemotherapy. There are also phase III trials with those drugs. MAGNITUDE is a study with niraparib in combination with abiraterone for the treatment of men with mCRPC who will be evaluated for

HRR status and then will be assigned to one of the 2 cohorts based on their biomarker status [58]. TALAPRO2 is a randomized, phase III trial, double-blind, comparing talazoparib plus enzalutamide vs.

placebo plus enzalutamide in patients with mCRPC [59]. Both studies are currently ongoing, table 1 shows currently trials with iPARP in mCRPC.

Study	Status	Clinical Trials Identifier
CASPAR - A Phase III Trial of Enzalutamide and Rucaparib as a Novel Therapy in First-Line Metastatic Castration-Resistant Prostate Cancer	Suspended	NCT04455750
A Phase 3, Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants With Metastatic Castration-resistant Prostate Cancer (mCRPC) Who Are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment With One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)	Recruiting	NCT03834519
TRITON3: A Multicenter, Randomized, Open Label Phase 3 Study of Rucaparib versus Physician’s Choice of Therapy for patients With Metastatic Castration Resistant Prostate Cancer Associated With Homologous Recombination Deficiency	Recruiting	NCT02975934
A Randomised, Double-blind, Placebo-controlled, Multicentre, Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer (PROpel Study)	Active, not recruiting	NCT03732820
A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment With a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound)	Active, not recruiting	NCT02987543
A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Talazoparib With Enzalutamide in Metastatic Castration-resistant Prostate Cancer (TALAPRO2)	Recruiting	NCT03395197
A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Metastatic Prostate Cancer (MAGNITUDE)	Recruiting	NCT03748641

Table 1: Current phase 3 clinical trials ongoing in metastatica CRPC [64].

In abiraterone-treated patients with mCRPC, tumors with PTEN loss by IHC were associated with worse outcomes [60]. Therefore, combined inhibition of the AR and PI3K-Akt-mTOR pathways may result in improved benefit for patients with mCRPC. Ipatasertib (GDC-0068) is a potent, novel, selective ATP-competitive small-molecule inhibitor of all three isoforms of Akt [60]. In IPATential150 trial patients with mCRPC were randomized 1:1 to receive ipatasertib (400 mg/d) + abiraterone (1000 mg/d) + prednisone (5 mg bid) or placebo + abiraterone + prednisone. Coprimary endpoints were investigator-assessed radiographic rPFS by PCWG3 criteria in patients with PTEN loss tumors by immunohistochemistry and in the overall ITT. The results, presented at ESMO 2020 [62] and updated at ASCO GU 2021 [63], demonstrated an rPFS benefit for the combination of ipatasertib with abiraterone in patients with mCRPC. This benefit was seen in the ITT population as well as when patients were stratified by PTEN expression (defined by immuno-

histochemistry). In ITT population, rPFS was 19.2 months with ipatasertib and 16.6 months with placebo (HR: 0.84; 95% CI: 0.71, 0.99; p = 0.0431). In PTEN loss patients the median rPFS was 18.5 versus 16.5 months (HR 0.77; 95% CI 0.61,0.98; p = 0.0335). Serious adverse events (AEs) occurred in 40% and 23% of ipatasertib and placebo patients, respectively; AEs leading to discontinuation of ipatasertib/placebo occurred in 21% and 5%. The researchers also examined outcomes based on NGS. Of 1,104 patients, NGS was evaluable for 743 patients, and PTEN loss by NGS was evaluable in 518 patients. Overall, the agreement between the two was 85.5%; among 208 patients with PTEN loss by NGS, 190 patients (91.3%) had PTEN loss by IHC as well. Among 247 patients with PTEN loss by IHC, 76.9% had PTEN loss by NGS. The analysis found that combination ipatasertib and abiraterone was superior regarding radiographic progression-free survival in patients with PTEN loss as measured by NGS (HR 0.65, 95% CI [0.45, 0.95]). Furthermore,

it also offered significant benefit in the group of patients with other *PIK3CA/AKT1/PTEN* alterations, as determined by NGS (HR 0.63, 95% CI [0.44, 0.88]).

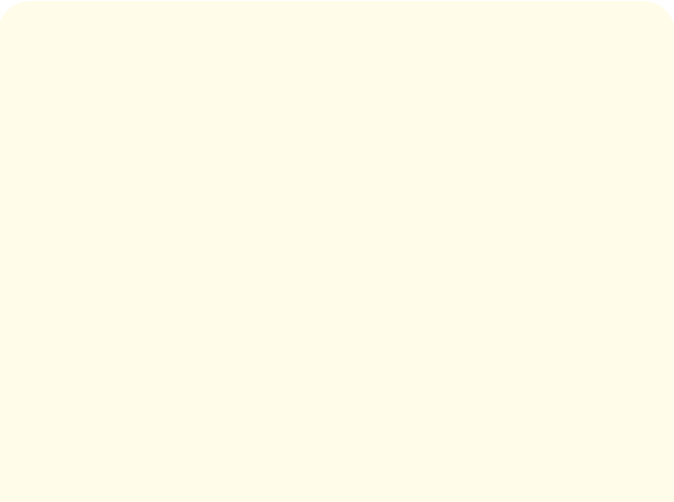


Figure 1A: The picture portrays hypothalamic-pituitary-testes-axis, the mechanism by which prostate cell proliferates by androgen binding to androgen receptor and steroid biosynthesis. It also, shows the pathways where prostate cancer treatments take place, illustrating LHRH agonist and antagonist action.

Figure 1B: The picture illustrates first-generation antiandrogen competing for androgen receptors in nucleus cytoplasm, second-generation antiandrogens such as enzalutamide, apalutamide and darolutamide preventing AR translocation to the nucleus.

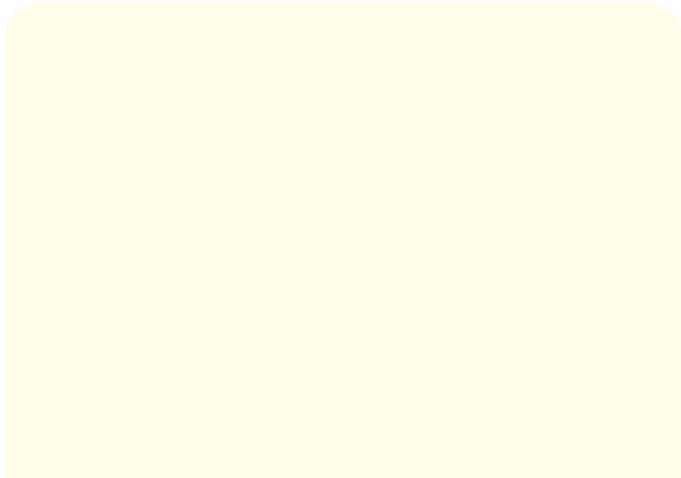


Figure 1C: The picture portrays steroid biosynthesis that takes place in adrenal gland and in the genital tissue, it also shows second-generation antiandrogens such as abiraterone acetate preventing androgen biosynthesis.

Figure 1D: The picture illustrates PARP inhibitors mechanism of action

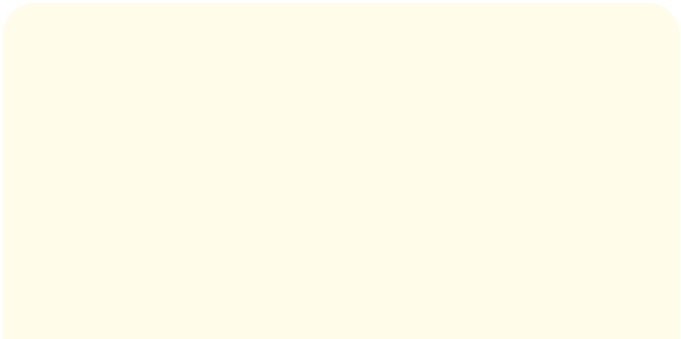


Figure 2: Timeline of the development of therapies for prostate cancer, illustrating significant events and studies for clinical applicability.

Conclusion

Since the seminal study of Huggins [5], the field of prostate cancer has experienced a constant evolution with the development of multiple therapeutic options, as shown in figure 2. For a long time, research has focused on the androgen receptor pathway. When androgens, like testosterone and DHT bind to the AR, they induce conformational change, activation and subsequent translocation of the AR into the nucleus. Nuclear AR binds to androgen responsive elements in the DNA, resulting in transcriptional activity that can induce cellular proliferation and cellular differentiation [15]. Therefore, the blockade of the hypothalamic-pituitary-testes-axis was the target of several studies resulting in the development of agonists and antagonists of LHRH. Recently, the appeal for less invasive treatments has resulted in the development of relugolix, an oral LHRH antagonist, which has interesting PSA control rate and important reduction in cardiovascular events when compared to LHRH agonists [25]. The most comprehensive knowledge of the mechanisms of resistance of androgenic pathway such as alternative AR signaling, AR amplification, alternative splicing, intratumoral androgen production, or adrenal gland testosterone production evolved new therapeutic options such as abiraterone, enzalutamide, apalutamide and darolutamide [7-10,28].

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