Review Article

The Treatment of Metastatic Prostate Cancer Using Hormonal Therapy: A narrative review

ABSTRACT

The incidence of prostate cancer in men has increased significantly, making it one of the most prevalent malignancies in the male population. Over the past two decades, there has been a substantial shift in the approach to managing metastatic prostate cancer, with the approval of novel medications resulting from multiple pivotal phase III trials. These medications offer a range of therapeutic alternatives to patients, with varying modes of action. Despite the progress made in prostate cancer treatment, early metastases and drug resistance continue to pose significant challenges. In this narrative review, we examined the evidence regarding the effectiveness of hormone therapy in the treatment of metastatic prostate cancer, drawing on data from important clinical trials of hormonal therapy. In addition, we conducted a search of ClinicalTrials.gov to identify ongoing and upcoming trials related to metastatic and resistant prostate cancer. Finally, we present an overview of the pathophysiology of these residual effects and review relevant translational research and observational cohort studies.

KEYWORDS: Metastatic prostate cancer; Castration-resistant prostate cancer; Androgen deprivation; Hormonal therapy

INTRODUCTION

Between the bladder and the penis lies the prostate, an accessory gland of the male reproductive system [1]. Prostate cancer (PC) is the most prevalent form of cancer among men in many parts of the world [2]. It is the second most common malignancy in older men and accounts for over 80% of cases in individuals above 65 years of age; however, only 10% of these cases result in mortality [1]. Annually, an estimated 1.6 million men are diagnosed with prostate cancer, and 366,000 succumb to the disease [3]. Incidences of prostate cancer are more frequently reported in affluent nations than in developing countries. In 2016, prostate cancer was the leading cause of all incidental cancers in the United States, with an estimated 180,890 patients affected [3].

The process of aging constitutes a notable risk factor for the development of prostate cancer, with a higher likelihood observed in individuals who exhibit a positive genetic predisposition. The risk of developing prostate cancer is found to be 2 to 3 times greater in those with a familial history of the disease in comparison to those without such history. The utility of genetic markers has been demonstrated in enhancing the diagnostic potential for prostate cancer, particularly in identifying high-risk tumors, thus aiding in the

screening and treatment process. Furthermore, obesity and a high-fat diet have been shown to contribute to the growth and progression of prostate cancer, with foods high in fat, such as grilled or barbecued red meat, significantly increasing the risk of disease.

On the other hand, individuals with a low risk of prostate cancer may develop tumors that produce minimal discomfort, which may not necessitate intervention. In addition, studies have identified a correlation between race and increased susceptibility to prostate cancer, with black men having a greater likelihood of developing the disease compared to white men. Late detection, genetic variations, environmental factors, and socioeconomic status are also factors that have been implicated in the onset and progression of prostate cancer [4].

Metastasis is known to cause a rapid advancement in prostate cancer cases. Recent studies indicate that men shorter than 5 feet 6 inches are less susceptible to aggressive forms of prostate cancer compared to their taller counterparts [5]. While hormone therapy can effectively suppress the growth of hormone-dependent tumors, the standard treatment for prostate cancer still heavily relies on surgical and radiological interventions for patients who are unsuitable for those procedures [6]. Unfortunately, hormone-independent prostate cancer can emerge and cause complications, leading to metastasis and recurrence. Hormones such as luteinizing hormone-releasing hormone (LHRH) and androgens like testosterone and dihydrotestosterone fuel the growth of prostate cancer. In this paper, we discuss the significance of hormone therapy as a treatment option for prostate cancer, including the strategies that prostate cancer employs to resist hormone therapy, ultimately leading to castration resistance. We also highlight the latest studies that seek to advance the field of hormone therapy for the treatment of prostate cancer.

MECHANISM OF PROSTATE CANCER DEVELOPMENT (GENE MUTATION)

A gene mutation, which may be hereditary or acquired, is the genetic etiology of the disease cancer. Compared to breast cancer (1.2 per Mb) and colorectal cancer (3.1 per Mb), non-metastatic prostate cancer has a lower average mutation rate of 0.7 mutations per megabase (Mb). A higher amount of genomic instability and chromosomal rearrangements can also be linked to prostate cancer. Single nucleotide variants cause prostate cancer with a few insertions, deletions, rearrangements, abnormal methylation patterns, or changes in the number of gene copies [6]. Exome sequencing research was carried out on 50 autopsies of castration-resistant prostate cancer that had already received treatment in Grasso's analysis. Nine genes, including TP53, ZFHX3, AR, RB1, PTEN, CDK12, APC, MLL2, and OR5L1, were found to frequently exhibit mutations. The data ensemble reveals that the aberrations in androgen receptors (AR) and their associated proteins, such as protein remodelers and the ETS genes referred to be AR co-regulators, are frequently changed or mutated in prostate cancer [7]. However, about 12 genes were frequently mutated in primary prostate cancer study, which examined 112 primary tumors with a median of 30 non-synonymous single nucleotide variants [7]. These genes included TP53, PTEN, PIK3CA, SPOP, FOXA1, MED12,

CDKN1B, ZNF595, THSD7B, NIPA2, C14 or F49, and SCN11A. In the androgen-signaling pathway, a few of these genes have significant roles. The CDH1 gene encodes a chromatin remodeling enzyme that requires ATP. Research has demonstrated that the level of its deletion rises in proportion to the tumor grade and is more common in ERG fusion-negative cancer than fusion-positive cancer [6].

The functional investigation demonstrates the significance and necessity of CDH1 expression for effectively recruiting AR at various responsive gene promoters, which accounts for why CDH1 deletion limits the creation or generation of ERG rearrangement [6]. The metabolism of dehydroepiandrosterone (DHEA) is accelerated by the transformation of growth factor b1 (TGF-b1) into androgens and prostate-specific antigens. Both stromal and epithelial (LAPC-4) cells are grown concurrently in this prostate tissue type. Red clover isoflavones block the effects of transforming growth factor b on androgenicity, and the mechanisms governing and regulating these processes are investigated. The three hydroxysteroid dehydrogenases involved in the conversion of DHEA to testosterone, 3b-HSD, HSD-17b1, and HSD-17b5 were investigated. To TGF-b1/DHEA-induced PSA in LAPC-4 co-culture, individual HSD depletion in 6S cells is reduced [8]. A million people have died from this disease due to late discovery, lack of access to appropriate care, and the requirement for a viable treatment method.

FIRST-LINE PROSTATE CANCER HORMONAL TREATMENT (CASTRATION/HORMONAL THERAPY)

When it comes to how testosterone deprivation and the ensuing testosterone therapy affect the development of prostate cancer, this has historically been a disputed topic. This concept has its roots in the research of Kutscher and Wolbergs, who found that the prostates of humans and monkeys contain a sizable quantity of acid phosphatase [9]. Huggins and Hodges concluded in 1945 that giving testosterone (an androgen) to men with testosterone deficiency would cause prostate cancer. With the skeptical view that androgen removal prevents the progression of prostate cancer to metastatic prostate cancer resulted in the development of androgen deprivation therapy (ADT) [10]. According to several studies conducted over the past ten years, men receiving testosterone therapy, those with high testosterone levels, or those who underwent a prostatectomy after receiving exogenous testosterone do not run a higher risk of developing advanced stages of prostate cancer [11–17].

The Saturation Model was introduced by Morgentaler and Traish in 2009 and postulated that androgen receptors, a ligand-dependent transcription factor, control the onset and progression of prostate cancer, with testosterone having a maximum effect on the tumor's growth [18]. The saturation model is still the subject of some contention, albeit [19]. Studies have indicated that the development and spread of PC cancer are aided by AR signaling pathways. Nevertheless, ADT can inhibit PC growth and metastasis and produce a reduction or loss of androgen receptors (AR) [20].

As the first-line treatment for metastatic prostate cancer, ADT can be administered via surgical bilateral orchiectomy or via medical castration using antiandrogens, luteinizing hormone-releasing hormone (LHRH) agonists, or luteinizing hormone-releasing hormone antagonists (LHRHA), either in combination or individually [21]. Diethylstilbestrol (DES) was initially employed to accomplish androgen deprivation, despite having a markedly increased cardiovascular mortality rate [22]. However, it has been demonstrated that they can lessen cardiovascular toxicity when used in small dosages. Furthermore, the hypothalamic-pituitary-gonadal axis is affected negatively by DES, which lowers LH secretion and, in turn, lowers androgen production [23]. Therefore, ADT's main objectives in treating advanced prostate cancer were to increase castrate testosterone levels while reducing cardiovascular damage. Lei and Liu concluded that complete radical prostatectomy (RP) or radiation therapy (RT) with ADT could both be used as the first-line therapy for high-risk prostate cancer while also taking into account the individual's phenotypic and genotypic characteristics through a systemic review and meta-analysis of the survival outcome of first-line treatment options [24].

LUTEINIZING HORMONE-RELEASING HORMONE (LHRH) AGONIST

GnRH is a decapeptide produced by the hypothalamus that regulates serum testosterone levels by stimulating the anterior pituitary gland to release Luteinizing Hormone [25]. A concomitant reduction in LH secretion is seen when the Luteinizing Hormone Releasing Hormone (LHRH) agonist treatment scheme is initiated via the downregulation of LHRH receptors and severing of the LHRH signal transduction mechanism. With the modifications of GnRH decapeptide by amino acid substitution or chemical alterations, GnRH agonists like Leuprolide, Goserelin, Triptorelin, and Histrelin are now commercially available in a variety of forms [26]. With a perspective to lower testosterone levels and attain the most outstanding efficiency of achieving medical castration, Triptorelin is the most puissant LHRH agonist, followed by Leuprolide and Goserelin [27]. The adverse effects of these medications include initial flare, loss of libido, erectile dysfunction, anemia, and muscle fatigue, as well as musculoskeletal, hematologic, and cardiovascular events [28, 29]. Therefore, before initiation of treatment, patients should be familiarized with the expected side effects and the efficient and effective methods of managing them, including lifestyle modifications and complementary medications [29].

ANTIANDROGENS

Anti-androgens stunt cancer growth by binding the androgen receptors at the cellular level. They are also called androgen receptor antagonists [30]. A few commercially used antiandrogens include Flutamide, Bicalutamide, and Nilutamide. To circumvent androgen flare, it is preferred to administer antiandrogen in the first month of using an LHRH agonist. Androgen synthesis is achieved 90 to 95% by the Testes and 10% by the Adrenals. To attain maximum androgen blockage, the LHRH agonist should be affixed with antiandrogens to reduce the testosterone produced by the Testes and Adrenals to castrate levels [28].

LUTEINIZING HORMONE-RELEASING HORMONE (LHRH) ANTAGONISTS

LHRH antagonists, commonly referred to as gonadotropin-releasing hormone [GnRH] antagonists, can perform medical castration. Without causing a hot flare aftereffect, LHRH antagonists function by blocking the antigen receptors and inhibiting the production of gonadotropins and testosterone [21,31]. Abarelix was the first LHRH antagonist medication licensed by the US Food and Drug Administration (FDA) for metastatic prostate cancer with a higher rate of medical castration in 2004; nonetheless, it has been associated with a systemic allergic reaction that could be fatal [32]. However, during a clinical trial, more than 2,000 patients received medical castration with the synthetic peptide Degarelix in 2008 without experiencing any immediate or delayed systemic adverse reactions [33].

Due to prostate cancer's resistance to ADT and the high likelihood of transmuting into castrate-resistant prostate cancer (CRPC), the therapy landscape for metastatic prostate cancer has significantly changed over time [34]. Drugs including Docetaxel, Abiraterone, Enzalutamide, and Apalutamide are used in this therapeutic environment, and some trials have shown improvements.

CASTRATION-RESISTANT PROSTATE CANCER

In 80 to 90% of instances of metastatic prostate cancer, the early effect of ADT often involves a sharp reduction in serum prostate-specific antigen (PSA) [35, 36]. Castrate-resistant prostate cancer, on the other hand, develops in some prostate cancer patients who become resistant to hormonal therapy [37, 38]. The FDA has approved the supracastration hormonal therapies abiraterone and enzalutamide for treating CRPC in patients who have never received chemotherapy and those who have developed a resistance to it, respectively. Enzalutamide and abiraterone functionally prevent testosterone from binding to the androgen receptor [39, 39]. When prostate cancer spreads while receiving androgen deprivation therapy, it is said to be "castration-resistant" (ADT). It is characterized by an ongoing rise in prostate-specific antigen (PSA) blood levels. Prostate cancer hormonal therapy can be avoided using a variety of methods. The primary tumor escape strategies involved in castrate-resistant prostate cancer were histologic transformation, cancer stem cell target modification, and bypass signaling, which included partial obstruction of AR-ligand signaling, AR amplification, AR mutations, aberrant AR co-regulator activities, and AR splice-variant expression [37, 40].

BYPASS SIGNALING PATHWAYS

Androgen receptors can increase autonomously by going through signaling pathways. This takes place through the transactivation of AR, which is prompted by cytokines, growth factors, and neurotransmitters [41]. Below, a number of the signaling bypass's mechanisms are covered.

ANDROGEN RECEPTOR AMPLIFICATION

Castration-resistant cells that express such a high level of AR can withstand low levels of androgen during ADT and give rise to recurrent clonal proliferation. About 30% of all patients who progressed to CRPC had X-chromosome polysomy and X-q12 gene amplification, but not in hormone-naive tissues. Additionally, having more than one copy of the AR gene increases the expression of the AR mRNA and protein, which promotes the growth of new cancers [40, 42].

The prostate is an androgen-dependent organ, and prostate cancer is an androgen-dependent condition. Androgen mediates androgen actions through the androgen receptor (AR), a hormone-activated transcription factor. The direct control of gene expression is brought about by the binding of androgens (testosterone and dihydrotestosterone) to the androgen receptor [43]. The spontaneous or chromosomal rearrangements mutation of androgen receptors makes them resistant to receptor-targeted treatment. For example, H874Y and T877A mutations have been found in the circulating cell-free DNA of patients who no longer respond to abiraterone therapy [44]. When antiandrogen therapy was terminated, Suzuki et al. found that expression of this mutation in CRPC patients was associated with a considerable drop in prostate-specific antigen [36]. Similar to this, the AR antagonists ARN-509 and enzalutamide become agonists when the AR-LBD missense mutation (F876L) is present [45].

SPLICE VARIANTS

AR splice variants are significant for CRPC patients who have developed resistance to enzalutamide and abiraterone, which happens as primary resistance in 20 to 40% of cases and as subsequent resistance in virtually all instances despite initial remission [46]. AR splice variants produce a different form of the AR protein that has a working N-terminal domain and a partially or fully functional DNA binding domain (DBD) that can interact with DNA and AR co-receptors but lacks the C-terminal ligand-binding domain (LBD) [47]. The majority of AR-V7 is expressed in CRPC metastases, while AR-V3 and AR-V9 may also co-express [48, 49].

ALTERATION OF AR CO-REGULATORS

Co-regulators are protein complexes that bind to AR to control translational activity, they comprise coactivators, inhibitors, and chromatin remodelers [50]. Maximum regulation of androgen activity depends on the balance of AR-mediated transcription, whereas an imbalance may cause higher or lower AR activity [49]. Less antagonist activity brought on by antiandrogen medication is observed in CRPC due to an increase in AR coactivator and a decrease in AR co-inhibitor [50, 51]. CHD1 is a tumor-suppressor gene that prevents the development of prostate tumors. The CHD1 gene loss in CRPC increases the transcriptional activities that fuel prostate carcinogenesis [51, 52]. Another coactivator for prostate cancer growth is homeobox B13 or HOXB13. HOXB13 mRNA is overexpressed in prostate cancer, and further research has demonstrated that HOXB13 mediates the AR-V7 oncogenic activity [53]. However, in the

presence of androgen co-inhibitors, Src protein kinase gene silencing activity most effectively prevents AR inhibitors from leading to CRPC [54].

HISTOLOGIC TRANSFORMATION AND CANCER STEM CELLS

A small percentage of individuals with advanced prostate cancer experience histologic change into tiny neuroendocrine cells as a mechanism of treatment resistance [55]. Neuroendocrine cells are not frequently present in normal prostatic tissue as secretory cells [57]. In prostate adenocarcinomas, immunohistochemistry can identify various neuroendocrine cells [40, 56]. Squamous cell carcinoma (SCC), an uncommon and aggressive cancer, can also develop from prostate adenocarcinoma [57]. Tumor cells that have the capacity for self-renewal, differentiation, and proliferation are known as cancer stem cells (CSCs) [55].Tumors are resistant to therapy form due to cancer cells adapting to the therapeutic environment [57].

CANCER HORMONOTHERAPY CLINICAL TRIALS

Clinical trials are human research initiatives designed to improve medical treatment and quality of life for people with a particular ailment. New interventions and treatments are researched, and their effects on human participants are assessed in clinical trials. For example, the TAX and SWOG studies [58, 59] used Docetaxel as the first cytotoxic agent to establish survival improvements for the treatment of CRPC, which was in 2004. These trials also altered a new generation of likely clinical studies that contrast the outcome of a post-docetaxel context. The CHAARTED, STAMPEDE, and GETUG-AFU 15 phase III trials, as well as the development of several more trials, were sparked by the question of whether Docetaxel could offer an early survival benefit when taken in metastatic hormone-sensitive prostate cancer. The characteristics of these trials are shown in table 1.

Table 1. CLINICAL TRIALS SHOWING OVERALL SURVIVAL OUTCOMES

SIDE EFFECTS	Fatigue, sensory neuropathy, infection		Neutropenic fever, nausea, vomiting, and Cardiovascular events	Febrile neutropenia and fatigue	Symptomatic skeletal events	Abnormali-ties in mineralo-corticoid and liver function test.	Endocrine disorders, febrile neutropenia		Rash, hypothyroidism, and fracture	Grade 3 hypertension and hypokalemia
P-VALUE	0.009 (D3P)	0.36 (D1P)	0.02	< 0.001	< 0.001	0.01	0.006	0.022	< 0.001	< 0.001

P-VALUE	SIDE EFFECTS
0.03	Chills, fever, and headache
0.022	Fatigue and hypertension
< 0.001	Mineralo-corticoid excess
< 0.001	Anemia, seizures
< 0.001	Anemia
< 0.001	Febrile neutropenia
0.001	Fatigue and Musculo-skeletal events
< 0.001	Anemia, abdominal pain

CLINICAL STATE	STUDY	NCT NO.	N	INTERVENTIONS	TARGET	EXP. ARM	CON. ARM	HR (95% CL)
mHRPC	TAX 327 [58]	ND	1006	Docetaxel + Prednisone versus Mitoxantrone + Prednisone	AR	18.9	16.5	0.76 (0.62-0.94)
						17.4	16.5	0.91 (0.75-1.11)
mAIPC	SWOG 99 – 16 [59]	NCT00004001	770	Docetaxel + Estramustine versus Mitoxantrone + Prednisone	AR, Tubulin and Microtubules	17.5	15.6	0.80 (0.67-0.97)
mHSPC	CHAARTED [60]	NCT00309985	790	ADT + Docetaxel versus ADT	Bcl-2 phosphorylation	57.6	44	0.61 (0.47-0.80)
mHSPC	STAMPEDE [61]	NCT00268476	1917	ADT + Abiraterone + Prednisone versus ADT	CYP17	83% at 3 years	76% at 3 years	0.63 (0.52-0.76)
mCRPC	COU-AA 302 [62]	NCT00887198	1088	Abiraterone + Prednisone versus Placebo + Prednisone	CYP17	ND	27.2	0.75 (0.61-0.93)
SmHSPC	STAMPEDE [63]	NCT00268476	2962	ADT + Docetaxel versus ADT	AR	81	71	0.78 (0.66-0.93)
				ADT + Docetaxel + Zoledronic acid versus ADT	AR, Bone marrow	76	71	0.82 (0.69-0.97)
nmCRPC	SPARTAN [64]	NCT01946204	1207	Apalutamide + ADT versus Placebo + ADT	AR	40.5	16.2	0.28 (0.23-0.35)
mHSPC	LATITUDE [65]	NCT01715285	1199	ADT + Abiraterone + Prednisone versus ADT + Placebo + Placebo	CYP17	ND	34.7	0.62 (0.51-0.76)

CLINICAL STATE	STUDY	NCT NO.	N	INTERVENTIONS	TARGET	EXP.ARM	CON. ARM	HR (95% CL)
mCRPC	IMPACT [66]	NCT00065442	512	Sipuleucel-–t versus Placebo	PAP	25.8	21.7	0.78 (0.61-0.98)
mCRPC	PREVAIL [67]	NCT01212991	1717	Enzalutamide versus Placebo	AR	76	71	0.82 (0.69-0.97)
Post-docetaxel mCRPC	COU-AA 301 [68]	NCT00638690	1195	Abiraterone + Prednisone versus Placebo + Prednisone	CYP17	14.8	10.9	0.65 (0.54-0.77)
CRPC	AFFIRM [69]	NCT00974311	1199	Enzalutamide versus Placebo	AR	18.4	13.6	0.63 (0.53-0.75)
mCRPC	ALSYMPCA [70]	NCT00699751	921	Alpharadin versus Placebo	Bone metastasis	14.9	11.3	0.70 (0.58-0.83)
mCRPC	TROPIC [71]	NCT00417079	755	Cabazitaxel + Prednisone versus Mitoxantrone + Prednisone	Tubulin	15.1	12.7	0.70 (0.59-0.83)
nmCRPC	PROSPER [72]	NCT02003924	1401	Enzalutamide + ADT versus Placebo + ADT	AR	67	56.3	0.80 (0.61-0.89)
mHSPC	ARCHES [73]	NCT02677896	1150	ADT + Enzalutamide versus Placebo + ADT	AR	ND	19	0.39 (0.30-0.50)

CLINICAL STATE	STUDY	NCT NO.	N	INTERVENTIONS	TARGET	EXP.ARM	CON. ARM	HR (95% CL)	P-VALUE	SIDE EFFECTS
mHSPC	ENZAMET [74]	NCT02446405	1125	Enzalutamide versus LHRHA	AR	80% at 3 years	72% at 3 years	0.67 (0.52-0.86)	0.002	Fatigue, seizures
mHSPC	TITAN [75]	NCT02489318	1052	Apalutamide + ADT versus ADT + Placebo	AR	82.4% at 2 years	73.5% at 2 years	0.67 (0.51-0.89)	0.005	Rashes
mHSPC	ARASENS [76]	NCT02799602	1306	Darolutamide + ADT + Docetaxel versus Placebo + ADT + Docetaxel	AR	32.5% increase than con. arm	ND	0.68 (0.57-0.80)	< 0.001	Fatigue
mCRPC	IPATential150 [77]	NCT03072238	1097	Ipatasertib + Abiraterone + Prednisone versus Placebo + Abiraterone + prednisone	AR	19.2	16.6	0.84 (0.71-0.99)	0.043 (not sig. at 0.01)	Rash, hyperglycemia, high aminotransferase, and diarrhea

Abbreviations: n, sample size; NCT no, National Clinical Trial number; CI, confidence interval; HR, Hazard Ratio; Exp. Arm, Experimental Arm; Con. Arm, Control Arm; mCRPC, metastatic Castration-Resistant Prostate Cancer; ADT, androgen deprivation therapy; CI, confidence interval; nmCRPC, non-metastatic Castration-Resistant Prostate Cancer; mHSPC, metastatic hormone-sensitive prostate cancer; ND, not

described; PAP, Prostatic Acid Phosphatase; mHRPC, Metastatic Hormone-Refractory Prostate Cancer; mAIPC, Metastatic Androgen-Independent Prostate Cancer; D3P, Docetaxel 3 × Weekly + Prednisone; D1P, Docetaxel 3 × Weekly + Prednisone;

ACTIVE CLINICAL TRIALS

The Clinical trial (ENZAMET) sponsored by the University of Sydney and registered under the identifier NCT02446405 is one of the ongoing trials being conducted. The Randomised Phase 3 Trial encompasses a cohort of 1125 participants. The primary objective is to evaluate the effectiveness of enzalutamide in comparison to a conventional non-steroidal antiandrogen (NSAA), when combined with a luteinizing hormone-releasing hormone analog (LHRHA) or surgical castration, as the initial course of androgen deprivation therapy (ADT) for recently diagnosed individuals with metastatic prostate cancer. The anticipated completion date for this comprehensive study is estimated to be December 2024.

Also, conducted under the study identifier NCT03821792, a Phase 2 clinical investigation is currently underway, focusing on ascertaining the efficacy of abiraterone acetate, prednisone, and apalutamide in the treatment of male patients afflicted with hormone-naïve metastatic prostate cancer (HNMPCa). The trial aims to evaluate the extent to which the aforementioned medications effectively counteract the progression of prostate cancer cells that are stimulated by androgen. Through the implementation of antihormone therapy, specifically abiraterone acetate and apalutamide, it is anticipated that the production of androgen within the body will be attenuated. M.D. Anderson Cancer Center serves as the sponsor for the study, with the National Cancer Institute (NCI) acting as a collaborative partner. The estimated date for primary completion of this trial, involving 60 participants, is October 2023.

Another trial, sponsored by AstraZeneca, aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of AZD5305 when administered alongside new hormonal agents (NHAs) in individuals diagnosed with Metastatic Prostate Cancer. Termed PETRANHA, this Multi-arm, Open-label Phase I/IIa Study encompasses the evaluation of AZD5305 in conjunction with new hormonal agents such as Enzalutamide, Abiraterone Acetate, and Darolutamide. Commencing on June 2, 2022, the study is expected to reach its primary completion by March 15, 2029, and involves the participation of 520 individuals. The study identifier for reference is NCT05367440.

CONCLUSION

Risk factors for prostate cancer include genetic mutation, advancing age, a positive family history, smoking, and ethnicity (mainly in black Americans). Prostate cancer is a multi-genetic disease that is a global health concern. The use of hormone therapy as a prostate cancer treatment option is underutilized, although several hormone therapies can both treat and halt the progression of the disease. More choices for hormone therapy must be developed due to expanding understanding to contain further and eradicate prostate cancer globally.

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