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Advances in Prostate Cancer Immunotherapy: Current Options and Emerging Novel Approaches

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Abstract

Prostate cancer (PCa) is a significant malignancy in men, contributing considerably to the rise in male mortality rates worldwide. Men diagnosed with PCa may have either localized or advanced stages of the disease. Globally, it ranks as the second most common and fifth most aggressive cancer type in males. The likelihood of developing prostate cancer in a man's lifetime is approximately one in seven. Epidemiological research has linked various environmental and genetic factors to the abnormal growth of prostate cells, which leads to the formation of cancerous cells. Men experiencing a recurrence of prostate cancer or presenting with metastasis typically undergo androgen deprivation therapy (ADT), along with salvage radiotherapy and chemotherapy. While current treatment methods are more effective when used in combination, prostate cancer remains incurable. Research efforts are focused on exploring alternative treatments, including traditional medicine, nanotechnology applications, and gene therapy, to address drug resistance and mitigate the side effects associated with existing treatments. This article provides an overview the current treatment methods, and ongoing research into new treatment alternatives.

Key words clinical trials, gene therapy, nanotechnology, prostate cancer, immunotherapy

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Introduction

PCa is a significant global health issue, with over 1.4 million new diagnoses and around 375,000 deaths annually [1]. Managing the disease has a substantial effect on patients' quality of life. In many Western nations, PCa ranks as either the leading or second-leading cause of cancer-related deaths in men. The disease presents a considerable burden since many individuals live with the condition for an extended period, often exceeding 15 years. For patients with localized cancer, treatment stratification is becoming more critical and complex, especially with emerging therapies like focal treatment. Identifying which patients have cancers with a high likelihood of metastasis or fatality remains challenging. A review of unmet research priorities in PCa highlighted the urgent need for enhanced methods to differentiate between high-risk and low-risk prostate cancers [2]. The multifocal nature of most prostate cancers complicates both molecular research and clinical management. Typically, malignant regions in the prostate are considered separate foci if there is at least 2 mm of normal tissue between two cancerous areas [3]. Notably, approximately 75% of patients present with more than one malignant focus in the prostate [4]. The origin of this multifocality remains a topic of debate, with theories suggesting monoclonal [5], multiclonal [6], or mixed clonality origins [7]. Further, hypotheses on tumor development range from a genetic predisposition to a tumor-promoting environment. Genetic predisposition could be due to germline or early somatic mutations occurring before organ development, potentially creating a tumor-friendly environment similar to hereditary cancer syndromes, such as those with APC gene mutations who develop multiple colon polyps [8], or possibly mosaic inactivation of BRCA1 or BRCA2, akin to findings in other cancers (**Figure 1**) [9]. Another theory is that the initial cancer focus triggers a tumor-promoting environment, possibly via an epigenetic field effect or field cancerization [10]. The slow-growing nature of most prostate tumors may also contribute to the formation of additional malignant foci over time [11]. Since the introduction of prostate-specific antigen (PSA) testing in the 1990s, PCa is increasingly being detected at earlier stages. As a result, many of the tumors identified today are smaller compared to those diagnosed before the 1990s [12]. In recent years, significant advances in early detection methods, such as magnetic resonance imaging (MRI) [13] and ultrasound fusion biopsy [14], have emerged. Additionally, improvements in imaging technologies have led to organ-sparing treatments, such as ablation or focal therapy, which may enhance quality of life compared to whole-gland treatments like radical prostatectomy or radiation therapy [15].

The pathogenesis of PCa involves a gradual and ongoing progression characterized by the development of small tumors that slowly transform into distinct clonal entities, each with varying clinical outcomes [16]. Research has indicated that chronic inflammation is commonly observed in the prostates of older men and is linked to a heightened risk of developing PCa [17]. However, the precise mechanisms behind chronic prostate inflammation and its clinical significance in the progression of PCa remain uncertain. In spite of this, clinical data indicates that persistent inflammation could be a risk factor for the advancement of the disease and poor clinical results [18].

Innovative strategies are critical for advancing immunotherapies in prostate cancer (PCa). The success of Sipuleucel-T has shown that T-cell-based therapies can be clinically effective, opening the door to further progress in this field. One of the most promising new strategies is the use of bispecific T-cell engagers, particularly in treating non-inflamed tumors like PCa. These agents work by targeting cancer-specific epitopes, such as prostate-specific membrane antigen (PSMA), and linking them to a portion of the T-cell receptor. This redirection of T-cells to the tumor environment stimulates an immune response by activating T-cells and recruiting them to the tumor site. This review will explore immunotherapy strategies for PCa that have the potential to revolutionize the management of both localized and advanced disease stages [19].

Immunotherapy

Immunotherapy has played a limited role in treating PCa and has not significantly improved clinical feedback. Ongoing trials are exploring the use of immune checkpoint inhibitors (ICI) in specific patient subgroups. The Phase 3 KEYNOTE-641 trial is a double-blind, randomized, placebo-controlled study that compares the effectiveness of pembrolizumab and enzalutamide in treating patients with metastatic castration-resistant prostate cancer (mCRPC) who have not received prior treatment with biratterone or who have progressed after receiving biratterone but have not had chemotherapy [20]. Similarly, Pembrolizumab in combination with docetaxel and prednisone is being tested in KEYNOTE-921, a Phase 3 randomized, double-blind, placebo-controlled trial, in patients with metastatic colorectal cancer (mCRPC) who had previously received new hormonal therapies but no chemotherapy [21]. The study's primary objectives, which included increases in overall survival and radiographic progression-free survival (rPFS), were not met, according to an announcement made by the sponsor on August 3, 2022. The KEYNOTE-991 trial is also a Phase 3 study investigating Pembrolizumab in combination with Enzalutamide and ADT versus placebo combined with Enzalutamide and ADT for mCRPC patients who have not been treated with novel hormonal agents previously. The findings of these trials could change the way immunotherapy is used to treat PCa and are anticipated to be available in 2025–2026 [22]. A multicohort Phase Ib/II trial called KEYNOTE-365 is evaluating pembrolizumab in combination with three different treatments: enzalutamide (Cohort C), docetaxel and prednisone (Cohort B), and olaparib (Cohort A). According to preliminary data, the PSA response rates for Cohorts A, B, and C are 9%, 28%, and 22%, respectively. The study's final findings have not yet been released [23].

Immunotherapy resistance of prostate cancer

Numerous clinical trials targeting immunotherapy for PCa have focused on metastatic disease, particularly regarding advancements in novel treatments for castration-resistant prostate cancer (CRPC). Patients with metastatic PCa often present with a dysfunctional and compromised immune system [24]. One important aspect impacting the strategy for using immunotherapy to eradicate tumors is the immunogenicity of cancer cells. Cancer cells normally do not express foreign antigens since they are part of the immune system and are incorporated into the body. However, they can display tumor self-antigens that may elicit an immune response. Tumor neoantigens arise from somatic mutations accumulated in proliferating cancer cells and are clinically correlated with the mutation burden [25]. The mutation load within tumors has been linked to immunotherapy outcomes; nevertheless, the immunogenicity of tumors is shaped by various factors regulated by the cancer cells themselves [26].

Patients with metastatic PCa exhibit disrupted cellular immunity and a tumor microenvironment characterized by heightened immunosuppressive features. The compromised immune response in these patients is marked by reduced natural killer (NK) cell activity and renewal, as well as diminished expression of CD3 on NK and T cells, potentially leading to a decrease in T cell receptors and NK cell-activating receptors [27]. Additionally, myeloid-derived suppressor cells and regulatory T cells are more
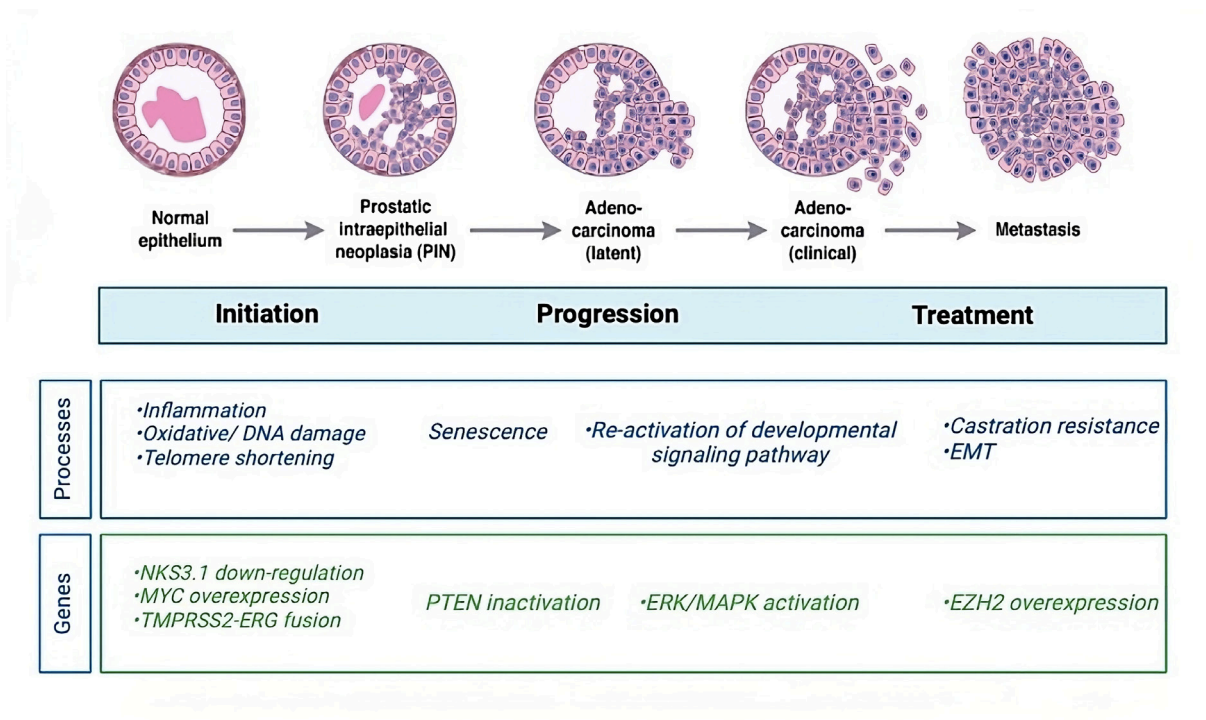
Figure 1. Schematic overview of prostate cancer progression. The molecular mechanisms, genes, and signaling pathways that are significant at various stages of cancer serve as indicators of the stages of cancer initiation and progression. Prostate gland inflammation brought on by unchecked cell division is the initial indication of prostate cancer. Mutations brought on by damaged DNA are the source of this unrestrained cell division. Telomerase shortening at the end of the chromosome is the first step in the development of prostate cancer at the chromosomal level. Prostatic telomeres can be shortened by oxidative stress brought on by inflammation of the prostate gland. Studies on the Nkx3.1 homeobox gene have demonstrated how the gene affects the start phase of prostate cancer in mice. No one tumor suppressor gene has been implicated in the development or spread of prostate cancer. Nonetheless, a number of genes, including NKX3.1, MYC, PTEN, and TMPRSS2-ERG gene fusions, are linked to the development of prostate cancer. The primary molecular subtype of prostate cancer is caused by fusions between the TMPRSS2-ERG genes. The disease develops as a result of the gene fusion's activation of the ERG oncogenic pathway. Prostate cancer metastasis is caused by the reactivation of cell division pathways, which leads to unchecked cell division and proliferation and ultimately cancer spread. According to the results of gene expression profiling, metastatic prostate cancer is associated with an overexpression of EZH2 mRNA and proteins. EZH2 is a unique target for prostate cancer because of its roles in apoptosis and proliferation.

prevalent in the tumor microenvironment and bloodstream of patients with mCRPC [28], and they also often have fewer total T cells [29]. The delayed evolution of PCa may also be a contributing factor to immunotherapy resistance and tolerance [30]. De novo resistance to immunotherapy may also arise as a result of the low mutational burden seen in PCa patients (**Figure 2)** [31]. However, this perspective is still debated, as recent genomic analyses have suggested that PCa patients may actually exhibit a higher tumor mutation burden compared to those with renal cell carcinoma [32]. Additional research is needed to clarify the specific pathological mechanisms contributing to the resistance of PCa patients to immunotherapy, ultimately aiming to develop effective immunotherapeutic strategies for metastatic PCa.

Vaccine based treatments

Most immunotherapy vaccines currently available for PCa are still considered experimental. Sipuleucel-T is the only FDA-approved vaccine specifically for this condition and is regarded as the most effective in clinical practice [33]. Autologous peripheral blood mononuclear cells containing antigen-presenting cells (APCs) activated by exposure to PA2024, a recombinant fusion protein combining prostatic acid phosphatase (PAP) and the costimulatory factor GM-CSF, make up the majority of this autologous active cellular immunotherapy vaccine. Patients with mCRPC saw a 22% decrease in the relative risk of death and an increase in overall survival (OS) of 4.1 months in a Phase III trial (IMPACT: NCT00065442). But the trial found very little antitumor response [34].

DNA vaccines have primarily been studied in animal models as a potential cancer treatment. Their application in humans remains contentious due to the associated risks versus benefits [35]. These vaccines provide a novel approach compared to traditional anti-tumor vaccinations, offering advantages such as ease of administration and the absence of infectious agents. DNA vaccines for PCa are currently being studied in a number of Phase 1 clinical trials. One such experiment, NCT02411786 by Madison Vaccines Inc., targets androgen receptors using the pTVG-AR and MVI-118 designs [36]. Furthermore, a Phase I/II trial involving patients with biochemically relapsed PCa has assessed Inovio Pharmaceuticals'
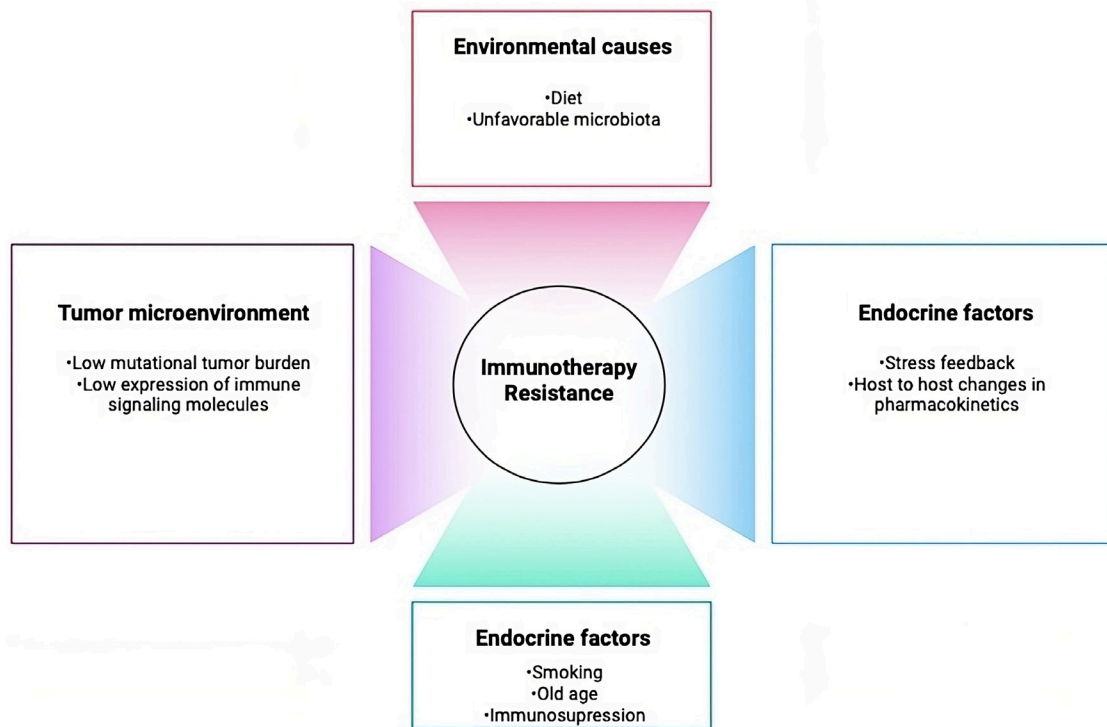
Figure 2. Factors that lead to immunotherapy resistance. Numerous possible host-related, tumor-related, and environmental factors have the potential to cause immunotherapies to be resistant.

dual-antigen DNA vaccine INO-5150, which combines elements of PSMA and PSA [37].

In order to elicit an immunological response in the body, the commercial vaccine PROSTVAC uses a recombinant strain of vaccinia in conjunction with transgenes, boosts from the fowlpox vector, and co-stimulatory molecules [38]. PSA-specific T-cell counts have increased in patients receiving PROSTVAC treatment [39]. PROSTVAC may be beneficial for patients with mCRPC, according to two Phase II studies. In one research, PROSTVAC or a placebo was randomly assigned to 125 mCRPC patients with a Gleason score of ≤7 [40]. Patients receiving the placebo had a median survival rate of 16.3 months, while those treated with PROSTVAC had a median survival rate of 24.4 months [41]. In an attempt to explore this theory further, a recent Phase III trial was carried out, however it failed to show any appreciable therapeutic improvement [39]. Despite being well-tolerated and able to stimulate the immune system, the vaccine offered very little in the way of survival benefits [42].

Using genetically engineered entire prostate cancer cells, known as GVAX, the tumor cells can act as the source of antigen for immunotherapy since they release the immune-stimulatory cytokine granulocyte-macrophage colony-stimulating factor [43]. GVAX has demonstrated safety and effectiveness as a potent cytokine, producing a significant immune response that is dose-dependent. Patients treated with GVAX typically experienced only mild side effects, such as flu-like symptoms and fever. Nevertheless, due to several unsuccessful Phase 3 trials involving this vaccine, further research has largely been discontinued [44].

Adoptive cell therapy

Adoptive Cell Therapy (ACT) has demonstrated effectiveness in the treatment of metastatic melanoma [45]. This therapeutic approach involves using T-lymphocytes that are specifically engineered to target certain viruses or tumors. By isolating and modifying patient T-lymphocytes with particular antigen receptors and subsequently reinfusing them, patients can mount an immune response akin to immunization against specific cancer antigens [46].

Chimeric antigen receptors (CAR)-modified epithelial cell adhesion molecule (EpCAM)-targeted T-cells have shown promise in a range of cancer immunotherapies utilizing this stem cell antigen. Studies on low-expression human prostate cancer cells have shown that these cells are highly effective at preventing tumor growth in both vitro and in vivo settings [47]. Additionally, it appears that the Natural Killer Group 2D (NKG2D) receptor is a viable target for CAR T-cell treatment. In conjunction with the IL-7 gene, it has demonstrated efficacy in the management of PCa [48].

To achieve more precise targeting of prostate cancer, CAR T-cells have frequently been developed against PSMA. In the first-in-human Phase 1 trial of PSMA-targeting CAR T-cells armed with a dominant-negative TGF-β receptor (NCT03089203) in patients with castration-resistant prostate cancer (CRPC), 5 out of 13 patients experienced cytokine release syndrome (CRS) of grade 2 or higher, and 4 patients showed decreases of 30% or more in PSA levels. Notably, one patient exhibited a greater than 98% reduction in PSA, along with evidence of significant clonal expansion of CAR T-cells. However, this patient subsequently developed enterococcal sepsis 30 days post-infusion, resulting in multi-organ dysfunction and death [49]. Three of the nine patients in a different ongoing clinical trial with PSMA-targeting CAR for
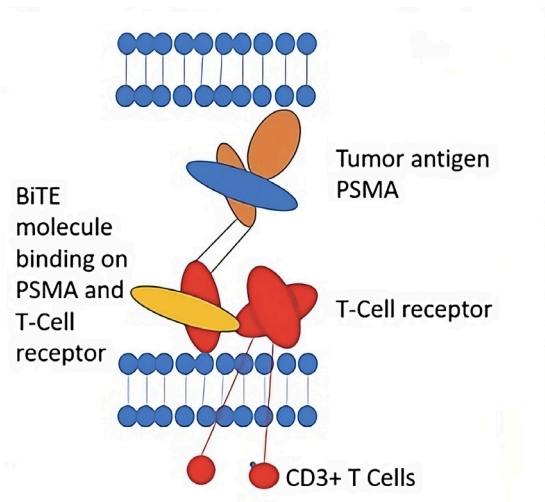
Figure 3. Bispecific T-cell engager. Modified according to Strohl et al. [80].

metastatic CRPC saw improvements in PSMA positron-emission tomography imaging and a drop in PSA levels of more than 50% [49]. One patient achieved total clearance of detectable illness for almost five months, while three others had CRS of grades 1-2 [50]. Even though these studies' findings are encouraging, CAR T-cell treatment still faces several obstacles. Overcoming the immunosuppressive tumor microenvironment (TME), which is full of growth factors and immunosuppressive cytokines, as well as possible toxicities related to the therapy are major constraints.

Another approach to ACT is Tumor-Infiltrating Lymphocyte (TIL) therapy, which focuses on analyzing specific lymphocytes found around tumors. In this method, T-cells that are most effective at recognizing malignant tumor cells are isolated, treated, and stimulated to proliferate in the tumor environment. However, incorporating TIL-based immunotherapy into PCa treatment poses challenges due to the disease's T-cell exclusive nature [51]. This difficulty can be attributed to the relatively low genomic complexity of prostate cancer cells compared to other cancers [52]. Recent studies have shown that it is feasible to extract functional and tumor-reactive TILs from prostate cancer. In one study, researchers successfully extracted and expanded twenty-eight prostate-TIL cultures in the laboratory, achieving an expansion frequency of approximately 50% across all samples. Following expansion, these TILs exhibited clear expression of chemokine receptors. Further exploration of this therapeutic approach could lead to new treatment modalities for patients [53].

A significant challenge in both CAR T-cell therapy and TIL therapy is maintaining long-term proliferation in immunosuppressive environments. Consequently, there is a growing emphasis on research aimed at enhancing the survival rates of CAR T-cells, particularly through the integration of TILs expressing 4-1BB and CD137 receptors [54]. The incorporation of such therapies into patient care represents an effective treatment strategy with fewer side effects compared to other cancer treatment modalities.

Bispecific T-cell engager

PSMA Bite is the most advanced bispecific T-cell engager for the treatment of prostate cancer (**Figure 3**). Since PSMA is present on prostate cancer cells and their metastases, therapies targeting these cells such as LU-PSMA radioligand therapy benefit from having it as a target [55]. A cutting-edge investigational treatment called PSMA Bite is intended for those with mCRPC. By targeting both CD3 and PSMA, this bispecific antibody construct activates and reroutes T-cells to attack cells that express PSMA.

Bispecific T-cell engagers (BiTEs) have already been successfully implemented in treating various malignancies. The first BiTE therapy to receive approval was Blinatumumab, a bispecific monoclonal antibody construct designed to enable CD3-positive T-cells to recognize and target CD19-positive B-cells. Blinatumumab is indicated for patients with refractory or relapsed precursor B-cell acute lymphoblastic leukemia (B-ALL). In comparison to chemotherapy, blinatumumab demonstrated a survival advantage for patients with pretreated B-ALL, with a median overall survival (OS) of 7.7 months in the blinatumumab group versus 4.0 months in the chemotherapy group (HR = 0.71; 95% CI 0.55 to 0.93; p = 0.01) [56].

Given the encouraging results in treating hematological diseases, researchers are currently exploring the potential of bispecific T-cell engagers (BiTEs) for solid tumors. A Phase I trial was conducted to evaluate the tolerability and efficacy of pasotuximab (PSMA Bite) in patients with mCRPC. This study involved 68 participants divided into two groups receiving either subcutaneous (s.c.) or intravenous (i.v.) administration. All patients had undergone at least one prior taxane treatment and were refractory to abiraterone acetate (AAP) or enzalutamide. The trial aimed to assess the maximum tolerated dose in both groups while monitoring PSA responses. However, in the subcutaneous cohort, all patients developed anti-drug antibodies, resulting in the early termination of this treatment group [57].

In the Phase I study of pasotuximab (PSMA Bite), patients in the subcutaneous (s.c.) cohort showed a PSA decline of −24.7%. In the intravenous (i.v.) cohort, the median best PSA reductions were −22.0%, −37.7%, and −54.9% for the 20, 40, and 80 μg/d dose groups, respectively. One patient in the i.v. group experienced a PSA reduction of less than 50% for 50 weeks and stable disease for 337 days, while another patient had nearly complete regression of lymph node and bone metastases, as seen on PSMA-PET CT. Long-term responders in the i.v. cohort showed PSA progression after 11–17 months, suggesting dose-dependent activity of the treatment. The most common adverse events (AEs) were fever, seen in 81% of the s.c. cohort and 94% of the i.v. cohort, injection site reactions in the s.c. group (77%), chills (23% in s.c. and 69% in i.v. groups), and fatigue (36% in s.c. and 31% in i.v. groups). Treatment-emergent AEs were frequent, with anemia occurring in 39% of the s.c. group, while decreased lymphocyte counts (44%) and infections (31%) were common in the i.v. cohortition to PSMA [57], other targets for bispecific T-cell engagers are under investigation, including Glypican-1, ADAM 17P-1 [58-60]. Overall, bispecific T-cell engagers represent a promising new therapeutic option, showing early signs of clinical efficacy. While further studies are necessary to fully establish their safety and effectiveness, early clinical trials are encouraging.

Gene therapy

This therapeutic approach involves modifying a DNA sequence, either by inserting or deleting base pairs, to correct a genetic abnormality in a particular protein or to target specific molecular pathways. For use in gene therapy, a number of gene-editing tools are being developed. Gene therapies usually entail the encapsulation of DNA nucleotides in vectors, which can be viral or non-viral, and then employ those vectors to transfer the gene to a target area. Once delivered, the gene is integrated into the human genome to modify the DNA sequence and control cellular functions [61]. The core concept of gene therapy is the delivery

of foreign nucleotides to targeted DNA regions within cells of different tissues. Viruses are highly effective in transferring their genetic material to a host, enabling infection. Viral vectors can be administered via intravenous injection or directly into the target tissue. Non-viral vectors, like polymers and nanoparticles, have also been studied for their possible application in gene therapy, namely in the management of prostate cancer. Usually, these non-viral carriers use electrostatic forces to compress DNA, shielding it from deterioration. Since uncontrolled cell growth can arise from a cell's inability to perform programmed cell death, gene treatments also investigate the role of apoptosis in the genesis of cancer [62]. In cancerous cells, genetic mutations often result in the suppression of apoptosis. Gene therapy for PCa focuses on targeting cellular apoptosis pathways by introducing genes that encode mediators or inducers of apoptosis in defective cells. Genes that induce apoptosis, such as caspases, promote cell death specifically in cancerous cells [63]. Despite several challenges ahead, such as improving the efficiency of DNA transfer to cells and overcoming immune responses that hinder gene expression, gene therapy is poised to become a prominent future treatment for prostate cancer. Clinical trials investigating PCa gene therapy have explored the use of various transgenes, including p53 and herpes simplex tk [64]. Current gene therapy approaches for PCa seek to enhance the immune system's anticancer response, correct aberrant gene expression, target essential cellular functions, take advantage of programmed cell death mechanisms, activate mutant or cell-lytic suicide genes, and combine treatment with chemotherapy or radiation therapy [65]. Since the majority of the therapeutic dose was given directly to the prostate in animal tests, intraprostatic delivery of gene therapy systems has proven more effective. The therapy was also able to reach metastases of PCa thanks to this tailored delivery. Two adaptable proteins that can attach to iron-binding proteins—which are frequently overexpressed in prostate cancer cells are lactoferrin and transferrin. [66]. Because high quantities of iron can have negative effects such as increasing the risk of bacterial infections, producing free radicals, and encouraging the oxidation of ferrous ions (Fe^{2+}) into ferric ions (Fe^{3+}), these proteins are essential for controlling free iron levels. Transferrin and lactoferrin have been used in a number of animal experiments to actively target prostate cancer cells. One potential marker for PCa is the surface antigen known as prostate stem cell antigen (PSCA), which is expressed in both androgen-dependent and androgen-independent prostate cancer cells. Another useful marker is the human epidermal growth factor receptor 2 (HER2), which can be targeted for PCa treatment due to tumor cell overexpression resulting from mutations [67]. In a study using prostate cancer-induced xenograft mice, inhibition of HER2 and the epidermal growth factor receptor (EGFR) by targeting tumor-initiating cells significantly enhanced chemotherapy efficacy in treating castration-resistant PCa with activated STAT3. Additionally, it prevented metastasis by blocking EGF-induced STAT3 phosphorylation, a key factor in PCa spread [68]. Immune response therapies have also been investigated through a variety of gene-targeting techniques. For example, the use of a DAB-Lf dendriplex expressing IL12 has significantly reduced tumor size in PC3 and DU145 prostate tumor models. A number of microRNAs (miRNAs) are downregulated in patients with prostate cancer; these include miR-205, miR-455-3p, miR-23b, miR-221, miR-222, miR-30c, miR-224, and miR-505. These miRNAs are linked to tumor-suppressive activities that affect aerobic glycolysis, invasion, and cell proliferation. MiR-663a and miR-1225-5p have been linked to PCa development and show potential as candidate markers, though their specific roles in promoting PCa growth and tumor progression remain unclear [69-71].

Nanotechnology

Pharmacology, biomedical science, and nanotechnology are all combined in the interdisciplinary subject of nanotechnology. The characteristics of nanoparticles include improved medication efficacy, ease tumor penetration, resistance to drug degradation, and the ability to be tailored to target particular tissues [72]. Numerous nanoparticle types have been extensively researched for potential use in the diagnosis and treatment of prostate cancer. Polymers, metal nanomaterials, liposomes, and porous silicon nanoparticles are a few of them. When creating active targeting nanoparticles, peptides, oligosaccharides, antibodies, or modified surfaces are utilized. These targeting ligands direct the nanoparticles to receptor cells on cancer cells, such as PSMA receptors on prostate cancer cells [73]. Nanoparticles are being explored for PCa therapy due to limitations in current treatment options. In a study conducted at Mount Sinai in New York involving 16 patients, gold silica nanoparticles were used to treat localized prostate cancer. These nanoparticles were designed to absorb infrared light at wavelengths that could penetrate biological tissues. The gold nanoparticles exhibited plasmon resonance, which helped minimize therapy-related side effects. Patients received intravenous injections of gold nanoparticles followed by laser ablation, and tumor growth was monitored using MRI at 48 and 72 hours post-treatment. The results showed a reduction in tumor size with no adverse side effects. A study on targeted and controlled release for PCa therapy has just entered clinical trials, resulting to the development of BIND-014, a nanoparticle prototype encapsulating docetaxel, despite the fact that very few medicines based on nanoparticles have made it that far [74]. Future PCa treatments may benefit greatly from liposomal encapsulation, according to encouraging preclinical and clinical developments in liposomal drug delivery. Nanocarriers have proven useful in combination therapies by addressing pharmacokinetic variations in chemotherapeutic agents [75]. By integrating nanotechnology with other therapeutic strategies, drug efficacy can be significantly improved. Nanotechnology is used in PCa for both therapeutic and diagnostic purposes. In addition to being effective drug delivery vehicles, nanoparticles also improve the solubility of medications that have low water solubility. Multifunctional nanoparticles show excellent selectivity for urological malignancies, such as tumors of the bladder, kidneys, and prostate. A study performed using nanocarriers to co-deliver docetaxel (DOC) and doxorubicin (DOX) showed that these agents enhanced each other's therapeutic efficacy in a xenograft mouse model of androgen-dependent and androgen-independent prostate cancer cell lines [76]. Additionally, the safety and effectiveness of BIND-014, a docetaxel-containing nanoparticle formulation, were investigated in a multicenter phase II open-label clinical trial including 42 patients with progressing mCRPC. Targeting PSMA, this nanoparticle demonstrated therapeutic efficacy in decreasing circulating tumor cells in patients by the targeted administration of docetaxel [77].

Clinical trials for PCa have extensively investigated the use of magnetic nanoparticles as a contemporary method of tumor heating. In one study, magnetic nanoparticle thermotherapy was investigated, either in isolation or in conjunction with permanent seed brachytherapy. The viability and tolerability of this approach were evaluated using the first prototype of an alternating magnetic field applicator. The results showed that, even at modest magnetic field strengths of 4-5 kA/m, magnetic nanoparticle thermotherapy may cause hyperthermia and raise the prostate's temperature to thermoablative levels [78]. With advances in molecular techniques, a new generation of large-scale, population-based studies has been initiated to evaluate both the individual and combined effects of these treatments [79].

Conclusions

Prostate cancer ranks among the leading causes of death in men worldwide, second only to lung disease. Mutations in specific genes, proteins, and pathways linked to an increased risk of PCa can serve as biomarkers, offering insights into the stage and underlying causes of the disease. These biomarkers can also help determine the most appropriate treatment. Current treatments, such as chemotherapy, radiotherapy, and hormonal therapies, benefit only a limited number of patients. Drug resistance also poses a major challenge in cancer treatment. While these therapies still provide some therapeutic benefit in clinical settings. Still up for debate, though, are the best ways to administer these new drugs to patients and classify them. More research is required to investigate the potential impact of reordering previous treatment sequences on the effectiveness of novel immunotherapies.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021, 71(3): 209-249.

2. Kouspou MM, Fong JE, Brew N, Hsiao ST, Davidson SL, Choyke PL, Crispino T, Jain S, Jenster GW, Knudsen BS et al: The Movember Prostate Cancer Landscape Analysis: an assessment of unmet research needs. Nat Rev Urol 2020, 17(9): 499-512.

3. Løvf M, Zhao S, Axcrona U, Johannessen B, Bakken AC, Carm KT, Hoff AM, Myklebost O, Meza-Zepeda LA, Lie AK et al: Multifocal primary prostate cancer exhibits high degree of genomic heterogeneity. Eur Urol 2019, 75(3): 498-505.

4. Andreoiu M, Cheng L: Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. Human Pathol 2010, 41(6): 781-793.

5. Wei L, Wang J, Lampert E, Schlanger S, DePriest AD, Hu Q, Gomez EC, Murakam M, Glenn ST, Conroy J et al: Intratumoral and intertumoral genomic heterogeneity of multifocal localized prostate cancer impacts molecular classifications and genomic prognosticators. Eur Urol 2017 71(2): 183-192.

6. Lindberg J, Klevebring D, Liu W, Neiman M, Xu J, Wiklund P, Wiklund F, Mills IG, Egevad L, Grönberg H et al: Exome sequencing of prostate cancer supports the hypothesis of independent tumour origins. Eur rol 2013, 63(2): 347-353.

7. Su F, Zhang W, Zhang D, Zhang Y, Pang C, Huang Y, Wang M, Cui L, He L, Zhang J et al: Spatial intratumor genomic heterogeneity within localized prostate cancer revealed by single-nucleus sequencing. Eur Urol 2018, 74(5): 551-559.

8. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, Albertsen H, Joslyn G, Stevens J, Spirio L, Robertson M et al: Identification and characterization of the familial adenomatous polyposis coli gene. Cell 1991, 66(3): 589-600.

9. Shen MM, Abate-Shen C: Molecular genetics of prostate cancer: new prospects for old challenges. Genes Dev 2010, 24(18): 1967-2000.

10. Amirrad F, Pytak PA, SadeghianiPelar N, Nguyen J, Cauble EL, Jones AC, Bisoffi M: Prostate field cancerization and exosomes: Association between CD9, early growth response 1 and fatty acid synthase. Int J Oncol 2020, 56(4): 957-968.

11. Tretiakova MS, Wei W, Boyer HD, Newcomb LF, Hawley S, Auman H, Vakar-Lopez F, McKenney JK, Fazli L, Simko J et al: Prognostic value of Ki67 in localized prostate carcinoma: a multi-institutional study of > 1000 prostatectomies. Prostate Cancer Prostatic Dis 2016, 19(3): 264-270.

12. Catalona WJ, Smith DS, Ratliff TL, Basler JW: Detection of organ-confined prostate cancer is increased through prostate-specific antigen-bases screening. JAMA 1993, 270 (8): 948-954.

13. Hole KH, Axcrona K, Lie AK, Vlatkovic L, Geier OM, Brennhovd B, Knutstad K, Olsen DR, Seierstad T: Routine pelvic MRI using phased-array coil for detection of extraprostatic tumour extension: accuracy and clinical significance. Eur Radiol 2013, 23(4): 1158-1166.

14. Baco E, Ukimura O, Rud E, Vlatkovic L, Svindland A, Aron M, Palmer S, Matsugasumi T, Marien A, Bernhard JC: Magnetic resonance imaging-transectal ultrasound image-fusion biopsies accurately characterize the index tumor: correlation with step-sectioned radical prostatectomy specimens in 135 patients. Eur Urol 2015, 67(4):787-794.

15. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, Bottomley D, Eggener S, Ehdaie B, Emberton M et al: Focal therapy: patients, interventions, and outcomes-a report from a consensus meeting. Eur Urol 2015, 67(4): 771-777.

16. Abeshouse A, Ahn J, Akbani R, Ally A, Amin S, Andry CD, Annala M, Aprikian A, Armenia J, Arora A et al: The molecular taxonomy of primary prostate cancer. Cell 2015, 163(4): 1011-1025.

17. Platz EA, Kulac I, Barber JR, Drake CG, Joshu CE, Nelson WG, Lucia MS, Klein EA, Lippman SM, Parnes HL et al: A prospective study of chronic inflammation in benign prostate tissue and risk of prostate cancer: linked PCPT and SELECT cohorts. Cancer Epidemiol Biomarkers Prev 2017, 26(10): 1549-1557.

18. Iczkowski KA, Torkko KC, Wilson RS, Lucia MS, Bostwick DG: Prostatic atrophy: its spatial proximity to carcinoma and intraepithelial neoplasia based on annotation of digital slides. Hum Pathol 2014, 45(1): 54-58.

19. Kim TJ, Koo KC: Current status and future perspectives of checkpoint inhibitor immunotherapy for prostate cancer: a comprehensive review. Int J Mol Sci 2020, 21(15): 5484.

20. Graff JN, Liang LW, Kim J, Stenzl A: KEYNOTE-641: a Phase III study of pembrolizumab plus enzalutamide for metastatic castration-resistant prostate cancer. Future Oncol 2021, 17(23): 3017-3026.

21. Petrylak DP, Ratta R, Gafanov R, Facchini G, Piulats JM, Kramer G, Flaig TW, Chandana SR, Li B, Burgents J et al: KEYNOTE-921: Phase III study of pembrolizumab plus docetaxel for metastatic castration-resistant prostate cancer. Future Oncol 2021, 17(25): 3291-3299.

22. Gratzke C, Niu C, Poehlein C, Burgents J: 346 KEYNOTE-991: Phase 3 study of pembrolizumab plus enzalutamide and androgen

deprivation therapy (ADT) for patients with metastatic hormone-sensitive prostate cancer (mHSPC). J Immunother Cancer 2020, 8: A371.

23. Joshua AM, Gurney H, Retz M, Tafreshi A, Fong PC, Shore ND, Romano E, Augustin M, Piulats JM, Berry WR et al: 217O Pembrolizumab (pembro) combination therapies in patients with metastatic castration-resistant prostate cancer (mCRPC): Cohorts AC of the phase Ib/II KEYNOTE-365 study. Ann Oncol 2020, 31: S1325.

24. Kumar V, Patel S, Tcyganov E, Gabrilovich DI: The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol 2016, 37(3): 208-220.

25. Chabanon RM, Pedrero M, Lefebvre C, Marabelle A, Soria JC, Postel-Vinay S: Mutational landscape and sensitivity to immune checkpoint blockers. Clin Canc Res 2016, 22(17): 4309-4321.

26. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, Jamal-Hanjani M, Wilson GA, Birkbak NJ, Hiley CT et al: Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016, 351(6280): 1463-1469.

27. Liu G, Lu S, Wang X, Page ST, Higano CS, Plymate SR, Greenberg NM, Sun S, Li Z, Wu JD et al: Perturbation of NK cell peripheral homeostasis accelerates prostate carcinoma metastasis. J Clin Invest 2013, 123(10): 4410-4422.

28. Pal SK, Moreira D, Won H, White SW, Duttagupta P, Lucia M, Jones J, Hsu J, Kortylewski M et al: Reduced T-cell numbers and elevated levels of immunomodulatory cytokines in metastatic prostate cancer patients de novo resistant to abiraterone and/or enzalutamide therapy. Intl J Mol Sci 2019, 20(8): 1831.

29. Chi N, Tan Z, Ma K, Bao L, Yun Z: Increased circulating myeloid-derived suppressor cells correlate with cancer stages, interleukin-8 and-6 in prostate cancer. Intl J Clin Exp Med 2014, 7(10): 3181-3192

30. Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, Takahashi H, Kuk C, Kovylina M, Aldaoud N et al: Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst 2013, 105(14): 1050-8.

31. Maleki Vareki S: High and low mutational burden tumors versus immunologically hot and cold tumors and response to immune checkpoint inhibitors. J Immunother Cancer 2018, 6(1): 157.

32. Chen YP, Zhang Y, Lv JW, Li YQ, Wang YQ, He QM, Yang XJ, Sun Y, Mao YP, Yun JP et al: Genomic analysis of tumor microenvironment immune types across 14 solid cancer types: immunotherapeutic implications. Theranostics 2017, 7(14): 3585-3594.

33. Cheever MA, Higano CS: PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. Clin Cancer Res 2011, 17(11): 3520-3526.

34. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R et al: Sipuleucel-T immunotherapy for castration-resistant prostate cancer. New Engl J Med 2010, 363(5): 411-422.

35. Kobiyama K, Jounai N, Aoshi T, Tozuka M, Takeshita F, Coban C, Ishii KJ: Innate immune signaling by, and genetic adjuvants for DNA vaccination. Vaccines 2013, 1(3): 278-292.

36. Kyriakopoulos CE, Eickhoff JC, Ferrari AC, Schweizer MT, Wargowski E, Olson BM, McNeel DG: Multicenter phase I trial of a DNA vaccine encoding the androgen receptor ligand-binding domain (pTVG-AR, MVI-118) in patients with metastatic prostate cancer. Clin Cancer Res 2020, 26(19): 5162-5171.

37. Shore ND, Morrow MP, McMullan T, Kraynyak KA, Sylvester A, Bhatt K, Cheung J, Boyer JD, Liu L, Sacchetta B et al: CD8+ T cells impact rising PSA in biochemically relapsed cancer patients using immunotherapy targeting tumor-associated antigens. Mol Ther 2020, 28(5): 1238-1250.

38. Gulley JL, Madan RA, Tsang KY, Jochems C, Marté JL, Farsaci B, Tucker JA, Hodge JW, Liewehr DJ, Steinberg SM et al: Immune impact induced by PROSTVAC (PSA-TRICOM), a therapeutic vaccine for prostate cancer. Cancer Immunol Res 2014, 2(2): 133-141.

39. Kantoff PW, Gulley JL, Pico-Navarro C: Revised overall survival analysis of a phase II, randomized, double-blind, controlled study of PROSTVAC in men with metastatic castration-resistant prostate cancer. J Clin Oncol 2017, 35(1): 124-125.

40. Gulley JL, Borre M, Vogelzang NJ, Ng S, Agarwal N, Parker CC, Pook DW, Rathenborg P, Flaig TW, Carles J et al: Phase III trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. J Clin Oncol 2019, 37(13): 1051-1061.

41. Stenzl A: Re: Phase III Trial of PROSTVAC in Asymptomatic or Minimally Symptomatic Metastatic Castration-resistant Prostate Cancer. Eur Urol 2019, 77(1): 131-132.

42. Simons JW, Sacks N: Granulocyte-macrophage colony-stimulating factor− transduced allogeneic cancer cellular immunotherapy: The GVAX® vaccine for prostate cancer. Urol Oncol 2006, 24(5): 419-424.

43. Gamat-Huber M, Jeon D, Johnson LE, Moseman JE, Muralidhar A, Potluri HK, Rastogi I, Wargowski E, Zahm CD, McNeel DG et al: Treatment combinations with DNA vaccines for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Cancers 2020, 12(10): 2831.

44. Obradovic AZ, Dallos MC, Zahurak ML, Partin AW, Schaeffer EM, Ross AE, Allaf ME, Nirschl TR, Liu D, Chapman CG et al: T-cell infiltration and adaptive Treg resistance in response to androgen deprivation with or without vaccination in localized prostate cancer. Clin Cancer Res 2020, 26(13): 3182-3192.

45. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME: Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat Rev Cancer 2008, 8(4): 299-308.

46. Fu J, Shang Y, Qian Z, Hou J, Yan F, Liu G, Dehua L, Tian X: Chimeric Antigen receptor-T (CAR-T) cells targeting Epithelial cell adhesion molecule (EpCAM) can inhibit tumor growth in ovarian cancer mouse model. J Vet Med Sci 2021, 83(2): 241-247.

47. Bębnowska D, Grywalska E, Niedźwiedzka-Rystwej P, Sosnowska-Pasiarska B, Smok-Kalwat J, Pasiarski M, Góźdź S, Roliński J, Polkowski W: CAR-T cell therapy-an overview of targets in gastric cancer. J Clin Med 2020, 9(6): 1894.

48. He C, Zhou Y, Li Z, Farooq MA, Ajmal I, Zhang H, Zhang L, Tao L, Yao J, Du B et al: Co-expression of IL-7 improves NKG2D-based CAR T cell therapy on prostate cancer by enhancing the expansion and inhibiting the apoptosis and exhaustion. Cancers 2020, 12(7): 1969.

49. Narayan V, Barber-Rotenberg JS, Jung IY, Lacey SF, Rech AJ, Davis MM, Hwang WT, Lal P, Carpenter EL, Maude SL et al: PSMA-targeting TGFβ-insensitive armored CAR T cells in metastatic castration-resistant prostate cancer: a phase 1 trial. Nat Med 2022, 28(4): 724-734.

50. Rosa K: OncLive https://www.onclive.com/ view/p-psma-101-elicits-encouraging-response in metastatic castrationresistant prostate cancer (May 2022).

51. Krueger TE, Thorek DL, Meeker AK, Isaacs JT, Brennen WN: Tumor-infiltrating mesenchymal stem cells: Drivers of the immunosuppressive tumor microenvironment in prostate cancer? Prostate 2019, 79(3): 320-330.

52. Li W, Zhao K, Kirberger M, Liao W, Yan Y: Next generation sequencing technologies in cancer diagnostics and therapeutics: A mini review. Cell Mol Biol 2015, 61(5): 91-102.

53. Yunger S, Bar El A, Zeltzer LA, Fridman E, Raviv G, Laufer M, Schachter J, Markel G, Itzhaki O, Besser MJ et al: Tumor-infiltrating lymphocytes from human prostate tumors reveal anti-tumor reactivity and potential for adoptive cell therapy. Oncoimmunology 2019, 8(12): e1672494.

54. Lee HW, Nam KO, Park SJ, Kwon BS: 4-1BB enhances CD8+ T cell expansion by regulating cell cycle progression through changes in expression of cyclins D and E and cyclin-dependent kinase inhibitor

p27kip1. Eur J Immunol 2003, 33(8): 2133-2141.

55. Sartor O, De Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G et al: Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021, 385(12): 1091-1103.

56. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foà R, Bassan R et al: Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017, 376(9): 836-847.

57. Hummel HD, Kufer P, Grüllich C, Seggewiss-Bernhardt R, Deschler-Baier B, Chatterjee M, Goebeler ME, Miller K, de Santis M, Loidl W et al: Pasotuxizumab, a BiTE® immune therapy for castration-resistant prostate cancer: Phase I, dose-escalation study findings. Immunotherapy 2021, 13(2): 125-141.

58. Lund ME, Howard CB, Thurecht KJ, Campbell DH, Mahler SM, Walsh BJ: A bispecific T cell engager targeting Glypican-1 redirects T cell cytolytic activity to kill prostate cancer cells. BMC Cancer 2020, 20(1): 1214.

59. Yamamoto K, Trad A, Baumgart A, Hüske L, Lorenzen I, Chalaris A, Grötzinger J, Dechow T, Scheller J, Rose-John S et al: A novel bispecific single-chain antibody for ADAM17 and CD3 induces T-cell-mediated lysis of prostate cancer cells. Biochem J 2012, 445(1): 135-144.

60. Lin TY, Park JA, Long A, Guo HF, Cheung NK: Novel potent anti-STEAP1 bispecific antibody to redirect T cells for cancer immunotherapy. J Immunother Cancer 2021, 9(9): e003114.

61. Gori JL, Hsu PD, Maeder ML, Shen S, Welstead GG, Bumcrot D: Delivery and specificity of CRISPR/Cas9 genome editing technologies for human gene therapy. Hum Gene Ther 2015, 26(7): 443-451.

62. Chen YH, Keiser MS, Davidson BL: Viral vectors for gene transfer. Curr Protoc Mouse Biol 2018, 8(4): e58.

63. Jan R: Understanding apoptosis and apoptotic pathways targeted cancer therapeutics. Adv Pharm Bull 2019, 9(2): 205-218.

64. Verma AK, Mandal S, Tiwari A, Monachesi C, Catassi GN, Srivastava A, Gatti S, Lionetti E, Catassi C: Current status and perspectives on the application of CRISPR/Cas9 gene-editing system to develop a low-gluten, non-transgenic wheat variety. Foods 2021, 10(10): 2351.

65. Singh V, Khurana A, Navik U, Allawadhi P, Bharani KK, Weiskirchen R: Apoptosis and pharmacological therapies for targeting thereof for cancer therapeutics. Sci 2022, 4(2): 15.

66. Sharifi N, Salmaninejad A, Ferdosi S, Bajestani AN, Khaleghiyan M, Estiar MA, Jamali M, Nowroozi MR, Shakoori A: HER2 gene amplification in patients with prostate cancer: Evaluating a CISH-based method. Oncol Lett 2016, 12(6): 4651-4658.

67. Rossini A, Giussani M, Ripamonti F, Aiello P, Regondi V, Balsari A, Triulzi T, Tagliabue E: Combined targeting of EGFR and HER2 against prostate cancer stem cells. Cancer Biol Ther 2020, 21(5): 463-475.

68. Jiang FN, Liang YX, Wei W, Zou CY, Chen GX, Wan YP, Liu ZZ, Yang Y, Han ZD, Zhu JG, et al: Functional classification of prostate cancer-associated miRNAs through CRISPR/Cas9-mediated gene knockout. Mol Med Rep 2020, 22(5): 3777-3784.

69. Desai N, Momin M, Khan T, Gharat S, Ningthoujam RS, Omri A: Metallic nanoparticles as drug delivery system for the treatment of cancer. Exper Opin Drug Deliv 2021, 18(9): 1261-1290.

70. Mount Sinai School of Medicine: Gold Nanoparticles Shown to Be Safe and Effective Treatment for Prostate Cancer. 2019. Available online: https://www.sciencedaily.com/releases/2019/08/190827123513.htm (accessed on 21 July 2022).

71. Sanna V, Pala N, Sechi M: Targeted therapy using nanotechnology: focus on cancer. Int J Nanomedicine 2014, 9: 467-483.

72. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, Shao A et al: Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Front Mol Biosci 2020, 7:

193.

73. Friedman AD, E Claypool S, Liu R: The smart targeting of nanoparticles. Curr Pharm Des 2013, 19(35): 6315-6329.

74. Matowa PR, Gundidza M, Gwanzura L, Nhachi CF: A survey of ethnomedicinal plants used to treat cancer by traditional medicine practitioners in Zimbabwe. BMC Complement Med Ther 2020, 20(1): 278.

75. Sanna V, Pala N, Sechi M: Targeted therapy using nanotechnology: focus on cancer. Int J Nanomedicine 2014, 9: 467-483.

76. Li K, Zhan W, Chen Y, Jha RK, Chen X: Docetaxel and doxorubicin codelivery by nanocarriers for synergistic treatment of prostate cancer. Front Pharmacol 2019, 10: 1436.

77. Autio KA, Dreicer R, Anderson J, Garcia JA, Alva A, Hart LL, Milowsky MI, Posadas EM, Ryan CJ, Graf RP et al: Safety and efficacy of BIND-014, a docetaxel nanoparticle targeting prostate-specific membrane antigen for patients with metastatic castration-resistant prostate cancer: a phase 2 clinical trial. JAMA Oncol 2018, 4(10): 1344-1351.

78. He MH, Chen L, Zheng T, Tu Y, He Q, Fu HL, Lin JC, Zhang W, Shu G, He L et al: Potential applications of nanotechnology in urological cancer. Front Pharmacol 2018, 9: 745.

79. Habib A, Jaffar G, Khalid MS, Hussain Z, Zainab SW, Ashraf Z, Haroon A, Javed R, Khalid B, Habib P: Risk factors associated with prostate cancer. J Drug Deliv Ther 2021, 11(2): 188-193.

80. Strohl WR, Naso M: Bispecific T-cell redirection versus chimeric antigen receptor (CAR)-T cells as approaches to kill cancer cells. Antibodies 2019, 8(3): 41.