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Immune Checkpoint Inhibitors Therapy in Prostate Cancer: Lessons Learnt

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Review Article

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Abstract

Immune checkpoint inhibitors (ICIs) therapy has rapidly changed the treatment landscape for a number of cancers but resulted in only marginal success in prostate cancer (PCa). In order to bring about durable clinical benefit of immune check point inhibitor therapy in prostate cancer, it is critical to understand the current status of ICIs therapy for PCa and reasons for low/negligible outcomes. This article summarizes the current status of ICIs therapy in PCa and discusses how ICIs therapy can result in the successful treatment of a specific subset of PCa patients. In this article, we review how immunotherapy and different combination therapies are paving their way by incorporating the strategies of converting the "cold" PCa tumor into "hot", role of genomic landscape of PCa in influencing the outcome of ICIs therapy, what are the promising novel biomarker candidates, which can guide the patient selection for ICIs therapy and help in monitoring the efficacy of treatment. This article highlights that ICIs therapy hold a promising future in subset of PCa patients.

Keywords: Immune Checkpoint Inhibitors (ICIs); Prostate Cancer (PCa); Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Abbreviations: ICIs: Immune Checkpoint Inhibitors; PCa: Prostate Cancer; ADT: Androgen Deprivation Therapy; mCRPC: Metastatic Castration-Resistant Prostate Cancer; DCR: Disease Control Rate; ATM: Ataxia-Telangiesctasia Mutated; DDR: DNA Damage Repair; HRD: Homologous Recombination Deficiency; MANAs: Mutation-Associated Neoantigens; NSCLC: Non-Small-Cell Lung Cancer; HR: Homologous Recombination; DMMR: DNA Mismatch Repair; TIME: Tumor Immune Microenvironment; TAMs: Tumor-Associated Macrophages; RT: Radiation Therapy; OS: Overall Survival; BRD4: Bromodomain-Containing Protein 4; EZH2: Enhancer of Zeste Homolog-2; PARP: Poly ADP-Ribose Polymerase; IFN: Interferon.

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed malignant tumor in men, and a major cause of mortality, with more than a million new cases and 359,000 deaths world-wide, in 2018 [1]. The range of currently prevalent treatment options for PCa (surgery, radiation, androgen deprivation and chemotherapy) pose adverse effects and show very limited efficacy for metastatic and treatment resistant disease [2]. PCa patients respond to androgen deprivation therapy (ADT) initially but almost all patients progress to metastatic castration-resistant prostate cancer (mCRPC) [3]. Food and Drug Administration (FDA) approved chemotherapy treatments for mCRPC, docetaxel and cabazitaxel, in combination with enzalutamide, abiraterone and Sipuleucel-T (Sip-T dendritic cell vaccine) [4-9], only increase median survival benefit by 2-4 months [10,11]. Other therapies are therefore being explored to treat mCRPC patients, and one of the most promising ones is immunotherapy with immune check point inhibitors

(ICIs). Clinical data suggests that 5-12% of mCRPC patients benefit from immune check point blockade [12,13]. Immune checkpoint inhibitors are antibodies that target regulatory or co-inhibitory signaling molecules, including cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1). These three proteins are called immune check points, since overexpression of these proteins by tumor cells or T cells is one of the mechanisms that tumor cells employ to evade T cell mediated attack, enabling proliferation of tumor cells. Blocking these markers leads to activation of T cell and anti-tumor response [14]. PD-1/PD-L1 inhibition is one of the most promising immunotherapies across many different refractory cancers including melanoma, non-small-cell lung carcinoma, and renal cell carcinomas [15-16] and yet the effectivity of this approach in many cancers including PCa is very limited [17,18]. In this article, we focus on the current status of ICIs therapy for PCa, reasons for low/negligible objective responses, ways to make ICIs therapy a viable option with durable clinical benefit in PCa and the associated challenges to achieve this goal.

Monotherapy with ICIs in PCa

Ipilimumab, an antibody against CTLA-4, known to block the inhibition of T cell response and allow immune cells to recognize and kill tumor cells, was approved by FDA in 2011 to treat metastatic melanoma [19]. Randomized Phase III clinical trials with Ipilimumab in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve castration-resistant prostate cancer showed some clinical antitumor activity but subsequent Phase III trials failed to show significant difference in overall survival [18,20]. Therapies targeting the PD-1, Nivolumab also did not result in significant objective clinical responses for PCa patients [16,21]. In spite of these early disappointing results, the enthusiasm to investigate ICIs in PCa remains high and the monotherapy clinical trials using anti-PD1 antibody, Pembrolizumab in mCRPC for PD-L1 positive, PD-L1 negative and bone metastasis/non-measurable disease (NCT02787005) are still active. The currently available results from these clinical trials indicate that the median overall survival ranged from 7.9 to 14.1 months, and that the disease control rate (DCR) are 10%, 9% and 22% in PD-L1-positive, PD-L1-negative, and bone-predominant non-measurable disease patients, respectively [22]. Though these results indicate only modest antitumor activity, further analysis displayed marginal increase in response with patients harboring mutations in breast cancer gene (BRCA1/2) or Ataxia-Telangiesctasia mutated (ATM) gene (objective response rate (ORR) 11%) [22]. Similarly, other clinical trial results [23,24] also suggest that monotherapy with PD-1/PD-L1 ICIs is not enough to deliver significant responses.

Combination Therapy with ICIs in PCa

Despite the low success rate of PD-1/PD-L1 therapy in PCa, PD-1/PD-L1 axis remains an area of therapeutic interest in advanced PCa as the expression of PD-L1 is up regulated in mCRPC4, and PD-L1 expression increases with other treatments [25-27], drawing attention to the PD-L1 blockade in combination with other therapeutic modalities. A CRPC preclinical study, using radiotherapy in combination with anti-PD-1 and anti-PD-L1 increased the median survival rates to 70% and 130%, respectively, compared to the drug alone, demonstrating that robust responses are achievable in PCa by combining anti-PD-1/PD-L1 blockade therapy with other modalities [28]. Several clinical trials using PD-1/PD-L1 antibodies with different therapies/vaccines like PROSTVAC (NCT02933255), pTVG-HP (NCT03600350), chemotherapy (NCT03572478, NCT03170960, NCT03673787), radium-223 (NCT03093428, NCT02814669), Sip-T (NCT03024216), and CTLA-4 checkpoint inhibitors (NCT03333616) are in progress to assess the efficacy of ICIs combination therapy for PCa. A clinical trial (Phase Ib/II) for mCRPC patients, involving Pembrolizumab with anti-hormonal therapy, docetaxel, or targeted therapy with poly-ADP ribose polymerase (PARP) inhibitor (KEYNOTE-365) is currently active and showing promising outcomes. In another phase II study, where 10 patients were treated with enzalutamide (anti-androgen drug) and Pembrolizumab (anti-PD-1 antibody), 5 patients showed reduction in PSA levels and tumor size [12].

The anti-CTLA-4 antibody, Ipilimumab, is also being tested in clinical trials with radiation (NCT03477864), Nivolumab (anti-PD-1 antibody) [NCT03333616, NCT03061539, NCT02985957 (Checkmate 650)], chemotherapy (NCT03098160, NCT01688492), and AST (NCT01498978).

The combination of Nivolumab and Ipilimumab for mCRPC patients (Checkmate650) displayed impressive clinical responses in patients who showed PD-L1-positivity, DNA damage repair (DDR) mutations, homologous recombination deficiency (HRD), and high tumor mutational burden (TMB). The outcome of this study has generated enthusiasm, to explore the role of genomic landscape to improve clinical outcomes in PCa patients, using ICIs therapy.

Genomic Landscape of PCa and ICIs

Large-scale genomic analysis identifying specific genetic mutations will enhance our understanding, and how genomic characteristics of tumor can shape the future of ICIs therapy in PCa. It is known that tumors that have high somatic mutational load, especially nonsynonymous alterations, lead to more mutation-associated neoantigens (MANAs) that are recognized by the T cells which attack the

tumor [29]. PD-1 therapy has proved to be successful in both Melanoma [19,30] and Non-Small-Cell Lung Cancer (NSCLC) cancers [31,32] which show a high mutational load. PCa is generally not considered a cancer with high mutational load since on average, PCa has between 50–100 nonsynonymous DNA alterations per cancer exome (i.e. 1-2 mutations per Mb) [33]. A comprehensive multi-institutional study of mCRPC tumors done by Robinson, et al. revealed that 8-12% of patients harbor either germ line mutations or 20-25% acquires somatic mutations in genes involved in homologous recombination (HR) repair [34]. The association of HR mutations, including mismatch repair (MMR) mutations with high PD-L1 expression and increase in T cell infiltration, makes ICIs therapy a very relevant option for HR-deficient advanced PCa patients [35]. A study by Pritchar, et al. [36], indicates that 5-12% of advanced PCa patients may be hypermutated due to MMR gene mutations and Microsatellite Instability-High (MSI-H) phenotypes [37]. This subgroup of patients may benefit from Pembrolizumab, an FDA approved drug for treatment of solid tumors with DNA mismatch repair (dMMR) mutations.

A comprehensive analysis of genomics, transcriptomics, and clinical data from 124 mCRPC patients allowed the identification of two distinct dMMR-associated mutational signatures that are prevalent in advanced PCa [38]. These mutational signatures were also associated with higher immune cell infiltration (including subsets of T cells, NK cells, and myeloid cells), increased expression of T cell related transcripts, and PD-L1 and PD-L2 expression, indicating that in some dMMR metastatic CRPC patients, the efficacy of ICIs can be enhanced via developing different combination strategies aimed at depleting the myeloid subsets in tumor.

Another interesting report identified a novel genetic subtype of PCa, where mutations in the transcription-regulating gene CDK12 [39] were associated with a very high neoantigen burden and increased infiltration of T cells, recommending this subset of PCa patients as a good candidate for ICIs therapy. A phase II trial of 17 mCRPC patients treated with PD-L1 inhibitor, Durvalumab, and Olaparib, a PARP inhibitor, indicated that 35% (6/17) who harbored DNA Damage Repair (DDR) mutation (all at BRCA2 lesions) responded better to the combination therapy [40]. The trial is now expanding to recruit 50 mCRPC patients.

Study from Abida, et al. [41] using tumor and germline sequencing for 1033 PCa patients demonstrated that 3.1% of the patients show MSI or dMMR characteristic [41]. Out of 11 patients, 4 patients showed radiographic response, after undergoing PD-1/PD-L1 therapy. They also noticed that 21.9% of the patients had germ line mutations and the rest of them acquired somatic mutations during the disease.

In addition to expression of immune check point molecules and genomic landscape of PCa, the success of ICIs therapy is governed by the type of tumor immune microenvironment (TIME) present in the tumor.

Tumor Immune Microenvironment (TIME): Hindrances to ICIs Therapy

One of the reasons for very limited success of PCa to ICIs, is the presence of antitumor immune suppressive TIME which leads to paucity of immune cell infiltration (immunological "cold" microenvironment) [42,43]. Combinations therapies with ICIs which can change the "cold" PCa TIME to immunologically "hot" by decreasing the immune suppression and driving the T-cells back to the tumor, will bring the long-waited breakthrough for use of ICIs in PCa. The current evidences show that TIME of PCa mainly consists of a sub-population of Tregs and pro-tumorigenic M2-subtype, tumor-associated macrophages (TAMs). TAMs secrete high levels of TGF-β and create an immune suppressive environment in a variety of ways [44,45]. Presence of TGF-β has been shown to favor immune exclusion by influencing the environment towards poor infiltration of TIL [46]. T-regs lead to dampening of the immune response and produce inhibitory cytokines to maintain self-tolerance [47,48]. The presence of chemokines in TIME further contributes to orchestrating the responses towards immune suppression [49-53]. Clinical trials of therapies/agents which reprogram the TIME, leading to immune infiltration, activation of T-cells and enhancing tumor immunity, along with ICIs to remove the breaks, will provide stable clinical benefits in PCa. Developing new non-invasive methods to monitor the efficacy of employed combination therapies will provide insights and explain why some combination therapies are unable to deliver the desired outcomes and how to overcome these barriers.

Converting "Cold Tumor" to "Hot Tumor": Combination Therapy with ICIs

Conventional Therapies: Radiation therapy (RT) alters the TIME by leading to immunogenic cell death, inducing inflammatory cytokines, recruiting dendritic cells and activating tumor-specific T cells [54]. The induction of a potent immune response at the sites of irradiated disease, as well as at distant locations ("abscopal effect") [55,56] makes combination of ICIs with RT an attractive option. Since the immunomodulatory properties of RT depend on dose, fractionation, and site [57-60], incorporating these factors while designing the combination therapy trials will be important for successful outcomes of combination therapy with ICIs. Current evidences from liver and lung cancer studies indicate the safety of the combination of RT with Ipilimumab however no overall survival (OS) benefit to most

patients was noted [60]. The current efforts for RT with ICIs combination in PCa are listed in Table 1.

Chemotherapy in combination with ICIs is currently used as the standard of care in triple-negative breast cancer and lung cancer [61-64]. Cytotoxic chemotherapy with ICIs has been shown to reduce tumor burden, activate antigen cascade, and reduce MDSCs [65,66]. Chemotherapy with ICIs becomes an attractive option for a cancer like PCa which is sensitive to taxane, allowing docetaxel and paclitaxel to be investigated. The ongoing clinical trials of chemotherapy with ICIs are mentioned in Table 1.

Therapies	Active Clinical Trials
Radiotherapy	NCT03543189, NCT03795207,NCT03217747,NCT01303705
Chemotherapy	NCT03951831, NCT03879122, NCT03248570, NCT03834506
TGF-β	NCT03685591, NCT02452008,
IL-8	NCT03689699
Adenosine pathway	NCT03454451, NCT03629756, NCT04089553
Androgen Deprivation Therapy	NCT03016312, NCT03753243, NCT03543189
PARP Inhibitors	NCT03572478, NCT03330405, NCT02484404, NCT03810105

Table 1: Active Clinical Trials for Combination Therapy with ICIs.

Epigenetics Factors: Epigenetics factors, like p300, bromodomain-containing protein 4 (BRD4) and the enhancer of zeste homolog-2 (EZH2), have shown promising outcomes in PCa treatment [67-69]. PD-L1 correlated with p300 has been involved in progression of PCa [70] and targeting of p300, by p300/CBP inhibitor, A485, combined with anti-PD-L1 antibody, reactivates T-cells function towards anti-tumor immunity, suggesting that the combination of epigenetic factor inhibitor with ICIs enhances the efficacy of ICIs in PCa [70].

EZH2 is involved in chronic inflammation and tumor immune tolerance [71] in the TIME. EZH2 is over-expressed in prostate cancer and is known to negatively regulate IFN response genes [72], affect antigen presentation, Th-1 chemokine signaling [73], and PD-L1 [74]. EZH2 inhibition, combined with PD-1, significantly enhanced anti-tumor response and reprogrammed the TIME by significantly increasing the intra-tumoral trafficking of activated CD8+ T-cells and M-subtype TAMs with concurrent loss of M2-subtype TAMs. Interestingly, monotherapy of EZH2 inhibition or PD-1 fail to display a similar outcome, indicating that the inhibition of EZH2 has the potential to enhance PCa response to PD-1, ICI therapy.

Cytokines: TGF-β present in TIME contributes to the immune suppressive environment and mediates immune resistance in PCa [75]. Hence, altering the level of TGF-β in TIME could offer ways to overcome the barriers in the success of ICIs therapy. Evidence indicates that the combination therapy of ICIs with an anti–TGF-β antibody induced changes in TIME environment and polarized the CD4+ T cells to the Th-1 cell subset with increase in expansion of CD8+ effector memory cells to control tumor growth [76]. Clinical trials investigating the role of TGF-β in combination therapy are listed in Table 1.

IL-8, a proinflammatory cytokine modulated by androgens, has been shown to increase the infiltration of MDSCs [77] and a clinical trial for the use of an IL-8 antibody in combination with Nivolumab and ADT are underway (Table 1).

Adenosine Pathway: Adenosine signaling has evolved as a powerful immuno-metabolic checkpoint in tumors, to target the inhibitory mechanisms in the TIME and reprogram it towards anti-tumor immunity [78]. Initial results of a phase I trial evaluating the A2A receptor inhibitor AZD4653 (which blocks the adenosine from its receptor), alone or in combination with the anti–PD-L1 antibody Durvalumab, showed a response rate of 37.5% in mCRPC patients, with a durable PSA decline greater than 99% in 25% of the patients [79]. Further trials are underway to explore this pathway in PCa patients (Table 1).

Androgen Deprivation Therapy (ADT): ADT is currently used among the first line therapies for mCRPC. Growing evidence indicates that androgens and androgen deprivation have profound effects on the immune system [80], besides affecting prostate tumor cells directly. The interest in use of ADT to modulate tumor cell sensitivity to T-cells and increase the infiltration of T-cell into the prostate [81] is therefore enormous. Clinical trials are currently investigating combinations of ADT and ICIs in mCRPC patients (Table 1).

Poly ADP - Ribose Polymerase (PARP) Inhibitors: Recent evidence show that PARP inhibition can alleviate the resistance and enhance the efficacy of ICIs therapy by promoting cross-presentation and modifying TIME [82-84].

The preliminary results from clinical trial (NCT02484404) indicate that the combination therapy of Olaparib and Durvalumab effectively reduced the tumor burden (measured by PSA reduction> 50%) in 8/17 unselected mCRPC patients [85]. Mutation in DNA damage response (DDR) emerged as a favorable biomarker, to indicate the outcome of the combination therapy (12-month progression-free survival probability of deficient DDR vs. proficient DDR, 83.3% vs. 36.4%, P = 0.03) [85,86]. Additional trials evaluating the efficacy of ICIs and PARP inhibitors combination in mCRPC patients are underway (Table 1).

It is becoming apparent that ICIs therapy in PCa can produce a durable response in subsets of patients. Identification of the subsets of patients who can show favorable/durable response to ICIs therapy is the major challenge. Therefore, the immediate need is to develop reliable biomarkers which can guide patient selection and allow monitoring the efficacy of ICIs therapy.

Predictive Biomarkers for Patient Selection and Response to ICIs Therapy: An Existing Challenge

Currently, most clinical trials do not employ upfront stratification/selection, to enrich the sensitive patient populations. The clinical trial design based on biomarker(s)-based patient-enrichment strategies will offer multi-faceted benefits, like avoiding toxic side effects for patients who do not respond, saving cost, improving the quality of life and better outcome/response rate.

Considering the tumor immune contexture and molecular landscape of PCa, it appears that while single biomarker may pose substantial limitations, a combination of biomarkers which can reveal the interaction of host and tumor could enable a precision medicine approach in ICIs therapy. Potential biomarkers capable of selecting the patients and guiding the ICIs therapy in PCa are discussed below.

PD-L1 Expression: The overexpression of PD-L1 is generally associated with the response rate to ICIs therapy, and whether this holds true in case of PCa, requires further investigation. Using expression of PD-L1 in tumor cells, the initial clinical trial (KEYNOTE-028) insinuated that PD-L1 expression could predict response to ICIs [87,88], but the larger trial (KEYNOTE-199) revealed no change in response rates between the PD-L1-and PD-L1+ cohorts [89], suggesting that PD-L1 may not be a prefect predictive biomarker. Lack of standardization makes this true even in malignancies where it has been associated with clinical outcomes [90-93]. Due to usage of different criteria and assays employed across the trials, the debate is still on to define the parameter that constitutes positivity. Discrepancies in the results could also be attributed to significant inter-tumoral and intra-tumoral heterogeneity of PD-L1 expression, where one tumor sample may not provide adequate representation [94]. Studies also demonstrate that PD-L1 expression is inducible and its expression can change over the course of clinical treatment; hence the use of archival tissue for measuring static PD-L1 may not reflect the true status to guide patient selection and response to ICIs therapy.

Recent studies indicate that tumor cells release exosomes carrying PD-L1, which exert immunomodulatory effects [95], suppress T-cell function and antagonize anti-PD-1 response [96]. The comparison of tumor cell PD-L1 with exosomal PD-L1 suggest that exosomal PD-L1 could be a better choice for being a predictive biomarker, as it reflects the state of the whole-body system and can predict the dynamic progress of the disease. The non-invasive methods of measuring the exosomal PD-L1 will allow testing at multiple time points, will overcome the problems related to tumor heterogeneity and offer differentiation of responders and non-responders during therapy. The changes in level of exosomal PD-L1 itself could be a strong indicator for evaluating the efficacy of anti-PD-1 therapy. In PCa, the level of CD274, which encodes PD-L1 mRNA, is higher than melanoma, which responds well to PD-L1 blockade. This indicates that most of the translated PD-L1 was secreted extracellularly by exosomes, which in fact could be inhibiting the T-cell function and contributing to the resistance to PD-L1 blockade treatment. Removal of exosomal PD-L1 allowed to overcome the resistance to PD-L1 blockade [70,97]. The results from other studies in melanoma and lung cancer [98] further corroborate this concept. All these evidences show strong potential for exosomal PD-L1 as a biomarker for improving the efficacy of ICIs therapy, which could provide appropriate information on clinical outcomes.

Since PCa actively suppresses antitumor immune responses by creating an immune-suppressive microenvironment, the identification of predictive biomarkers that would access the changes in the immune suppressive environment and predict a shift in anti-tumor immunity along with the status of exosomal PD-L1 would be most beneficial. We are currently focused on developing the biomarker(s) to assess the immune suppression status in PCa, which will aid in selecting the specific targeted population for ICIs combination therapy and assessing the outcome of therapy during treatment.

Genomic Biomarkers: As discussed above, tumor mutation burden (TMB), MSI-H/dMMR, CDK12 mutation and DDR defects show potential in identifying the subset of PCa patients who could generate favorable outcome upon ICIs therapy. In this section, we will explore the potential of these to be predictive reliable biomarkers for ICIs therapy.

TMB is a promising biomarker which has been correlated with clinical outcomes in several malignancies [87,99] and the efficacy of PD-1 inhibitors [100]. TMB in metastatic PCa is generally low and only 3 to 8 percent of advanced PCa show tumors with high TMB [41,101]. The possibility also exists that high TMB could be a genomic manifestation of dMMR [99]. Currently, there is no standardized cutoff for TMB, and ICIs responses are observed even with low TMB. Furthermore, detection of TMB requiring whole-exome sequencing, a highly complex and expensive process, makes this biomarker not very well suited for routine clinical use.

Patients with MSI-H or mismatch repair–deficient (dMMR) tumors are approved to receive ICI Pembrolizumab and MSI-H is believed to exist in approximately 3% of men with mCRPC [34,38,41,102]. Higher responsiveness of mismatch repair-deficient cancers to immune checkpoint inhibition, presumably due to the increased immunogenicity, which results from excessive DNA mutations [103], generated interest in this biomarker to guide the optimal ICIs therapy in the clinic.

Wu YM, et al. [39] proposed the possibility of biallelic somatic loss-of-function mutations in CDK12 as a biomarker for response to ICIs, as CDK12 alterations associated with focal tandem duplications led to gene fusions and generation of neoantigens. The results with alterations in CDK12 (approximately 6.9% of mCRPC patients) showing a high infiltration of T- cells suggested that mutation in CDK12 could allow selection of patients, who might have positive outcomes to ICIs therapy. Clinical trials (NCT03570619 and NCT03810105) to assess the efficacy of ICIs in patients with CDK12 alterations are underway.

Tumor DDR defects are well known in determining the response to chemotherapeutics and RT. Up regulation of PD-L1 expression in response to double-strand break damage in different cancer cell lines, including PCa [104] makes DDR an interesting candidate to be explored as a biomarker. In PCa, 22.7% of patients show DDR alterations (BRCA2 and ATM as most frequently affected) [34]. The outcome of a phase II trial where mCRPC patients responded better to the combination therapy that harbored DDR mutation, further establishes the association between tumor DDR status and ICIs response [40]. However, in order to utilize DDR to predict ICIs therapy response, parameters like sequencing depth, mutational frequency thresholds, and comparability of mutational definitions (genetic terminology) need to be defined clearly, so that the differences in the definitions of what is considered a mutation (monoallelic versus biallelic) should not hamper the progress [105].

Conclusion

As novel therapies are advancing, and rational combination therapies are emerging, the success of ICIs in PCa will soon bloom. The findings from different clinical trials indicate that the success of ICIs therapy is achievable in specific subsets of PCa patients with a durable response. The key elements which govern this success will require the use of therapies which allow reprogramming of TIME, reliable predictive biomarkers to select the patients for specific combination therapy and monitoring the response to ICIs therapy. The use of predictive biomarkers can bring a long-desired shift in developing personalized ICIs combination therapy for PCa patients.

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