Abstract

Context

The role of immune checkpoint inhibition (ICI) in the treatment of prostate cancer (PC) still remains elusive. It has been proposed that combination of ICI with other molecules increases the efficacy of immunotherapy in PC.

Objective

To systematically review the literature to assess the potential role of ICI in combination with additional therapies for the management of metastatic castration-resistant PC (mCRPC).

Evidence acquisition

A systematic review using Medline and scientific meeting records was carried out in September 2020 according to the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines. Ongoing trials of immunotherapy with standard mCRPC therapeutics were identified via a systematic search on ClinicalTrials.gov.

Evidence synthesis

A total of five full-text papers, ten congress abstracts, and 15 trials on ClinicalTrials.gov were identified. Preclinical evidence suggests that combinational approaches might be considered to enhance the efficacy of ICI in PC patients. This led to the design of more than 50 immunotherapy-based clinical trials. The majority of the studies focus on ICI combinations with vaccines, androgen deprivation therapy, chemotherapy, PARP inhibition, radiotherapy, and prostate-specific membrane antigen–guided radioligand therapy. Preliminary analyses reported promising findings for the use of ICI in combination with other anticancer therapies. However, no phase 3 trial has yet reported final results, so no level 1 evidence with long-term outcomes currently supports the combination of ICI with mCRPC therapies.

Conclusions

Preclinical and clinical trials have demonstrated that combining immunotherapy with standard mCRPC treatment options has the potential to provide a synergistic effect. Nonetheless, a better understanding of the mechanism and of the optimal treatment approach is still needed.

Patient summary

We reviewed the literature on immunotherapy in combination with standard treatments for patients with metastatic castration-resistant prostate cancer (mCRPC). Current evidence supports the hypothesis that immunotherapeutic drugs might be effective in mCRPC if combined with other treatment options. However, results of ongoing trials are still awaited before this novel treatment approach can be implemented in the daily practice.

Keywords

- **Metastatic castration-resistant prostate cancer**
- **Immunotherapy**
- **Combination therapies**

Introduction

The advent of immune checkpoint inhibition (ICI) has revolutionized the therapeutic approach for different malignancies including metastatic renal cell carcinoma and bladder cancer, for which different Programmed cell death 1 (PD-1), Programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated Protein 4 (CTLA-4) inhibitors have been included in disease-specific therapeutic pathways [1, 2]. Although previous studies demonstrated that immunotherapy with an autologous active cellular immunotherapy (sipuleucel-T) might improve overall survival (OS) for men with metastatic disease, mounting evidence supports the notion that prostate cancer (PC) is less immunogenic than initially assumed. This is also reflected in most clinical trials using active or passive immunotherapy, which failed to demonstrate relevant benefits from adaptive T-cell therapy or ICI in most patients [3, 4]. This might be related to different reasons: (1) the prostate tumor microenvironment (TME) is unsuitable for tumor-infiltrating immune cells with antitumor activities; (2) prostate tumors harbor fewer $CD8^+$ T cells compared to other tumor entities; (3) PC has a lower tumor mutational burden (TMB) than other cancers; (4) regulatory T cells (Tregs) are enriched in both the tumor and peripheral blood in PC; (5) there are a limited number of tumor-associated antigens and neoantigens in the TME [4, 5, 6]; and (6) PD-L1 might be downregulated in many advanced PC cases, which might partly explain the negative results observed in trials with PD-1/PD-L1 antibodies. This is true even if higher PD-1/PD-L1 expression has been reported in aggressive variants of the disease [7, 8].

Nevertheless, in a distinct subset of PC patients, underlying genomic alterations could portend greater sensitivity to immune checkpoint blockade. These genomic alterations include mutations in homologous recombination defect (HRD) genes occurring in 23% of cases, Fanconi anemia genes in 5%, *CDK12* in 6%, and mismatch repair (MMR) genes in 4%[9]. Most noteworthy, assessment of biallelic alterations of *BRCA1/2*has been incorporated into the biomarker development of Poly-ADP-Ribose Polymerase (PARP) inhibitors in metastatic castration-resistant PC (mCRPC) [10, 11]. It has been reported that the above alterations are associated with a higher TMB and potentially greater sensitivity to immune checkpoint blockade, particularly in the setting of combinatorial therapy. Similarly, PC with microsatellite instability high (MSI-H) detected in circulating tumor DNA is highly responsive to the PD-1 inhibitor pembrolizumab [12].

One possible way to improve the efficacy of ICI in PC is to use combinational therapies based on different forms of immunotherapy or on immunotherapy combined with other PC treatment options. For example, Checkmate 650, a phase 2 study assessing the combination of two different immunotherapies (nivolumab plus ipilimumab) in chemotherapy-naïve mCRPC, reported an overall responses rate (ORR) of 26%, thus giving new hope for a role of

immunotherapeutic agents in PC [13]. Given the availability of new data and an increasing number of ongoing studies in the field of ICI, we set out to systematically review and critically discuss the potential role of advanced combinational approaches in the setting of mCRPC.

Evidence acquisition

We performed a systematic review of the literature (PubMed) according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement (Fig. 1). In addition, conference reports from the past five years from the most important urological and oncological meetings (annual meeting of the American Society of Clinical Oncology (ASCO), ASCO Genitourinary Cancers (ASCO GU), European Society of Medical Oncology (ESMO), European Association of Urology, American Urological Association (AUA), American Association for Cancer Research (AACR)) up until the ASCO 2020 meeting on May 29–31, 2020 were screened. The inclusion criteria encompassed studies including patients with mCRPC who underwent treatment with a combination of ICI plus a standard mCRPC treatment (namely, chemotherapy, androgen deprivation therapy (ADT), radiotherapy (RT), radium-223, PARP inhibition, or lutetium-labeled prostate-specific membrane antigen (PSMA) ligand therapy). Search results were restricted to studies published in English. Keywords included “mCRPC” AND “clinical trial” AND (“immunotherapy” OR “immune checkpoint blockade”) AND (“androgen deprivation therapy” OR “chemotherapy” OR “abiraterone” OR” enzalutamide” OR” radiotherapy” OR” PARP inhibition” OR” PSMA lutetium therapy”). Studies on ICI monotherapy, those combining ICI with ICI, and ICI with experimental mCRPC treatment approaches (eg, antiantiogenic therapies) were excluded, as well as all preclinical studies.

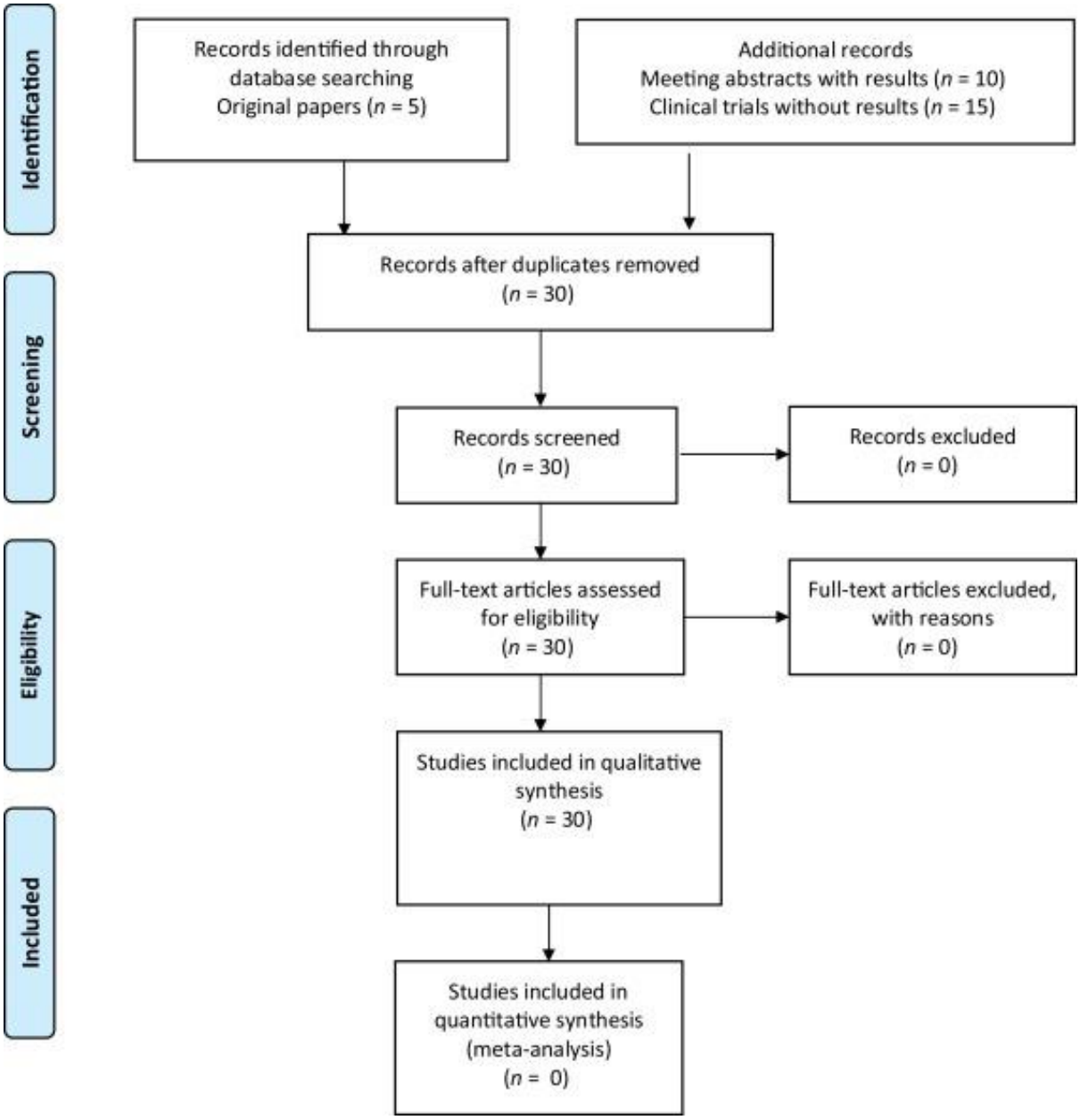

Fig. 1 Overview of the study selection process according to Preferred Reporting Items for Systematic Review and Meta-analyses guidelines.

Evidence synthesis

Features of studies included in the systematic review

Fig. 1 shows the PRISMA flowchart. A total of five full-text papers, ten congress abstracts, and 15 trials on ClinicalTrials.gov were identified. For ICI with concomitant ADT, one full-text paper has been published and six studies are ongoing (two phase 3, four phase 2). Four trials (two phase 3 and two phase 2) are currently investigating ICI in combination with chemotherapy. For ICI plus radiation, three trials have been published as full-text papers, two phase 3 studies have been completed, and five phase 2 studies are still ongoing. The combination of PARP inhibition plus ICI has been investigated in six phase 1/2 trials. Among

these, one study has been published. One phase 1b study is currently assessing radioligands and two studies (phase 1b and 2) are investigating cancer vaccines in combination with ICI. Table 1 presents detailed information (immunotherapeutic agent, NCT number, number of treatment groups, sample size, clinical phase, completion date, and current study stage) for the ongoing studies.

Table 1: Overview of clinical studies combining ICI with metastatic castration-resistant prostate cancer treatment options.

	Combination partner	ICI	Identifier	Tx groups	(Planned) sample size	Clinical phase	(Expected) completion date	Current stage/reference
Androgen inhibition	Leuprolide + bicalutamide	Ipilumumab	NCT00170157	1	112	2	06.2013	Completed, no final results
	Any LHRH A/AA	Ipilumumab	NCT01498978	1	10	2	08.2019	Completed (PMID 32850444)
	Enzalutamide	Pembrolizumab	NCT02312557	1	58	2	01.2022	Active, not recruiting, interim results
		Pembrolizumab	NCT02787005	5	370	2	12.2021	Active, not recruiting, interim results
		Pembrolizumab	NCT03834493	2	1200	3	04.2024	Active, interim results
		Atezolizumab	NCT03016312	2	771	3	09.2020	Terminated in April 2020, interim results
		Nivolumab	NCT03338790	3	330	2	11.2021	Active, not recruiting, no results yet

	Combination partner	ICI	Identifier	Tx groups	(Planned) sample size	Clinical phase	(Expected) completion date	Current stage/reference
CTx	Docetaxel	Nivolumab	NCT03338790	3	330	2	11.2021	Active, not recruiting, interim results
		Nivolumab	NCT04100018	2	984	3	06.2024	Active, recruiting, no results yet
	Docetaxel	Pembrolizumab	NCT02861573	4	400	1b/2	12.2023	Active, recruiting, interim results
		Pembrolizumab	NCT03834506	2	1000	3	02.2023	Active, recruiting, no results yet
Radiation	Radiation	Ipilimumab	NCT02232230	1	20	3	06.2018	Completed, no results yet
		Ipilimumab	NCT01057810	2	837	3	07.2015	Completed (PMID 28034081)
		Ipilimumab	NCT00861614	2	988	3	08.2015	
		Nivolumab	NCT03543189	1	34	1/2	09.2021	Completed (PMID 24831977)
		Sipuleucel-T	NCT01807065	2	51	2	12.2019	
		Sipuleucel-T	NCT02232230	1	20	3	06.2018	Active,

	Combination partner	ICI	Identifier	Tx groups	(Planned) sample size	Clinical phase	(Expected) completion date	Current stage/reference
		Sipuleucel-T	NCT01818986	2	36	2	12.2020	recruiting, no results yet Competed (PMID 30682445) Completed, no results yet Active, not recruiting, no results yet
	Radium-223	Pembrolizumab	NCT03093428	2	45	2	06.2024	Active, recruiting, no results yet
		Avelumab	NCT04071236	2	99	2	01.2023	Active, recruiting, no results yet
		Sipuleucel-T	NCT02463799	2	36	2	12.2020	Active, recruiting, interim results

	Combination partner	ICI	Identifier	Tx groups	(Planned) sample size	Clinical phase	(Expected) completion date	Current stage/reference
PARP inhibition	Olaparib	Pembrolizumab	NCT02861573	4	400	1b/2	12.2023	Active, recruiting, interim results
		Pembrolizumab	NCT04123366	1	300	2	12.2023	Active, recruiting, no results yet
	Olaparib	Durvalumab	NCT02484404	6	384 (solid tumors)	1/2	12.2022	Completed (PMID 30514390)
	Rucaparib	Nivolumab	NCT03572478	4	12	1/2	12.2021	Active, recruiting, no results yet
		Nivolumab	NCT03338790	3	330	2	11.2021	Active, recruiting, no results yet
	Talazoparib	Avelumab	NCT03330405	13	214 (solid tumors)	2	08.2021	Active, recruiting, no results yet

	Combination partner	ICI	Identifier	Tx groups	(Planned) sample size	Clinical phase	(Expected) completion date	Current stage/reference
Radioligand	^{177}Lu-PSMA-617	Pembrolizumab	NCT03805594	3	43	1b	08.2022	Active, recruiting, no results yet
Cancer vaccines	Sipuleucel-T	Atezolizumab	NCT03024216	2	37	1b	11.2025	Active, not recruiting, interim results
		Ipilimumab	NCT01804465	2	50	2	08.2020	Active, not recruiting, no results yet

ICI = immune checkpoint inhibitor; Tx = treatment; LHRH A/AA = luteinizing hormone–releasing hormone agonist/antagonist; CTx = chemotherapy; PSMA = prostate-specific membrane antigen.

In general, a large number of clinical trials investigating various ICIs in different stages of PC were initiated because preclinical studies demonstrated promising results. However, in contrast to other tumor entities, ICI monotherapies showed limited clinical benefit in PC, so there is a need for novel strategies to overcome this problem. Besides combining two different ICI agents to boost their activity, an ICI can be combined with standard therapeutic options. Here we discuss ICIs in combination with mCRPC treatment options.

ICIs with concomitant ADT

Several preclinical studies examined immune-based treatments in combination with ADT and demonstrated that androgen depletion can positively or negatively affect the immune response generated during immunotherapy treatment [14]. On the basis of these findings, combining ADT with immunotherapy might represent a reasonable option for improving its efficacy. The combination of CTLA-4 inhibition and ADT in mCRPC was assessed in a prospective phase 2 trial (NCT00170157) using ipilimumab (a fully human monoclonal antibody targeting CTLA-4) plus ADT (leuprolide) plus bicalutamide versus ADT monotherapy. 55% of patients achieved undetectable prostate-specific antigen (PSA) levels after 3 months (mo) of combined therapy, compared with 38% of patients treated with androgen ablation alone [15].

The study was completed in 2013 after enrolment of 112 patients. However, to the best of our knowledge the final results have not been published so far. The results of a similar phase 2 study (NCT01498978) that evaluated the impact of ipilimumab plus androgen suppression in mCRPC patients with an incomplete response to ADT monotherapy were released in August 2020. Overall, ten patients were enrolled and treated with ipilimumab 10 mg/kg (every 3 weeks (wk) for up to four doses) with maintenance ipilimumab every 12 wk if no progression was observed. No patient met the primary endpoint, defined as undetectable PSA. However, 30% of the patients demonstrated a >50% PSA reduction, with one patient achieving a PSA decrease of >90%. Interestingly, assessment of peripheral blood mononuclear cells revealed that patients with clinical responses had an increase in effector memory T-cell subsets as well as an increase in T-cell expression of T-bet, suggesting induction of a Th1 response [16].

Evidence supporting the combination of a second-generation antiandrogen (eg, abiraterone or enzalutamide) with ICI is inconclusive. Enzalutamide resistance is associated with increased expression of PD-L1/2^{+} dendritic cells (DCs) in blood compared to patients responding to treatment, as well as with a high frequency of PD-1^{+} T cells [17]. However, abiraterone or enzalutamide did not affect the expression of PD-L1 on circulating myeloid suppressor cells in mCRPC patients. Admittedly, baseline levels of the cytokines fibroblast growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 10 (IL-10), and IL-6 were significantly lower in responders compared to patients not responding to second-generation ADT. In addition, resistant patients showed significantly lower T-cell frequencies [18]. This incoherence may suggest that PD-1 can be highly expressed on Tregs, thereby promoting cell proliferation and suppressive activity. Conversely, when PD-1 is expressed on CD4 and CD8 effector cells, it negatively regulates their proliferation by inducing their differentiation into suppressive T cells upon binding to PD-1 antibodies [7].

A phase 2 single-institution study enrolled 30 mCRPC patients progressing on enzalutamide who were treated with pembrolizumab while continuing enzalutamide (NCT02312557). Interim results were presented at the ESMO 2019 meeting and showed that 13% of patients

achieved a PSA reduction ≥50%, and 25% of patients exhibited radiographic response after treatment with pembrolizumab in combination with enzalutamide. After median follow-up of 17.4 mo, median progression-free survival (PFS) was 5.6 mo (95% confidence interval [CI] 3.5–8.1) and median OS was 17.3 mo (95% CI 7.7–17.7) [19]. Although patient recruitment has been terminated, the estimated primary completion date is January 2021.

The encouraging findings presented at ESMO 2019 led to the design of a phase 3 trial (Keynote-641, Arm C; NCT03834493) that is currently recruiting patients. At the virtual AUA 2020 meeting, interim results were presented for 103 men treated for at least 27 wk with pembrolizumab plus enzalutamide. The PSA response rate was 21.8% in the overall population, the median time to PSA progression among patients who had a PSA response was 3.5 mo (95% CI 2.9–4.0), and the ORR among patients with measurable disease was 12.0% (95% CI 2.5–31.2%) with a disease control rate (DCR) of 32% (95% CI 14.9–53.5%). Two patients had a complete response, one had a partial response, and 11 had stable disease. Remarkably, 56% of patients with measurable disease showed a reduction in target lesion size from baseline, and in 24% of those patients the decrease was >30%. Concerning secondary endpoints, patients had median radiographic PFS (rPFS) of 6.1 mo (95% CI 4.4–6.5) and median OS of 20.4 mo (95% CI 15.5 mo to not reached [NR]). Grade 3–5 treatment-related adverse events (TRAEs) were observed in 39.2% of the cases; the most commonly reported ones were rash (7.8%) and fatigue (5.9%). Immune-mediated AEs were reported for 37.3% of the patients, including severe skin reaction (17.6%), hypothyroidism (14.7%), and colitis (2.9%) [20].

In line with Keynote-641, an update on the phase 2 Keynote-199 cohort 4 and 5 trial (NCT02787005) investigating pembrolizumab in mCRPC was presented at ASCO 2020 [21]. Cohort 4 (Response Evaluation Criteria in Solid Tumors [RECIST]-measurable disease) and Cohort 5 (bone-predominant disease) comprised chemotherapy-naive patients with mCRPC treated with enzalutamide plus pembrolizumab after progression with enzalutamide. At median follow-up of 13.7 mo, 107 of 126 patients had discontinued pembrolizumab, mostly because of disease progression. The ORR for patients with measurable disease (Cohort 4) was 12% (95% CI 6–11%). Of note, there were two complete responses among eight responses, and a duration of response (DOR) of 6 mo in 60% of those patients whose tumors responded. The reported DCR, defined as stable disease, complete response, or partial response for all patients, was 51% in Cohort 4 (95% CI 39–63%) and 51% in Cohort 5 (95% CI 36–66%) [22]. On the basis of these results, the authors concluded that addition of pembrolizumab to enzalutamide following enzalutamide resistance showed modest antitumor activity and a durable response in patients with RECIST-measurable and bone-predominant mCRPC (Table 1).
Besides pembrolizumab, the PD-1–blocking antibody nivolumab is currently being tested in combination with enzalutamide in men with mCRPC (CheckMate 9KD, Arm C; NCT03338790).

The phase 3 IMbassador 250 trial (NCT03016312) is the second trial reporting final results for ADT plus ICI. This study randomly assigned 759 patients with mCRPC, or locally advanced or incurable CRPC, to receive the PD-L1 inhibitor atezolizumab plus enzalutamide versus enzalutamide monotherapy until loss of clinical benefit or unacceptable toxicity. According to latest data presented at the AACR 2020 meeting, there was no significant improvement in OS or other outcomes with the addition of atezolizumab to enzalutamide, and the trial was terminated early in April 2020. Of note, no difference in OS was observed between the arms, with a median of 15.2 mo (95% CI, 14.0–17.0) for atezolizumab plus

enzalutamide compared to 16.6 mo (95% CI 14.7–18.4) for enzalutamide alone (hazard ratio [HR] 1.12, 95% CI 0.91–1.37; $p = 0.28$). Overall, rPFS and PSA progression rates were similar between the groups. The ORR was 14% with atezolizumab plus enzalutamide compared to 7% with enzalutamide. The median DOR was 12.4 mo with the atezolizumab combination and not estimable with enzalutamide alone [23]. Explanations for the negative results could be that novel second-generation antiandrogens such as abiraterone might downregulate PD-L1 in PC, as it has been demonstrated that tumors treated with ADT plus abiraterone have lower PD-L1 positivity compared with matched controls ($p = 0.062$) [24].

To summarize, while Keynote-641 (and phase 2 Keynote-199) demonstrated that addition of pembrolizumab to enzalutamide following enzalutamide resistance showed modest antitumor activity and durable response, IMbassador 250 (atezolizumab plus enzalutamide) was negative. Therefore, the implications of PD-1/PD-L1 expression in mCRPC patients treated with ADT require further elucidation in both preclinical and clinical settings, as there is evidence that not all hormone therapy agents interact with the immune system in the same way. Identification of patients who might benefit from the combinational treatment by stratification using clinical, pathological, or genomic parameters will play a major role in the future.

ICIs in combination with chemotherapy

Although chemotherapy is generally considered an immunosuppressive therapy, there is recent evidence of a positive immunologic effect of this approach. For example, chemotherapy regulates the composition and function of tumor-infiltrating lymphoid and myeloid cells. The exact immunogenic changes differ according to the type of chemotherapy and might be related to upregulation of NF-B, an increase in $CD8^+$ T cells, or higher PD-L1 expression on tumor cells [25, 26].

Chemotherapy might also induce death of immunogenic cells and genetic alterations in cancer cells, and could therefore induce immune responses and show synergistic effects when combined with ICI. At the ESMO 2019 meeting, interim results were presented for the phase 2 Checkmate 9KD trial (Arm B; NCT03338790) evaluating nivolumab in combination with docetaxel. Overall, 41 mCRPC patients underwent treatment with nivolumab (360 mg) + docetaxel (75 mg/m^2) for up to ten cycles, followed by nivolumab (480 mg) until disease progression or unacceptable toxicity up to 2 years (yr). Data revealed that the ORR among patients with measurable disease was 36.8% (95% CI 16.3–61.6%); one patient had a complete response and six had progressive disease. Among the 41 patients treated, the confirmed PSA response rate was 46.3% (95% CI 30.7–62.6%), the median rPFS was 8.2 mo (95% CI 6.6–not estimable), and the 6-mo rPFS rate was 71.5% [27]. On the basis of these promising results the consecutive phase3 trial CheckMate7DX (NCT04100018) is currently recruiting participants.

At the ASCO GU 2020 meeting, results presented for the phase 1b/2 umbrella trial revealed that docetaxel plus pembrolizumab had activity among patients treated with abiraterone or enzalutamide for mCRPC (Keynote-365 study, ARM B; NCT02861573) [28]. Among the 104 patients treated, the confirmed PSA response rate was 28% in the total population and the ORR for patients with RECIST-measurable disease who had follow-up of ≥27 wk was 18%. The DCR was 51% for the total population, 51% for those with measurable disease, and 52% for those with nonmeasurable disease. The median DOR for patients with

≥27 wk of follow-up was 6.7 mo, and five patients had a response ≥6 mo. The median time to PSA progression was 27.1 wk (95% CI 16.1–31.2), the median rPFS was 8.3 mo (95% CI 7.6–10.1), and the median and OS was 20.4 mo (95% CI 16.9–NR). Keynote-921 (NCT03834506), a randomized phase 3 trial assessing the efficacy and safety of pembrolizumab plus docetaxel and prednisone in chemotherapy-naive mCRPC patients progressing on enzalutamide or abiraterone, is recruiting patients. The primary endpoints of the study are rPFS and OS.

In conclusion, two phase 3 trials are assessing the impact of adding ICI to chemotherapy, with no results reported so far. Clinicians should be careful when assessing the potential side effects of the combination of ICI with chemotherapy.

ICIs in combination with cancer vaccines

Cancer vaccines prime and expand tumor-specific T cells by delivering tumor-associated antigens in an immunologic milieu that drives effective T-cell activation. Therefore, vaccination with antigen-specific blood-derived DCs, the most potent antigen-presenting cells of the immune system crucial for inducing adaptive immune responses, may be a potent treatment option [29, 30]. Sipuleucel-T is a US Food and Drug Administration (FDA)–approved cell-based vaccine composed of autologous antigen-presenting peripheral blood mononuclear cells (enriched for a DC fraction) that have been exposed to a recombinant protein consisting of GM-CSF fused to prostatic acid phosphatase (PAP), a protein expressed by PC cells. On administration, the vaccine may stimulate an antitumor T-cell response against tumor cells expressing PAP [31]. The IMPACT trial demonstrated a 4.1-mo improvement in OS among men with mCRPC, despite no obvious change in overall disease burden [31, 32].

STAND, a randomized, phase 2, open-label trial (NCT01431391), assessed for the first time almost 20 yr ago the sequencing of sipuleucel-T with ADT in patients with biochemically recurrent PC at high risk of metastasis, and found that sipuleucel-T followed by ADT appears to induce greater antitumor immune responses than the reverse sequence [33]. Currently, a phase 1b study is examining the efficacy of sipuleucel-T with atezolizumab (NCT03024216) to compare the safety and tolerability of sequential atezolizumab followed by sipuleucel-T (Arm 1) versus sipuleucel-T followed by atezolizumab (Arm 2) in patients who have asymptomatic or minimally symptomatic CRPC not previously treated with docetaxel or cabazitaxel. Results for 37 patients presented at the last ASCO GU meeting showed that after 6 mo, 11 patients had stable disease (seven in Arm 1 and four in Arm 2), 18 had progressive disease, and seven were not evaluable (three withdrew from study and four have yet to reach 6-mo evaluation). At this time point, PFS was 8.2 mo in Arm 1 and 5.8 mo in Arm 2 ($p = 0.054$) [34]. Moreover, sipuleucel-T combined with ipilimumab has shown clinical activity (NCT01804465) and is currently being assessed in mCRPC patients.

ICIs in combination with RT

The combination of immunotherapy and RT is an emerging treatment option for most cancers at different tumor stages. Recent evidence suggests that ionizing radiation can be immunostimulatory, as RT activates both the adaptive and innate immune systems by directly killing tumor cells, causing mutations in tumor-derived peptides, and inducing localized inflammation that increases immune cell trafficking to tumors [35, 36]. In addition, the

activated immune system may cause tumor-directed treatment responses away from the site of irradiation, that is, an abscopal treatment effect, which has the potential to treat disease throughout the body [37, 38].

A phase 2 trial already suggested 7 yr ago that ipilimumab exerts clinical antitumor activity in combination with RT. However, the subsequent phase 3 trial (CA184-095; NCT01057810) failed to demonstrate a significant difference between the ipilimumab and placebo groups in terms of OS [39]. A similar phase 3 (CA184-043; NCT00861614) randomized trial including 799 patients with osseous mCRPC evaluated the efficacy of RT (8 Gy) plus ipilimumab. The primary endpoint of OS was not reached. However, a survival advantage of 7 mo was observed in the subgroup of patients with a low tumor burden (22.7 vs 15.8 mo; $p = 0.0038$) [40]. Fizazi et al [41] very recently published long-term OS data from this trial demonstrating that OS rates at 3, 4, and 5 yrs were two to three times higher in the ipilimumab arm. Another phase 3 trial of ipilimumab in mCRPC patients treated with RT to one or more metastatic sites followed at least 28 days later by ipilimumab recently completed the recruitment phase and results are expected soon (NCT02232230).

A recent preclinical animal study demonstrated that anti–PD-1 or anti–PD-L1 antibodies combined with RT resulted in a decrease in tumor graft growth compared to ICI alone. This led to the hypothesis that a combinational approach might trigger a robust response against CRPC mediated via the immune system, causing both local and distant abscopal effects [42]. Currently a phase 1/2 study is assessing the safety, tolerability, and efficacy of nivolumab in patients with oligometastatic disease (defined as ≤3 sites of distant metastatic disease and/or positive lymph nodes confined to the pelvis) treated with definitive RT plus short-term ADT (NCT03543189). In a phase 2 trial, 51 mCRPC patients were randomized to sipuleucel-T alone or sipuleucel-T initiated 1 wk after completion of sensitizing RT (total 3000 cGy) to a single metastatic site. Sensitizing RT completed 1 wk before administration of sipuleucel-T did not affect the majority of the sipuleucel-T parameters or the ability to deliver the therapy; the authors concluded that RT did not enhance the humoral and cellular responses associated with sipuleucel-T therapy [43]. Results from a phase 3 multicenter trial enrolling mCRPC patients treated with a combination of RT and sipuleucel-T (NCT02232230) are expected in the next months.

A phase 2 study is currently evaluating stereotactic ablative body radiation to multiple metastatic sites to eradicate sites of bulky progressive disease, and to induce antigen presentation and immune stimulation, which is expected to act synergistically to concurrently administered sipuleucel-T and thereby significantly improve the treatment outcome for mCRPC (NCT01818986).Radium-223 is approved and clinically used as a third-line treatment option in osseous mCRPC, having demonstrated an OS benefit in large phase 3 trials [44]. Radium-223 binds to minerals in bone to deliver radiation directly to cancer that has spread to the bones while limiting damage to surrounding body tissues [45]. To enhance its efficacy, a phase 1/2 study is evaluating RT versus radium-223 plus RT-enhancing medication (M3814) versus radium plus M3814 plus the PD-L1 inhibitor avelumab for mCRPC patients (NCT04071236). At the ASCO GU 2020 meeting, interim results were presented for sipuleucel-T with or without radium-223 in 32 men with mCRPC (NCT02463799). After median follow-up of 5.3 mo, median PFS was longer in the combination arm (10.7 vs 3.1 mo; HR 0.35, 95% CI 0.15–0.81; $p = 0.02$). No safety concerns were raised [46]. Furthermore, radium-223 plus pembrolizumab (NCT03093428) is currently being investigated in a phase 2 study in men with asymptomatic or mild symptomatic bone-involved mCRPC.

In conclusion, although preclinical and early clinical trials have demonstrated promising results, phase 3 trials combining RT with ICI were negative. When considering radium-223, interim results are encouraging, as an increase in PFS was observed for patients treated with radium-223 plus sipuleucel-T.

ICIs in combination with PARP inhibitors

Tumors harboring mutations in the DNA damage repair (DDR) system are sensitive to PARP inhibition [47, 48]. In mCRPC patients with DDR alterations, PARP inhibitor treatment is associated with significant survival benefits compared to controls [49, 50]. However, patients without genetic alterations gain a partial benefit from PARP inhibitors for which a therapy improvement has been claimed (eg, via combinational therapeutic approaches). Mutations in MMR genes are associated with MSI in advanced PC and may serve as a biomarker for immunotherapy response [51]. In preclinical models, PARP inhibitors upregulated PDL-1 expression in breast tumor cell lines [52]. There is also evidence that combination therapy in PC using the IgG1 antibody–dependent cellular cytotoxicity–mediating monoclonal antibodies cetuximab (anti-EGFR) or avelumab (anti-PD-L1) combined with olaparib in metastatic PC cell lines increased tumor cell sensitivity to killing by natural killer cells independently of *BRCA* status or monoclonal antibody target upregulation [53]. On June 11, 2020, the FDA approved olaparib and rucaparib for treatment of mCRPC with homologous recombination repair (HRR) mutations.

Concerning combinations of PARP inhibitors with ICI, Karzai et al [54] investigated the activity of durvalumab, a human IgG1-K monoclonal antibody targeting PD-L1, plus olaparib in mCRPC with and without DDR mutations and observed median rPFS of 16.1 mo (95% CI 4.5–16.1) with a 12-mo rPFS rate of 51.5% (95% CI 25.7–72.3%). Activity was seen in patients with alterations in DDR genes, for whom median rPFS was 16.1 mo (95%CI 7.8–18.1). Overall, 53% of patients had a radiographic and/or PSA response. Patients with fewer peripheral myeloid-derived suppressor cells and with alterations in DDR genes were more likely to respond. Early changes in circulating tumor cell counts and in both innate and adaptive immune characteristics were associated with response to treatment [54].

At the ASCO GU 2019 meeting, preliminary results presented for the phase 1b/2 Keynote-365 trial (Arm A; NCT02861573) demonstrated that the combination of pembrolizumab plus olaparib is active in patients with wild-type HRR status who were previously treated with docetaxel and two or fewer novel antiandrogens [55]. An update presented at ASCO GU 2020 reported that 42 of 84 patients had discontinued therapy, primarily because of progression ($n = 29$). Of note, 26% were PD-L1$^+$, 26% had visceral disease, and 57% had RECIST-measurable disease. The median follow-up was 3 mo for all patients ($n = 81$) and 14 mo for patients with ≥27 wk of follow-up ($n = 41$). The confirmed PSA response rate was 8.5% in the overall population, including 10.6% among patients with RECIST-measurable disease and 5.7% among patients with nonmeasurable disease. The overall PSA decrease from baseline was 36.6%, including 11.0% for patients with a >50% decline [28]. The estimated completion date for the study is March 2022. At the ASCO 2020 meeting, data were presented for KEYLYNK-007 (NCT04123366), which is evaluating the antitumor activity and safety of olaparib plus pembrolizumab in patients with advanced solid tumors with HRR mutation and/or HRD. The primary endpoint of this trial is ORR; secondary endpoints include DCR, PFS, OS, and safety [56]. In addition, phase 1/2 studies investigating nivolumab in combination with the PARP inhibitor rucaparib (NCT03572478,

NCT03338790) or avelumab plus the PARP inhibitor talazoparib in locally advanced or metastatic solid tumors including PC (NCT03330405) are currently ongoing.
In conclusion, data on combinations of PARP inhibitors plus ICI are still preliminary and survival data are missing. Furthermore, to the best of our knowledge no phase 3 trial has been initiated so far.

ICIs in combination with PSMA-targeted radioligand therapies

PSMA-targeted radioligand therapies represent another pillar in the armamentarium of mCRPC treatment, both as monotherapy and as a component of combinatorial strategies [57]. A phase 1b trial study is currently assessing the dose and schedule of ^{177}Lu-PSMA-617 and pembrolizumab in three different experimental schedules for patients with mCRPC (NCT03805594). Recruitment of 43 patients up to August 2022 is planned in this open-label study.

In summary, combining PSMA-targeted radioligand therapies with ICI is still in its infancy.

Discussion

Substantial progress has been made in our understanding of the immunogenic landscape of PC. Owing to the immunosuppressive PC environment, use of ICI monotherapy poses a challenge, reflected by the fact that most clinical trials failed to reach their primary endpoints. Recent understanding of the inhibitory milieu within the TME has fostered the use of combinatorial strategies that not only target tumor cells but also capitalize on controlling inhibitory cell populations and cytokines that induce a hostile setting for immune cells.

Ongoing studies on the efficacy of ICI in mCRPC are investigating combinations with ADT, chemotherapy, RT, PARP inhibitors, and PSMA-targeted radioligand therapies. Preliminary studies have revealed promising results. However, no phase 3 trial has reported final results, so it is impossible to draw any final conclusions. In addition, a better understanding of the inflammatory pathophysiology of PC, especially in the TME, will shed more light on the development of new combination therapy approaches to define the optimal combinational approach. Beside the combination of ICI with standard mCRPC therapeutics, promising proof-of-concept therapeutic investigations include better comprehension of the TME to define promising new therapies such as bispecific antibodies and chimeric antigen receptor T cells, along with CD73/adenosine receptor inhibitors, VISTA-mediated signaling pathways, and immunotherapy targeting cancer stem cells.

Furthermore, biomarkers predicting therapy responses are warranted, as, in contrast to other tumor entities, PD-1/PD-L1 status is not a reliable marker for ICI therapy response. Early results suggest that patients with MSI-H/dMMR PC may respond to checkpoint inhibition and that MSI frequently develops as a somatic event in many of these patients, as only a small fraction of the patients had a germline MMR gene mutation.

In addition, it is important to select patients who should undergo a primary combination approach and patients for whom ICI should added when monotherapy does not bring the expected treatment response. Moreover, the optimal treatment sequence, the treatment line,

and the impact of previous mCRPC therapies on treatment outcomes have to be assessed. Last but not least, the side effects of combinational therapies have to be surveyed, which could further limit combinational treatment, especially when combining ICI with aggressive mCRPC agents such as chemotherapeutics considering that most PC patients are of older age and thus respecting the dogma “primum non nocere”. One approach to overcome this dilemma might be to reduce the cumulative chemotherapy dose when adding ICI and thus making the combination more compatible.

With positive results from many early clinical trials in PC, these novel ICI combination approaches hold promise for the future and hopefully will improve clinical outcomes and patient survival.

Conclusions

Preclinical and clinical trials have demonstrated that combining immunotherapy with standard mCRPC treatment options has the potential to provide a synergistic effect. Nonetheless, a better understanding of the mechanism and of the optimal treatment approach is still needed. Beside approved mCRPC treatments that are discussed in this review article, upcoming combinations such as ICI plus an antiangiogenic agent like cabozantinib are highly promising. In addition, ICI combinational treatment should also be considered in earlier stages or clinical states, such as (non)metastatic hormone-sensitive PC and nonmetastatic CRPC, for which numerous clinical trials are currently ongoing.

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Study concept and design: Heidegger, Gandaglia.
Acquisition of data: Heidegger, Gandaglia, Pircher, Necchi.
Analysis and interpretation of data: Heidegger, Gandaglia, Pircher, Necchi.
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