Therapeutic metastatic prostate cancer vaccines: lessons learnt from urologic oncology

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Introduction Therapeutic cancer vaccines have been recognized as a promising treatment option in clinical oncology for nearly three decades. However, despite many efforts, only one cancer vaccine – sipuleucel-T, activating the anti-PAP (prostatic acid phosphatase) immune response, has obtained Food and Drug Administration (FDA) approval.

Material and methods This review describes the most advanced research on the use of therapeutic cancer vaccines in the treatment of prostate cancer.

Results In addition to sipuleucel-T, which was approved in urologic oncology in 2010, four cancer vaccines were and have been tested in phase III clinical trials in patients with metastatic castration resistant prostate cancer (mCRPC): GVAX (prostate cancer variant) containing irradiated prostate cancer cell, PPV peptide vaccine, PCVAC/PCa dendritic cell-based vaccine and PROSTVAC anti PSA (prostate-specific antigen) vaccine. This review compares the most promising and best-studied cancer vaccines: sipuleucel-T and PROSTVAC. Currently, both vaccines have been tested in combination with other therapeutic approaches, including check point inhibitors.

Conclusions It seems possible that the efficacy of sipuleucel-T and PROSTVAC could be increased in combination therapy with other medications.

Key Words: therapeutic cancer vaccines ● sipuleucel-T ● PROSTVAC ● oncoimmunology

INTRODUCTION

Therapeutic cancer vaccination has long been considered as the most promising variant of active immunotherapy in oncology. However, despite extensive 30-year studies and many clinical trials conducted, the efforts did not bring the expected results and therapeutic cancer vaccines have not made significant progress in the treatment of cancer [1]. Although most of the cancer vaccine research has been focused on melanoma, because of well-established immunogenicity of this tumor, a relatively large number of cancer vaccine-based studies have been carried out in urological oncology on patients with prostate cancer. Prostate cancer is the most common type of cancer in men in highly developed countries (191,930 new cases are expected in the United States in 2020), and the second leading cause of deaths among all cancers (estimated 33,330 deaths in the United States in 2020) [2]. Localized disease may be cured with surgery or radiotherapy but in many patients, cancer progresses and eventually evolves into the stage of metastatic castration resistant prostate cancer (mCRPC) [3]. Over the last decade, the prognosis of patients with mCRPC improved, and currently available therapeutics for mCRPC include, in addition to docetaxel: second generation antiandrogen agents (abiraterone, enzalutamide, apalutamide, darolutamide), cabazitaxel, therapeutic cancer vaccine sipuleucel-T, radium-223, pembrolizumab, and quite recently, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors (olaparib and rucaparib) [3, 4].
Anticancer vaccines are aimed at induction of the T lymphocyte response by upregulating mechanisms of antigen presentation. Prostate cancer seems to be a perfect target for this immunotherapy, owing to tissue-specific antigens found exclusively within the prostate gland [5]. Furthermore, the disease usually progresses slowly due to the constant proliferation of cells [6], which makes sufficient time for an immune response to be elicited after vaccination, especially taking into account the necessity of repeated vaccination for an optimal anti-tumor immune response [7].

sipuleucel-T is the only therapeutic cancer vaccine that has been approved in clinical oncology [United States Food and Drug Administration (FDA) approval in 2010], recommended for asymptomatic or minimally symptomatic mCRPC in patients with good Eastern Cooperative Oncology Group (ECOG) performance status [3, 8]. However, this agent has not been licensed in Europe. The present review compares sipuleucel-T with another promising therapeutic cancer vaccine used for treatment of mCRPC, PROSTVAC, while offering suggestions how to optimize prostate cancer immunotherapy.

RESULTS

Intensive research on therapeutic cancer vaccines in mCRPC has been going on for the last two decades. Besides FDA-approved sipuleucel-T, the list of most promising vaccines that were tested have been investigated in advanced studies (phase III clinical trials) includes: GVAX (prostate cancer variant), personalized peptide vaccine (PPV), DCVAC/PCa, and PROSTVAC (PSA-TRICOM).

GVAX vaccine is composed of genetically modified, GM-CSF-secreting irradiated cells of two allogeneic prostate cancer cell lines (PC-3 and LNCaP). Two phase III trials, in which GVAX vaccine was administered either alone or in combination with docetaxel (VITAL-1 and VITAL-2, respectively), were terminated in 2008 due to a lack of therapeutic efficacy and safety concerns [9].

PPV is a personalized peptide vaccine consisting of prostate-specific peptides emulsified in Montanide ISA 51 in complete Freund’s adjuvant. The vaccine was tested in a phase III randomized, double-blind, placebo-controlled trial in Japan, recruiting HLA-A24-positive patients with mCRPC (in the vast majority with metastases) progressing within 12 months after docetaxel therapy. Unfortunately, the study demonstrated no difference in overall survival between PPV- and placebo-treated patients (16.1 vs 16.9 months, respectively) [10].

PCVAC/PCa is a cellular autologous cancer vaccine containing autologous dendritic cells (derived from blood monocytes) fed with killed LNCaP prostate cancer cells. The vaccine has been tested in a combination protocol, with docetaxel, in a phase III trial commenced in 2014 (VIABLE) (NCT02111577, EudraCT 2012-002814-38). The study is randomized, double-blinded, and multicenter. Men with mCRPC eligible for first-line chemotherapy have been included and results of the study are awaiting [11].

sipuleucel-T and PROSTVAC have been investigated and are currently tested in a number of clinical trials, either alone or in combinations with other medications. The time the vaccines have been tested in most advanced studies can be divided into 2 periods: 2000-2010 [12, 13] and 2011-present [14, 15].

Sipuleucel-T vs PROSTVAC in the first decade of the current century

sipuleucel-T (Provenge®, Dendreon Pharmaceuticals LLC, Seal Beach, CA) is a therapeutic cancer vaccine, containing antigen presenting cells (APC) prepared from peripheral blood mononuclear cells in the process of leukapheresis, incubated for 1.5–2 days with PA2024 recombinant protein consisting of prostate acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). PAP is a prostate-specific protein and GM-CSF enables maturation of antigen-presenting cells (APC), which can induce specific anti-PAP immune response and generation of PAP-specific cytotoxic T lymphocytes (CTL). In the full treatment protocol, sipuleucel-T was administered in 3 doses at approximately 2-week intervals. Sipuleucel-T was a subject of extensive research in 3 phase III clinical trials: randomized, double-blind, and placebo-controlled. The initial two trials (D9901 and D9902A) recruited patients with progressive metastatic prostate cancer enrolled in 2000–2003. Results of these trials suggested a survival benefit for patients treated with sipuleucel-T compared to the placebo group [16]. Sipuleucel-T was approved by the FDA in 2010 based on a pivotal, phase III trial (IMPACT, NCT00065442), in which patients survival in the vaccine arm was prolonged by 4.1 months, as compared to the placebo group (25.8 vs 21.7 months) [12] (Table 1). However, very important indicator of treatment effectiveness – time to objective disease progression – was similar in experimental and control arms. There were some criticisms concerning the control group. At disease progression, some patients from the placebo group were treated with sipuleucel-T-mimicking vaccine (APC8015F) prepared from cryopreserved cells, as a salvage option (unfortunately in a nonrandom-
ized manner), and next with docetaxel, while in the sipuleucel-T arm patients were given docetaxel at an earlier time. Overall, 57.2% patients received additional treatment with docetaxel in the sipuleucel-T group and 50.3% patients in the placebo group, suggesting that the control group in the IMPACT trial was not optimally treated as compared with the sipuleucel-T arm. However, the trend for prolonged survival in a APC8015F-treated subgroup versus control-only treated patients was reported in a subsequent analysis [17], showing that the benefit of using sipuleucel-T was even greater. Of note, median survival time in the IMPACT placebo group was comparable to that reported in other studies in prostate cancer involving similar populations of patients (15.5–21.7 months) [12].

PROSTVAC (PSA-TRICOM) therapeutic vaccine was tested in phase II clinical trials in the first decade of this century in parallel with sipuleucel-T. PROSTVAC is composed of recombinant viral vector containing transgenes: for human prostate-specific antigen (PSA) and three costimulatory molecules: B7.1 (CD80), leukocyte function-associated antigen-3 (LFA-3, CD58), and intercellular adhesion molecule-1 (ICAM-1, CD54). Therapeutic protocol confined 7 injections: one priming injection with vaccinia virus-based vector (rilimogene galvacirepvec, PROSTVAC-V) at first followed by six boosting immunizations with a recombinant fowlpox virus-based vector (rilimogene glafolivec, PROSTVAC-F). The treatment was accompanied by GM-CSF administration. Control arm patients were injected with empty vectors and saline instead of GM-CSF. In the largest phase II randomized, controlled, double-blinded trial with PROSTVAC, enrolling in 2003-2005 patients with minimally symptomatic mCRCP, very encouraging results were obtained (Table 1). Immunotherapy led to longer median survival time by 8.5 months (25.1 in the PROSTVAC arm vs 16.6 months in the placebo group) [13], corrected in the revised analysis [18] even to 9.9 months (26.2 vs 16.3 months). However, median survival in the control arm differed significantly from Halabi prognostic calculations and was about 4 months shorter. Despite much efforts during randomization, aimed at balancing patients’ assignment to the placebo arm, there were some notable differences favoring better survival in patients from the vaccine arm. Patients treated with PROSTVAC were apparently younger (median age 72 years vs 79 years in the control), and 4 important

### Table 1. Comparison of patient characteristics and results of the sipuleucel-T phase III and PROSTVAC phase II clinical trials conducted simultaneously in the first decade of the current century

|                        | Sipuleucel-T (active antigen: prostate acidic phosphatase – PAP) | PROSTVAC (active antigen: prostate-specific antigen – PSA) |
|------------------------|---------------------------------------------------------------|----------------------------------------------------------|
| **Enrolling period**   | 2003–2007                                                      | 2003–2005                                                 |
| **Eligibility criteria** | Asymptomatic and minimally symptomatic mCRPC; Gleason score ≤7 and next – any, ECOG 0 or 1, no visceral metastases, no more than 2 chemotherapy regimens before enrollment | Minimally symptomatic mCRPC, Gleason score ≤7, ECOG 0 or 1, no visceral metastases, no prior chemotherapy |
| **Treatment**          | Standard treatment, including docetaxel                        | Standard treatment, including docetaxel, or (in 49% patients) Sipuleucel-T-mimicking agent as a crossover treatment, first, and next standard treatment | No data |
| **Number of patients enrolled** | 341                                                            | 82                                                        | 40 |
| **Median age**         | 72                                                             | 72                                                        | 79 |
| **Serum PSA (median, ng/ml)** | 52                                                             | 36                                                        | 45 |
| **Patients with Gleason score more than 7 (%)** | 25                                                             | 0                                                         | 0 |
| **Additional treatment after completion of the treatment phase or after progression** | Standard treatment, including docetaxel | PROSTVAC as a crossover treatment in 48% patients after progression, other treatment – no data |
| **Progression-free survival (median, months)** | 3.7                                                            | 3.8                                                       | 3.7 |
| **Halabi-predicted survival (median, months)** | 20.3                                                           | 22.5                                                      | 20.4 |
| **Median overall survival (months)** | 25.8                                                           | 25.1*                                                     | 16.6* |

*According to the revised analysis, median overall survival was 26.2 and 16.3 months, respectively [18]. mCRPC – metastatic castration resistant prostate cancer; ECOG – Eastern Cooperative Oncology Group; GM-CSF – granulocyte-macrophage colony-stimulating factor.
prognostic parameters in the blood (PSA, lactate dehydrogenase, alkaline phosphatase, and hemoglobin) were better [13]. Unfortunately, no detailed information concerning additional treatment at disease progression, both in the active arm and in the placebo patients, were reported. One may assume that the best treatment available at that time was used (docetaxel) but since in approximately 50% of control patients PROSTVAC was offered after cancer progression, chemotherapy could be delayed in those patients. The above listed objections may partly explain the large difference in median survival time between the active and control arm but the fact cannot be ignored that cytotoxic T cells against PSA developed in some patients [19], which could kill prostate cancer cells and prolong survival.

Sipuleucel-T (PROCEED study) vs PROSTVAC (NCT01322490, EudraCT 2010-021196-85 trial) in the second decade of the current century

Following the FDA-approval of sipuleucel-T for treatment of mCRPC, the vaccine was recommended especially for asymptomatic patients with slowly progressing disease [20]. However, sipuleucel-T is not licensed in Europe and although the risk of severe adverse events of the treatment is relatively low, the costs of the therapy - relative to overall benefits – are huge. This drawback, together with controversy regarding the control group in the IMPACT study and concerns about detrimental effects of leukapheresis hampered the widespread use of the medication [21, 22]. In 2011–2017, the large observational study (registry) was conducted (PROCEED, NCT01306890), evaluating sipuleucel-T immunotherapy in mCRPC, and aimed at quantification of cerebro-vascular event (CVE) risk and overall survival [16] (Table 2). The registry included 1902 patients who had 1 or more sipuleucel-T infusions. Patients were enrolled without randomization and no blinding. Generally, baseline demographic and disease characteristics and other data were similar to that in the IMPACT study which was conducted 10 years earlier. However, major differences were also notable, related in part to new drugs and treatments introduced in urologic oncology after termination of the IMPACT study. In the PROCEED population, patients had shorter interval from diagnosis of prostate cancer to first sipuleucel-T infusion (median 5 months in comparison with 7.1 months in the IMPACT study) and much lower PSA in serum (15 vs 52 ng/ml). Percentage of patients with bone metastases >10 was lower in PROCEED than

Table 2. Comparison of patient characteristics and results of the sipuleucel-T PROCEED study and PROSTVAC phase III clinical trial conducted simultaneously in the second decade of the current century

|                                | Sipuleucel-T (active antigen: prostate acidic phosphatase – PAP) | PROSTVAC (active antigen: prostate-specific antigen – PSA) |
|--------------------------------|---------------------------------------------------------------|-------------------------------------------------------------|
| **Enrolling period**           | 2011–2017                                                    | 2011–2015                                                  |
| **Eligibility criteria/final status** | mCRPC                                                       | Asymptomatic or minimally symptomatic mCRPC, Gleason score – no data, ECOG 0 or 1 (in arms: 99.6, 99.3, 100%, respectively), visceral metastases (in arms: 9.5, 7.4, 8.3%, respectively) |
| **Treatment**                  | Sipuleucel-T                                                  | PROSTVAC                                                   |
| **Number of patients enrolled**| 1902                                                         | 432                                                        |
| **Age**                        | Median: 72                                                   | Mean: 71                                                   |
| **Serum PSA (ng/ml)**          | Median: 15                                                   | Mean: 71                                                   |
| **Halabi-predicted survival**  | No data                                                      | No data                                                    |
| **Additional treatment after completion of the treatment phase (% patients)** | Standard anticancer interventions (77.1%)                   | Standard-of-care treatment                                  |
|                                |                                                               | 69.7%                                                      |
| **Progression-free survival (median, months)** | No data                                                     | 66.0%                                                      |
| **Median overall survival (months)** | 30.7                                                        | 63.3%                                                      |

*The trial was stopped in September 27, 2017, after the third interim analysis, due to the meeting criteria of futility and the overall ineffectiveness of PROSTVAC vs placebo mCRPC – metastatic castration resistant prostate cancer; ECOG – Eastern Cooperative Oncology Group; GM-CSF – granulocyte-macrophage colony-stimulating factor.
in IMPACT (17.2 vs 42.8%) but proportion of patients with Gleason score ≥8 was higher in PROCEED (50.6 vs 24.6%). The number of African Americans was notably higher in the PROCEED study (11.6 vs 6.7% in IMPACT trial). The CVE incidence in the PROCEED was comparable to that observed in the Medicare database. The median survival time in the PROCEED registry was 30.7 months – much better than in the IMPACT trial (25.8 months). This improvement in survival may have resulted from more efficient treatment at disease progression, related to new FDA-approvals. Apart from sipuleucel-T, four life-prolonging therapeutics for treatment of prostate cancer have been approved in 2010–2013: enzalutamide, abiraterone, cabazitaxel and radium-223. As mentioned above, a higher proportion of African Americans were enrolled in the PROCEED study. This predictor [23], together with lower baseline PSA level, might have acted in favor of longer survival in PROCEED patients. Of note, unlike in Halabi analysis [24], age of patients in the PROCEED registry emerged as a statistically significant parameter influencing overall survival: younger patients with prostate cancer lived longer than older ones.

In parallel to the sipuleucel-T-based PROCEED study, phase III trial of PROSTVAC vaccine in asymptomatic or minimally symptomatic patients with mCRPC was conducted (EudraCT 2010-021196-85) [15] (Table 2). In this international multicenter study, patients were randomly assigned to three arms: PROSTVAC alone, PROSTVAC + GM-CSF, and placebo. The treatment regimen was the same as in very encouraging phase II study: priming with vaccinia virus vector containing PSA-TRICOM transgene (PROSTVAC-V) and boosting immunizations with PSA-TRICOM transgene-containing fowlpox virus (PROSTVAC-F). The arms were reasonably well balanced, and a total number of 1286 of patients were enrolled and analyzed for overall survival and for proportion of patients alive without events at 6 months post-random assignment. Unfortunately, after the third interim analysis, the trial was stopped because criteria of futility were met and, in fact, median overall survival times of patients in individual arms were similar (34.4 vs 33.2 vs 34.3 months in PROSTVAC alone, PROSTVAC + GM-CSF, and placebo arm, respectively). In light of the very encouraging results and large 8.5-months difference in median survival time between the active and control arm in phase II trial, results of the phase III study have been very disappointing. However, median survivals of patients in the phase III trial, independently of treatment, were relatively long. Certainly, life-prolonging therapeutic agents that were approved by FDA in 2010–2013, which were administered at the time of the disease progression in the long-term follow-up period, could negatively affect the likelihood of any effect of the PROSTVAC vaccine. No differences in overall survival between active arms and the control is much more difficult to explain. PROSTVAC vaccination induces T cells and increases infiltration of these cells into the tumor microenvironment in the treated patients [19, 25], but this immune response did not translate into clinical benefit. It is the question of debate and further studies, if strong immunosuppressive mechanisms in the microenvironment really prevented any T cell effect in prostate cancer.

**DISCUSSION**

There are two cardinal factors necessary for displaying superiority of the tested medication over the control in clinical trials: well-designed study (randomization of patients, double-blinding, homogenous population of patients, etc.), including posttreatment period, and the potency of the tested agent. Statistically significant effect can be obtained in experimental preclinical models using inbred animals even in case of a poorly active drug. However, in controlled, randomized, double-blinded studies it is not possible to avoid potential biases that can confound the final conclusions [26]. PROSTVAC and sipuleucel-T have been the most extensively studied therapeutic cancer vaccines in urologic oncology. As shown in Table 1, both vaccines were tested in the first decade of the current century in very similar patient populations (asymptomatic or minimally symptomatic mCRPC), conducted almost at the same period, with docetaxel as the only therapeutic option (phase III trial – sipuleucel-T, phase II clinical trial – PROSTVAC). Yet, finally, only sipuleucel-T got the approval (in 2010) and is currently recommended, as an option, preferentially in patients with asymptomatic or minimally asymptomatic mCRPC with prior novel hormone therapy and no prior docetaxel treatment [3]. PROSTVAC vaccine seemed to be a better candidate for treatment of mCRPC than sipuleucel-T, bringing about much longer median overall survival in phase II trial (8.4 vs 4.1 months, respectively) [12, 13]. However, despite these encouraging results, no survival benefit of PROSTVAC compared to placebo was reported in the pivotal phase III trial [15]. It is worth emphasizing, that in a parallel sipuleucel-T observational PROCEED study, conducted at the same time as phase III trial of PROSTVAC and recruiting similar patient population at the same landscape of treatment possible to use after disease progression, median overall survival time...
of prostate cancer patients seemed to be shorter than that in PROSTVAC vaccine-treated patients (30.7 vs 34.4 months, respectively). Of note, patients treated with PROSTVAC in phase III trial were characterized at the start of the study by ‘worse’ baseline level of PSA, a very important prognostic parameter, in comparison with sipuleucel-T-treated patients from PROCEED study (71.4 vs 15 ng/ml) [14, 15]. These data, like those from 10 years ago, suggested superior therapeutic activity of PROSTVAC cancer vaccine over sipuleucel-T in the treatment of prostate cancer patients. Addition of GM-CSF to PROSTVAC vaccine did not improve survival [15].

The most enigmatic finding in the phase III trial of PROSTVAC was almost identical median overall survival in PROSTVAC and placebo arms (34.4 vs 34.3 months). Since patients were perfectly matched for most important prognostic factors in both arms, investigators concluded that PROSTVAC vaccine simply did not work. They also considered possibility that standard life-prolonging drugs, used as additional treatment during disease progression, negatively affected the likelihood of achieving positive results [15]. However, the authors of the report of phase III trial of PROSTVAC did not consider the probable option of positive effects of the placebo administration. The overall antitumor defense is a result of complex interactions of both acquired (specific) and innate mechanisms (CTLs, antibodies, NK cells, Tγδ cells, NKT cells, cytokines, etc.) [27, 28]. The authors overlooked the fact that in the placebo group (patients injected with vaccinia or fowlpox vectors), the immune system was evidently activated, both locally and systemically in a similar degree as that in the active (PROSTVAC) arm (injection site erythema: 46.6 vs 46.3%, injection site induration: 10.7 vs 13.6%, influenza-like symptoms: 8.2 vs 7.5% patients, respectively) [15]. Therefore, one cannot rule out the possibility that the hypothesis: ‘PROSTVAC and placebo (the control) is not effective’ is false, and the hypothesis: ‘PROSTVAC and placebo work’ is true. Certainly, the fourth arm in phase III PROSTVAC study (saline injections) would be informative in this matter.

Interestingly, although checkpoint inhibitors in monotherapy were found effective in several cancers, e.g. renal cancer or melanoma, unacceptable low response rates (about 10%) are observed in mCRPC [29]. Prostate cancer is thought to be heterogenous disease with highly complexed tumor immune microenvironment [30]. The prostate is in some respects different from other human organs because, at least in the absence of cancer, it is immunologically ignored [7]. Furthermore, mCRPC is thought to produce an increased local immunosuppression, including impaired expression of CD3ζ in T cells, a key signaling molecule for T-cell receptor [29]. Another mechanism may involve different androgen-ablation effects with the variety of potential targets within immune system [30].

There are plenty of evidence, both experimental [31, 32] and clinical [33, 34], that non-specific activation of the immune system may lead to the measurable antitumor effect. The most evident example of beneficial effects of non-specific active immunotherapy are Bacillus Calmette-Guérin (BCG) intravesical infusions for treatment of superficial bladder cancer [35]. In case of mCRPC, it is thought that immunotherapy based on a single agent is unlikely to be efficient. The possible promising approaches taken into consideration comprise vaccine and cytokine combination therapy or vaccine and checkpoint inhibitor combination therapy [30] or CAR-T cell therapy through PSMA-based designs (NCT03089203).

In light of the above data, studies on the antitumor effect of PROSTVAC in prostate cancer patients are worth continuing.

CONCLUSIONS

Both sipuleucel-T and PROSTVAC induce specific antitumor T cells that are capable of infiltrating stroma of prostate cancer [25, 36]. This immune response was proved effective in case of sipuleucel-T, resulting in approval of this therapeutic in 2010 by FDA, but have not evidenced to work in PROSTVAC-treated patients [12, 15]. However, as noted in the ‘Discussion’ section, PROSTVAC cancer vaccine appeared to be as effective as sipuleucel-T.

In contrast to vaccination against infectious disease, the mechanisms of beneficial therapeutic effects of cancer vaccines in clinical oncology seem quite different and, in fact, the final effect is not mediated by the same components of the immune system. Several factors influence the efficacy of therapeutic cancer vaccines. It should be taken into account that:

- In case of cancer vaccines, the best results can be expected if both specific and nonspecific immune mechanisms are activated. Development of treatment-related adverse events, such as pyrexia or flu-like symptoms, if moderate, should be considered as desirable and having a positive prognostic significance, in the light of anecdotal case reports showing spectacular curative effects of hyperthermia in prostate cancer and effects of historical Coley’s toxins [37, 38].

- Application of cancer vaccines in a patient should be permanent, with the continuous modification of the vaccine antigens being preferred. It might have prevented tumor escape mechanisms.
– Preferential use of cancer vaccines should apply, as PROCEED observational study suggests [16], to selected patients, e.g., at an early stage of cancer development.

– It seems that the efficacy of therapeutic cancer vaccines can be increased by combination treatment aimed at modifying the strongly negative impact of immunosuppressive factors in the tumor microenvironment. This concept has currently been tested in several clinical trials in which sipuleucel-T and PROSTVAC vaccines are combined with immune checkpoint inhibitors [39].

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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