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Review

Developing immunotherapy strategies in the treatment of prostate cancer

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Abstract The clinical development of immunotherapy has gained significant impetus in recent years across the field of medical oncology. Mounting preclinical and clinical data have demonstrated the potential of immune-based treatments to augment anti-tumor immune responses. With one of the first modern immunotherapies approved in prostate cancer and multiple others in late stage development, immune treatment strategies need to be optimized to ensure the best clinical outcomes. Combination strategies with androgen deprivation therapy, anti-androgen therapy, radiation and chemotherapy have demonstrated the potential maximize immune response in prostate cancer patients. These combinations are currently being evaluated in clinical trials at every stage of prostate cancer from the newly diagnosed to the most advanced stages. Data from these studies will provide guidance for the future clinical implementation of immunotherapy in prostate cancer.

1. Introduction

Amid the significant excitement surrounding immunotherapy currently being developed for many types of cancer, it is easy to forget that the first immunotherapy developed as part of this immunoncology revolution was sipuleucel-T for prostate cancer in 2010 [1]. While much of the current focus of immunotherapy development is focused on immune checkpoint inhibitors, therapeutic cancer vaccines have less toxicity and may provide a means by which the efficacy of immune checkpoint inhibitors could be optimized [2]. Emerging preclinical and clinical data suggest that vaccines can also be combined with standard therapies such as chemotherapy, radiopharmaceuticals, and anti-androgen therapy based on synergistic properties of immune activation.

2. Clinical development of immunotherapy in prostate cancer

Sipuleucel-T is a therapeutic cancer vaccine that targets prostatic acid phosphatase (PAP) and has been approved by

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the United States Food and Drug Administration (FDA) for the treatment of metastatic castration resistant prostate cancer (mCRPC) [1,3] (Table 1). This treatment is generated from a patient's own immune cells which are processed *ex vivo* at a central processing facility. The process is initiated when patients have their peripheral blood immune cells extracted from circulation via apheresis. The immune cells are then shipped to the central processing facility where they are exposed to the target antigen PAP and granulocyte − monocyte colony stimulating factor over a 48 h period [3]. Once the processing is complete, immune release criteria are confirmed based on CD54 expression [4]. Immune cells are then shipped back to the patient's infusion center where they are re-infused into the patient's circulation. A full course of therapy consists of three infusions done every 2 weeks over the course of one month. Preliminary phase 1 studies with this therapy demonstrated that the strategy was well tolerated with limited toxicity include infusion reactions and transient flu associated symptoms [3].

The phase 3 study enrolled 512 patients with mCRPC and randomly assigned patients in a 2:1 fashion to either sipuleucel-T or placebo [1]. The findings of the study demonstrated a 22% reduction in the risk of death for patients randomly assigned to treatment with sipuleucel-T (hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.61 to 0.98; $p = 0.03$). In association with that finding was a median improvement in survival of 25.8 months in the sipuleucel-T arm of the study compared to 21.7 months in the patients treated with placebo. The treatment was again well tolerated similar to the phase 1 studies with transient fevers, chills and headache representing the most commonly observed toxicity. A recent analysis of the placebo arm of this trial suggests that a salvage therapy given as part of a planned cross-over in the definitive phase 3 trial resulted in survival times that were longer than expected in that group [5]. If that interpretation is accurate, the survival effect of sipuleucel-T in mCRPC may actually be underestimated in this study.

The most controversial finding of the study was the fact that disease progression was equivalent in both arms of the study. Although such findings are more commonly observed in immunotherapy trials since the publication of these results, this apparent paradox between improved survival despite lack of change in (short-term) progression free survival was relatively unique at that time [6]. Indeed this was not the first time this apparent discrepancy was observed. An earlier phase 3 trial evaluating sipuleucel-T which enrolled 125 patients, but demonstrated no difference between progression free survival despite an improved overall survival advantage (a benefit that was similar to the larger phase 3 trial) [1,7]. In fact, it was the findings of this initial phase 3 trial that led to the redesign and initiation of a subsequent phase 3 trial with overall survival as an endpoint. It is also worth noting that the same phenomenon (improved survival without a change in short-term progression) was observed in the metastatic melanoma trials with ipilimumab which led to its FDA approval and wide use [8]. Despite the apparent consistency between these two studies involving sipuleucel-T and the study of immunotherapy in melanoma, there was significant skepticism about the efficacy of sipuleucel-T and its true therapeutic benefit in men with advanced prostate cancer. Despite the randomized data and growing support for immunotherapy in general, much of this uncertainty remains to this day, limiting the number of patients who are actually treated with sipuleucel-T.

A subsequent clinical trial involving sipuleucel-T in the neoadjuvant setting has potentially provided immunologic mechanism of action data which has substantially contributed to the understanding of how sipuleucel-T may induce immune responses in patients with prostate cancer [9]. This trial enrolled men who are candidates for definitive radical prostatectomy to treat newly diagnosed prostate cancer. Patients were given neoadjuvant sipuleucel-T and then the prostate tissue was evaluated after surgical resection. The results suggested a greater than three-fold increase in infiltrating T cells at the benign

Table 1 Key trial results of Sipuleucel-T in prostate cancer.

Ref.	Trial and population	Patients (*n*)	Summary of key findings
Kantoff et al. [1]	Phase 3 trial in metastatic castration resistant prostate cancer	512	Demonstrated an improvement in overall survival of 25.8 months in the sipuleucel-T arm of the study compared to 21.7 months in the placebo arm (hazard ratio, 0.78; 95% confidence interval, 0.61 to 0.98; $p = 0.03$)
Schellhammer et al. [13]	Phase 3 trial in metastatic castration resistant prostate cancer	512	A retrospective analysis suggested that patients with a PSA less than or equal to 22.1 ng/mL had a 62.6% three-year estimated survival after treatment with sipuleucel-T compared to 41.6% in the placebo group. These data suggest that patients with lower tumor volume may benefit most from sipuleucel-T
Fong et al. [9]	A phase 2 study using sipuleucel-T in the neoadjuvant setting before radical prostatectomy	42	The study found a greater than three-fold increase in infiltrating T cells at the benign tissue-tumor interface within the prostate ($p < 0.001$) after treatment with sipuleucel-T compared to pre-treatment biopsies. This study suggested that sipuleucel-T can mobilize T cells to the tumor microenvironment

PSA, prostate specific antigen.

tissue–tumor interface within the prostate ($p < 0.001$) after treatment with sipuleucel-T compared to pre-treatment biopsies. These findings after radical prostatectomy were not seen in the control group of 12 untreated patients that were used for comparison. These findings suggest that sipuleucel-T activated immune cells and ultimately drove them to the primary tumor and its microenvironment.

Developing immune checkpoint inhibitors in prostate cancer has also been explored in mCRPC. Ipilimumab is an antibody targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a checkpoint molecule expressed by activated T cells. Blocking this molecule has been shown to mitigate auto-regulation by the immune system, lead to both autoimmune and anti-cancer effects [10]. This agent has demonstrated the ability to improve survival (also without a progression free survival benefit) in metastatic melanoma [8]. Ipilimumab has been evaluated in two phase 3 trials in mCRPC, involving patients who were both chemotherapy-naïve and those who had been previously treated with chemotherapy. The trial in the most advanced population, those had previously been treated with docetaxel, randomized patients to either placebo or ipilimumab included radiation [11]. All patients were also treated with low dose radiation to a limited number of metastatic bone lesions. This was not done for therapeutic purposes, but rather as an immune adjuvant based on preliminary data that suggested that such radiation could be combined with ipilimumab to enhance the immune responses [12]. Despite a trend to improved outcomes in patients treated with ipilimumab, the trial failed to meet its primary endpoint of overall survival (median overall survival of 11.2 months in the ipilimumab arm compared to 10 months in the control arm; HR, 0.85, 95% CI, 0.72–1.00; $p = 0.053$) [11]. To this point the trial in chemotherapy-naïve patients (NCT01057810), which randomized patients to either placebo or ipilimumab (without radiation) has not reported a survival benefit either. Therefore the role of immune checkpoint inhibitors as monotherapy in prostate cancer remains undefined.

3. Who should be treated with immunotherapy in prostate cancer?

Identifying the appropriate patients who could benefit from immunotherapy remains a challenge in medical oncology. Retrospective data in prostate cancer, however, suggest that patients with relatively less tumor burden and more indolent disease characteristics are more likely to have improved clinical outcomes after being treated with immunotherapy. These data provide some degree of clinical instruction for the use of sipuleucel-T in prostate cancer and also provide guidance in the development of new clinical trials investigating immunotherapy for prostate cancer.

Although there are many caveats about the use of prostate specific antigen (PSA) given interpatient variability, a retrospective analysis of the registration phase 3 trial for sipuleucel-T suggests that patients with a lower PSA derive the greatest benefit from treatment with the therapeutic cancer vaccine [13]. Of the 512 patients enrolled in the study, the quartile of patients which had the lowest PSA had values less than or equal to 22.1 ng/mL. The overall survival HR for these patients was 0.51 (95% CI, 0.31–0.85) and substantially better than the patients in the highest quartile, whose PSA values were greater than 134 ng/mL (HR, 0.84; 95% CI, 0.55–1.29). This analysis suggested that patients with a PSA less than or equal to 22.1 ng/mL had a 62.6% 3-year estimated survival after treatment with sipuleucel-T which demonstrated a substantial improvement compared to patients randomized to the control arm of the study (3-year survival was 41.6%). Despite the fact that PSA is not a perfect surrogate for tumor burden, these data suggest that patients with relatively lower tumor burdens are perhaps most appropriate for treatment with immunotherapy relative to patients with higher volume disease.

Similar findings were seen in a prespecified analysis of the ipilimumab trial in mCRPC that enrolled patients who have already been treated with docetaxel [11]. Although the study failed to meet its primary endpoint of overall survival (median overall survival of 11.2 months in the ipilimumab arm vs. 10 months in the control arm; HR, 0.85, 95% CI, 0.72–1.00; $p = 0.053$), there was a suggestion that patients with more favorable or indolent disease characteristics had a better clinical response to the ipilimumab and protocol-specified radiation to bone metastases relative to the control arm of the study. Patients receiving ipilimumab ($n = 146$) that had an alkaline phosphatase less than 1.5 times the upper limit of normal, a hemoglobin concentration greater than 110 g/L in the absence of visceral metastases had improved overall survival relative to patients with the same characteristics who were treated with placebo ($n = 142$). The median survival in this subgroup was 22.7 months compared to 15.8 months (HR, 0.62, 95%CI, 0.45–0.86; $p = 0.0038$), favoring patients treated with ipilimumab.

The findings demonstrated in these two phase 3 trial subgroup analyses was also seen in an earlier phase 2 trial with the pox viral based therapeutic cancer vaccine prostvac in mCRPC. A single arm phase 2 study of 32 patients evaluated patients who had a predicted survival of greater than 18 months and compared them to patients who had a predicted survival of less than 18 months using a contemporary and established predictive nomogram for mCRPC patients [14]. The findings of the study suggested that patients with a longer predicted survival had a median survival of greater than 37.3 months relative to a predicted survival of 20.9 months. For patients with a shorter predict survival of less than 18 months, after treatment with vaccine the median survival was 14.6 months compared to a median predicted survival of 12.3 months.

The combined data from these three trials does not provide rigid guidelines for who should be treated with immunotherapy in advanced prostate cancer, but they do provide a rationale to treat patients with relatively indolent disease characteristics or lower tumor burden with immunotherapy. While this cannot guarantee clinical benefit, it may provide appropriate clinical guidance for which patients are likely to benefit from such therapies. Also these data provide the basis for future clinical trial

designs evaluating immunotherapy in patients with similar characteristics.

4. Immunotherapy combination strategies

4.1. Androgen deprivation therapy

Although sipuleucel-T has demonstrated independent ability to extend survival in patients with advanced prostate cancer, there is a substantial amount of preclinical data suggesting potential immunologic synergy between other standard therapies in prostate cancer and immunotherapy. One example is androgen deprivation therapy which is the cornerstone of therapy for patients with metastatic disease [15]. Androgen deprivation therapy is also used in patients with intermediate or high risk disease who are treated with definitive radiation, and patients with biochemical recurrent disease who are unsuccessfully treated with definitive radiation or surgery and then develop recurrent disease which is only detected by elevated PSA levels. Preclinical data have suggested that androgen deprivation therapy can induce T cell migration to the prostate, decrease immune tolerance for self antigens, and lead to the increase of naïve T cells produced from the thymus [16—18]. These findings provide the rationale for combining immunotherapy with androgen deprivation therapy in prostate cancer.

A previous clinical trial has demonstrated the ability for androgen deprivation therapy to increase the production of naïve T cells from thymus in humans, corroborating the findings in preclinical models [18,19]. In this trial [18] patients were given a 3-month depot dose of a Gonadotropin-releasing hormone (GnRH) agonist, and were evaluated for both naïve T cell production as well as changes in T cell receptor excision circles (TRECS). The latter are the byproduct of T cell receptor gene rearrangement that occurs when naïve T cells are produced from the thymus, thereby providing an indirect measure of thymic activity. In this trial naïve T cells were found to increase from 3.25% of $CD3^+$ T cells to 3.95% of $CD3^+$ T cells ($p = 0.0060$). In addition, TRECs increased from 93 per 100,000 cells to 147 per 100,000 cells ($p = 0.0025$). These naïve T cells could enhance immune responses independently or, when androgen deprivation therapy is combined with immunotherapy, these new T cells could be activated and have enhanced immune targeting of prostate cancer cells.

Another trial evaluated sipuleucel-T in combination with androgen deprivation therapy. The study was designed to evaluate the optimal scheduling of a therapeutic cancer vaccine in conjunction with androgen deprivation therapy [20]. Patients were randomized to either sipuleucel-T followed by 12 months of androgen deprivation therapy or sipuleucel-T given three months after androgen deprivation therapy was initiated and continued for a total of 12 months. The findings suggested that optimal immune responses were seen when sipuleucel-T was given after androgen deprivation therapy as opposed to prior to androgen deprivation therapy. Relative increases were seen in multiple cytokine subsets as well as antigen specific immune responses in a group that received sipuleucel-T after androgen deprivation therapy. This could provide evidence that the naïve T cells induced by androgen deprivation therapy are being activated by the vaccine. Ultimately clinical outcomes related to the immune responses will be required to pursue this strategy further however, these data do provide further rationale for combining androgen deprivation therapy with immunotherapy.

4.2. Anti-androgen therapy

In recent years, substantial improvements have been made in the treatment of prostate cancer, including the development of new anti-androgen therapies such as enzalutamide and abiraterone [21]. Preclinical data have again suggested that enzalutamide is capable of inducing naïve T cells from the thymus, similar to androgen deprivation therapy. Preclinical studies in male C57BL/6 mice demonstrated that after 14 days there were statistically significant changes in thymic weight and TREC production [22]. In addition enzalutamide demonstrated the ability to induce immunogenic modulation of the tumor. Relative to controls enzalutamide was able to increase major histocompatibility complex class 1 (MHC1) expression by five-fold and Fas ligand expression by nearly two-fold. The former may be critical in helping the immune system recognize tumor cells while the latter may enable immune cells to engage and kill cancer cells. These findings were associated with increased antigen specific immune cell lysis of prostate cancer cells *in vitro*.

These results provide the basis for several ongoing clinical trials combining immunotherapy with enzalutamide. Two of the studies are combining enzalutamide with therapeutic cancer vaccine prostvac. One study is enrolling patients in mCRPC in an effort to determine if prostvac can enhance the time to progression already seen with enzalutamide alone (NCT01867333). A second trial combined prostvac with enzalutamide in a short 3-month course in patients with biochemically recurrent prostate cancer (NCT01875250). The latter group consisted of patients who had normal testosterone levels and therefore allowed for the evaluation of the immunologic impact of enzalutamide independent of androgen deprivation therapy. The preliminary findings from the study suggested that enzalutamide increased naïve T cell production as measured by TRECs [23]. Furthermore, substantial increases in natural killer cells and decreases in myeloid derived suppressor cells were also seen in these patients when baseline values were compared to post treatment assessments. These favorable immunologic findings not only support immunologic combination therapies with enzalutamide in prostate cancer, but also provide hypothesis generating data about the potential use of enzalutamide as an immune modulator in other cancers that are not driven by the androgen receptor. The clinical readouts from these and other trials will also be important in determining the role of enzalutamide and immunotherapy combinations in prostate cancer.

4.3. Radiation therapy

There is also strong preclinical and clinical data to support the role of radiation therapy as a companion treatment for

immunotherapy or even as an immune adjuvant. For years the concept of an abscopal effect has been described as an enigmatic biologic phenomenon, but the growing understanding of the antitumor effects of the immune system has provided better understanding of the potential etiology of such findings [24]. It now seems likely that radiation therapy in addition to killing cancer cells at the focal target may have a broader immunologic impact leading to responses beyond the radiation field. And although rare, reports have emerged where immunotherapy may augment these non-target immunologic effects, such as the findings reported with an immune checkpoint inhibitor given after radiation in a patient of melanoma, leading to a clinical response outside of the radiation field [25].

Preclinical data have suggested that radiation at doses lower than cytotoxic magnitude may induce immunogenic modulation of the tumor leading to increased antigen expression as well as expression of FAS ligand [26,27]. Similar to what was described with androgen deprivation therapy, enhancing the ability of the immune system to recognize the tumor as well as engage and kill the tumor cells may lead to better clinical responses. This may be an important concept to consider given that radiation does not likely hit each tumor cell with the maximum radiation dose intended. The potential role radiation in prostate cancer is also important for developing treatment strategies. Radiation can be used to cure patients in early-stage disease, salvage in patients who have had surgery that resulted in residual disease being left behind in the prostate bed, or palliative measures in advance disease. In addition to external beam radiation, radiopharmaceuticals are also used in patients with advanced mCRPC.

An earlier study demonstrated the ability of radiation can be combined safely with a therapeutic cancer vaccine strategy in newly diagnosed prostate cancer patients. This trial treated 30 patients, 19 of which received vaccine in addition to standard radiation therapy while 11 patients received radiation therapy alone [28]. The vaccine used in this trial was a pox viral-based vaccine designed to target PSA. The results indicated that 13 of the 17 evaluable patients to that vaccine radiation at a greater than three-fold increase in PSA specific T cells after both therapies. In patients who did not receive vaccine in addition to radiation there was no increase in PSA specific T cells. These data highlight the potential for radiation to augment immune responses when combined with immunotherapy.

Another clinical trial in more advanced prostate cancer combined the therapeutic cancer vaccine prostvac with samarium 153 in patients with mCRPC [29]. Samarium 153 is an FDA approved agent which has demonstrated the ability to provide palliation for men with advanced mCRPC [30]. This study which, also had a control arm consisting of samarium 153 alone, treated a very advanced population of patients who already had progressive disease on docetaxel-based therapy. The results of the study indicated that patients who receive the combination of samarium 153 and vaccine ($n = 21$) had a greater progression free survival relative to those who received samarium 153 alone ($n = 18$). The median progression free survival times were 3.7 months *vs.* 1.7 months respectively ($p = 0.041$, HR, 0.51). In addition, all of patients who had PSA declines greater than 30% ($n = 4$, three of which were greater than 50%) were in the samarium 153 with vaccine treatment arm of study [29].

Although findings are interesting, they take on a greater degree of clinical relevance given the approval of radium 223 based on a phase 3 trial that demonstrated its ability to improve overall survival in patients with mCRPC [31]. In addition to having the potential ability to extend survival, radium 223 is much less toxic to the bone marrow than samarium 153, perhaps allowing it to be used in earlier stages of disease. Building on this data with samarium 153 and vaccine, there is an ongoing trial which is investigating the combination of sipuleucel-T with radium 223 in mCRPC (NCT02463799).

4.4. Chemotherapy

Although oncologists are well versed in the consequences of immune suppression using chemotherapy, it is now clear that there are many chemotherapies that actually have a positive impact on the immune system and its ability to mount an anti-tumor immune response. Docetaxel has demonstrated the ability to improve survival at several stages of prostate cancer [32,33]. In the most advanced stages of prostate cancer, metastatic castration resistant disease, it improves overall survival and provides substantial relief of symptoms. In recent years, the potential of docetaxel in earlier stages of disease have also been unveiled. Docetaxel for six cycles has demonstrated the ability to substantially improve survival in men with newly diagnosed (castration sensitive disease) when combined with androgen deprivation therapy compared to androgen deprivation therapy alone (57.6 *vs.* 44.0 months; HR, 0.61; $p < 0.001$) [34]. In addition, a study that administered docetaxel after radiation therapy as part of a definitive treatment strategy for high risk localized disease again suggested the benefit of this taxane [35]. The 4-year overall survival favored patients treated with adjuvant docetaxel after radiation, 93% *vs.* 89%, 1-sided $p = 0.03$, HR, 0.68. Furthermore, recent data comparing a new taxane, cabazitaxel, with docetaxel in front line mCRPC were unable to demonstrate that cabazitaxel was superior to docetaxel [36]. These findings assure that docetaxel will continue to be the premier chemotherapy in prostate cancer for years to come.

There is a body of research that supports the use of docetaxel in combination with immunotherapy which is especially valuable in prostate cancer given the multiple indications. Preclinical data have demonstrated that docetaxel can enhance tumor associated antigen expression, potentially increasing immune recognition of cancer cells. Furthermore, docetaxel was able to increase FAS expression on cancer cells, which is an important molecule whereby immune cells can engage and kill cancer cells. In addition to these findings, docetaxel has demonstrated to induce antigen spreading when used with a vaccine targeting a single antigen, suggesting that immune combinations with docetaxel could induce a broad immune response which targets the cancer in a biologically diverse manner [37,38].

Therapeutic cancer vaccines have already been combined with vaccines in several studies. Important data

from a previous study that combine vaccine with docetaxel demonstrated that docetaxel given with vaccine did not diminish the ability of the vaccine to induce an antigen-specific immune response compared to vaccine alone [39]. Another study in breast cancer with a pox viral vaccine targeting MUC-1 and CEA demonstrated an increase in progression free survival when vaccine was given with docetaxel compared to docetaxel alone (median 7.9 vs 3.9 months, HR, 0.65, meeting prespecified statistical requirements) [40]. In light of these findings, several ongoing studies are combining vaccine with docetaxel in both metastatic castration sensitive prostate cancer and mCRPC (NCT02649855, NCT02111577, NCT02293707).

4.5. Combining immunotherapies

There is also a strong rationale to combine immunotherapies with each other immune-based treatments. Preclinical data have suggested that disparate therapeutic cancer vaccine strategies can activate different immune cells, suggesting that different immune approaches may stimulate different aspects of the immune system [41]. In addition, there are clinical data suggesting that vaccines could be combined with immune checkpoint inhibitors such as ipilimumab. The findings from these studies have taken on greater meaning since phase 3 studies of ipilimumab in advance prostate cancer did not demonstrate a clinical benefit (in terms of overall survival) for ipilimumab alone [11].

One study combined ipilimumab with the whole tumor cell vaccine GVAX. This study found that 7 of the 28 patients (25%) had a greater than 50% decline of PSA relative to baseline, with stable disease ranging from 3 to 27 months and one patient (of four with measurable disease) having a complete response [42]. Another study combined ipilimumab with the pox viral-based vaccine targeting PSA, prostvac. In this trial, six of 30 patients had major PSA declines greater than 50%, and the median overall survival for all patients was 34.4 months (95%CI 29.6 to $>$41), with a 2-year benchmark overall survival analysis indicating 73% of patients were still alive [43]. These findings are greater than what has been reported with prostvac alone in terms of overall survival and PSA responses, suggesting potential synergy between these two agents.

To this point, prostate cancer is not been found to be amenable to inhibitors that target the PD1/PD-L1 one axis. Similarly, PD-L1 expression on prostate cancer tumors has reported to be much lower than on other cancers. It is possible that therapeutic cancer vaccines could help stimulate immune cells in the periphery, driving them to the tumor microenvironment as suggested by the neoadjuvant study involving sipuleucel-T [9]. Interactions that occur between immune cells in the tumor microenvironment, perhaps mediated through the cytokine INFγ, may enhance PD-L1 expression and thereby potentiate such therapies in patients or tumors those were generally thought to be "PD-L1 negative" [44]. Several current clinical trials are exploring this potential synergy in prostate cancer. Additional future studies will investigate combining immune platforms such as vaccines with immune checkpoint inhibitors and other immune agents such as (immuno)cytokines.

5. Conclusion

Despite the fact that what could be considered the first modern immunotherapy (sipuleucel-T) was approved for the treatment of prostate cancer in 2010, subsequent clinical development immunotherapy has largely occurred outside of the field of prostate cancer research. With several vaccines currently in late stages of clinical development including prostvac, it is possible that there may be more agents available in the near future. Combining these agents together, with immune checkpoint inhibitors and with standard therapeutics such as anti-androgens, radiation, and chemotherapy, could yield superior clinical outcomes. Several clinical trials are currently ongoing investigating these types of immune combinations. If proven efficacious, it may be rational to move these therapies earlier on in the disease process, perhaps including the adjutant or neoadjuvant setting. In conjunction with definitive therapies such as surgery or radiation-based therapy, future trials may explore if immune-based platforms can increase the cure rate of high-risk disease and perhaps even locally advanced or minimally metastatic disease. Despite the recent improvements in prostate cancer therapy, the journey of the treatment development continues, with ongoing immunotherapy trials helping to chart the course forward.

Conflicts of interest

The authors declare no conflict of interest.

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