UCSF
UC San Francisco Previously Published Works

Title
Immunotherapy in genitourinary malignancies

Permalink

Journal

ISSN

Authors
Wattenberg, Max M
Fong, Lawrence
Madan, Ravi A
et al.

Publication Date

DOI

Peer reviewed

Immunotherapy in Genitourinary Malignancies

Max Wattenberg[1], **Lawrence Fong**[1], **Ravi A. Madan**[2], and **James L. Gulley**[2]

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA

[2]Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

Purpose of review—Active investigation suggests immune checkpoint inhibitor therapy and therapeutic cancer vaccines provide clinical benefit for genitourinary (GU) malignancies including prostate cancer, renal cell carcinoma (RCC) and bladder cancer. Recent developments in the utility of immune checkpoint inhibitor and vaccine therapy for the management of GU malignancies are highlighted in this review.

Recent findings—Dramatic responses to checkpoint inhibitor therapy have been demonstrated in RCC and bladder cancer with recent FDA approvals in both indications. No benefit to checkpoint inhibitor therapy has yet been shown for the management of prostate cancer. Therapeutic cancer vaccines have also shown benefit in the treatment of GU malignancies, specifically in the treatment of prostate cancer. Despite advances in these therapeutic modalities, benefit is limited to a subset of patients.

Summary—Current evidence supports the use of immune checkpoint inhibitor therapy and therapeutic cancer vaccines for the management of GU malignancies. Further development of biomarkers for predicting response and study of combination therapy is required to achieve optimal efficacy with these therapeutic interventions.

Keywords

CTLA-4; PDL-1; prostate cancer; renal cell carcinoma; bladder cancer; transitional cell carcinoma; vaccines

Introduction

Immunotherapy's emergence in the treatment of cancer is having a revolutionary impact on the therapeutic landscape for many diseases. Genitourinary (GU) malignancies are among those benefiting from these new therapeutic options. Immune checkpoint inhibitors in bladder and kidney cancer and therapeutic cancer vaccines in prostate cancer are providing evidence that immune-based treatments may substantially prolong survival for patients with genitourinary malignancies.

Corresponding author: James Gulley, gulleyj@mail.nih.gov.

Dr. Madan and I have no conflicts of interest.

Immune homeostasis is maintained in part by receptors that act as checkpoints that modulate immune-cell activity [1]. We are now able to manipulate these checkpoints to achieve antitumor immune responses. Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) was the first recognized target in the rapidly expanding field of immune checkpoint inhibition. CTLA-4 is a regulator of effector (T_{eff}) and regulatory T-cell (T_{reg}) function that binds antigen-presenting cell (APC)-expressed B7 receptors (CD80/CD86) and interrupts costimulatory signaling, partially via SHP-2 phosphatase recruitment [2–4].

Ipilimumab (Yervoy; Bristol-Myers Squibb, Princeton, NJ) is a fully humanized monoclonal antibody (mAb) targeting CTLA-4. It was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the treatment of advanced melanoma after phase III studies showed improvement in overall survival (OS) [5–7]. Along with OS benefit, a small proportion of patients treated with ipilimumab achieve long-term survival [8,9]. Given the success of ipilimumab in treating melanoma, interest has developed in expanding the use of anti-CTLA-4 therapy to a range of malignancies, including those of GU origin.

Signaling through another checkpoint, PD-1 binding to its ligand PD-L1, is associated with diminished T-cell function. Agents targeting PD-1 (nivolumab and pembrolizumab) or PD-L1 (atezolizumab) have shown rapid, deep, and durable responses across a wide range of different tumors, and have now received FDA approval for melanoma, non-small cell lung cancer, renal cell cancer, and, recently, bladder cancer.

Therapeutic vaccines have also been approved for prostate cancer (sipuleucel-T) and melanoma (talimogene laherparepvec or T-Vec). These agents are designed to work at least in part by generating or augmenting an antitumor immune response.

In this review we discuss the therapeutic implications of immune checkpoint blockade and therapeutic vaccines in the management of GU malignancies, evaluate available clinical trial data, and discuss active trials awaiting completion.

Prostate Cancer

While immune checkpoint inhibitors have yet to demonstrate clinical benefit in prostate cancer, the therapeutic cancer vaccine sipuleucel-T demonstrated an ability to extend OS in patients with metastatic castration-resistant prostate cancer (mCRPC) in a randomized phase III trial (25.8 vs. 21.7 months for placebo; HR = 0.78; p = 0.03) [10]. A subsequent analysis has suggested that patients in the control arm of this study who were later given cryopreserved immune cells as part of a planned crossover may have performed better clinically than would have been expected [11]. Therefore, the results of the phase III trial may have underestimated the actual therapeutic benefit of sipuleucel-T. Another therapeutic cancer vaccine in development is PSA-TRICOM (Prostvac, developed by the U.S. National Cancer Institute [NCI], licensed to BN Immunotherapeutics, Mountain View, CA), a poxviral-based vaccine targeting prostate-specific antigen (PSA), that has demonstrated an OS advantage in a randomized phase II study and has completed accrual to a phase III trial with results expected by early 2017 [12]. It is therefore likely that vaccines will have a growing role in the treatment of prostate cancer.

One obstacle to broad acceptance of sipuleucel-T is a lack of understanding of its mechanism of action and the development of companion biomarkers. Nonetheless, evidence of immunologic efficacy was seen in patients treated with sipuleucel-T, who demonstrated antigen spreading that was associated with improved outcomes [13]. Antigen spreading is a process whereby an activated immune response increases its breadth *in vivo* by targeting additional antigens beyond the primary target, in this case prostatic acid phosphatase. These additional targets come from tumor cells killed in an immunologically relevant manner and may become more diverse and clinically relevant over time. In a secondary analysis (n = 142) in patients treated with sipuleucel-T, increased IgG responses to the secondary antigens PSA and LGALS3 were associated with an OS advantage (p 0.05). These data suggest that patients who had the greatest breadth of immune response after treatment with sipuleucel-T had better clinical outcomes. Further evidence was provided by a neoadjuvant study of sipuleucel-T prior to radical prostatectomy [14]. These findings indicated that immune cells in the tumor microenvironment increased after treatment with sipuleucel-T, suggesting that immune cells activated by the vaccine subsequently migrated to the primary prostate cancer tumors in these patients. Together, these data provide compelling evidence of sipuleucel-T's ability to generate a meaningful antitumor immune response.

Another obstacle to broad acceptance of both these vaccines is the lack of consistent reports of PSA declines that could help to identify patients who are benefiting from this therapy. Although there are no data to support an intermediate biomarker of response, a retrospective analysis of sipuleucel-T suggests that patients with relatively lower baseline PSA levels had better treatment outcomes, perhaps providing some guidance in identifying the ideal candidates for treatment with vaccines [15]. A further clinical concern is that subsequent treatment with prednisone, a companion treatment of mCRPC therapies such as abiraterone and docetaxel, has potential immunosuppressive effects. However, data from a study combining abiraterone and prednisone with sipuleucel-T suggested no decrease in immune activation with concurrent use of prednisone and sipuleucel-T [16]. Furthermore, the initial phase III trial did not suggest a negative impact in patients who went on to be treated with docetaxel and prednisone after treatment with sipuleucel-T [10]. This growing body of data suggests substantial potential for therapeutic cancer vaccines in the treatment of mCRPC.

Preclinical studies set the stage for in-human trials of anti-CTLA-4 therapy in prostate cancer. Two important studies by Kwon *et al.* demonstrated the activity of anti-CTLA-4 therapy in a TRAMP prostate cancer cell line (C57BL/6 mouse model). Mice treated with anti-CTLA-4 mAb had a significant increase in tumor rejection compared to those treated with placebo, and this effect extended into a metastatic prostate cancer model [17,18]. Multiple combination strategies have been explored in the preclinical setting and have shown statistical benefit, including T_{reg} depletion prior to anti-CTLA-4 therapy, activation of the inducible costimulator (ICOS) pathway to enhance CTLA-4 blockade, and OX40 agonism combined with CTLA-4 blockade [19–21].

Building on available preclinical data, several phase I/II hypothesis-generating trials have suggested the clinical utility of ipilimumab in the treatment of prostate cancer. In phase I dose-escalation studies combining ipilimumab with the tumor-cell vaccine GVAX (Cell Genesys Inc., San Francisco, CA) or PSA-TRICOM, PSA declines > 50% from baseline

were seen in a minority of mCRPC patients [22,23]. A phase Ib study of mCRPC patients treated with ipilimumab plus GM-CSF also demonstrated PSA response. Low pre-treatment levels of surface PD-1 on T_{eff} cells were correlated with improved OS. In a separate analysis, responders (defined as > 50% PSA decline from baseline) were shown to generate Ab responses to a higher number of antigens than were non-responders [24–26]. Ipilimumab was combined with palliative radiation (XRT) in a phase I/II study. mCRPC patients were treated in a dose-escalation method with ipilimumab ± single-dose (8 Gy) XRT to bone metastases. Among patients treated with the highest dose of ipilimumab (10 mg/kg) ± XRT, 16% demonstrated PSA declines > 50% from baseline [27]. Although response rates were seen in these trials, they were generally low. Further optimizing timing and dosing of checkpoint inhibition in combination with alternative therapies, as well as defining predictors of response to therapy, requires further study.

A phase III, randomized, double-blinded, multicenter trial evaluated mCRPC patients with at least one bone metastasis amenable to XRT who had progressed on docetaxel. Patients were randomized to receive either bone-directed palliative radiation (XRT; single dose of 8 Gy) followed by ipilimumab 10 mg/kg or placebo. Median OS was 11.2 months in the ipilimumab group and 10.0 months in the placebo group (HR 0.85, 95% CI 0.72–1.00; p = 0.053), initially suggesting no clinical benefit from ipilimumab therapy. However, a crossover of the Kaplan-Meier curve was noted at 7 to 8 months, and on further analysis the proportional hazard assumption was violated. Modeling showed that the HR decreased over time; after 12 months the HR was 0.60 (95% CI 0.43–0.86), suggesting a late benefit from ipilimumab therapy. Also of interest, *post hoc* analysis showed possible benefit in patients with pre-treatment alkaline phosphatase < 1.5 times the upper limit of normal, hemoglobin > 11 g/dL, and no visceral metastasis [28]. Updated OS results at 3 years showed maintained results, as in the primary analysis, as well as a 3-year OS of 12% in the ipilimumab group versus 6% in the placebo group [29]. Although the primary endpoint was not met in this phase III trial, questions remain concerning the choice of ipilimumab and XRT dose and sequence of therapy, as well as the inclusion of patients with visceral metastatic disease and prior treatment with chemotherapy. A phase III trial for which results are not yet available included treatment-naïve patients with no visceral metastatic disease and may help answer the questions generated by the previously discussed trial (Table 1).

Recent studies have suggested limited antitumor immune infiltrates in prostate cancer with minimal associated PD-L1 expression [30]. This may explain the lack of objective response rate (ORR) seen to date with agents targeting PD-1 or PD-L1 in prostate cancer [31]. A recent phase II trial showed dramatic differential in response to anti-PD-1 therapy based on mismatch repair proficiency or deficiency. Mismatch repair mutation status is known to be important for the management of colorectal cancer, but this study suggested its use as a biomarker of response to checkpoint inhibition in the treatment of a range of solid malignancies. Mismatch repair deficiency may allow for increased burden of somatic mutations, leading to generation of tumor-associated antigens that are then targeted by a checkpoint inhibitor-generated immune response [32]. An analysis of prostate tumors has shown that up to 22% of tested samples had mutations in DNA repair/recombination genes, including MSH2 and MSH6, suggesting that mismatch repair could play a role in response to checkpoint inhibition in GU malignancies [33]. In addition, there are ongoing studies

combining vaccines with agents targeting this pathway to see if this combination approach can provide the underlying immune response (with vaccines) whose activity can be enhanced by blocking PD-1 or PD-L1 [34].

Renal Cell Carcinoma

Renal cell carcinoma (RCC) is considered to be immunotherapy-responsive. Anti-PD-1 therapy in the form of nivolumab (Opdivo; Bristol-Myers Squibb, Princeton, NJ) was recently FDA-approved for treatment of advanced RCC based on a phase III trial demonstrating significant OS benefit [35]. A recently published study in advanced RCC randomized patients who had one or two lines of prior antiangiogenic therapy to nivolumab (n = 410) or everolimus (n = 411). While progression-free survival was similar between the groups, the primary endpoint of OS favored nivolumab, with a 27% reduction in the risk of death (p = 0.002) [35]. Furthermore, those patients who received nivolumab had a higher ORR (25% vs. 5%), and a lower proportion of patients developed grade 3 toxicities (19% vs. 37%). This led to FDA approval of nivolumab for advanced RCC in 2015. There are a number of ongoing studies of PD-1 and PD-L1 inhibitors alone or in combination with other agents for RCC.

Despite the success of alternative immune checkpoint targets, CTLA-4 blockade monotherapy for the treatment of RCC has not been definitively examined in a phase III trial. In a mouse model of RCC, CTLA-4 blockade significantly inhibited tumor growth, and available phase I and II trial data suggest RCC response to monotherapy [36–38]. In a safety study, 61 patients with RCC were treated with ipilimumab monotherapy at doses of either 3 mg/kg followed by 1 mg/kg or 3 mg/kg stable dosing. Patients who developed enterocolitis on treatment were found to have an ORR of 35% versus 2% for patients who did not develop enterocolitis [37]. The meaning of this association is unclear. In a phase II trial, 40 patients with advanced RCC who had progressed on interleukin-2 (IL-2) therapy or were not eligible for IL-2 were treated with ipilimumab at 3 mg/kg. Based on RECIST criteria, an ORR of 12.5% was shown in this cohort, as was an association between immune-related adverse events and response to therapy [38]. Tremelimumab (MedImmune, Gaithersburg, MD), a humanized Ab against CTLA-4, was found to have dose-limiting toxicities in combination with sunitinib in a phase I trial in metastatic RCC, limiting further study [39]. Continued study of checkpoint inhibition for RCC is now focusing on combination therapy (Table 1).

Bladder Cancer

An expansion cohort of atezolizumab (IgG1 anti-PD-L1 mAb) in advanced urothelial cancer suggested surprising activity in this cancer that has seen no major advances in 30 years. Sixty-eight patients received atezolizumab, 67 of whom were evaluable for efficacy. About 25% of patients had an objective response, and 13/30 (43%) had PD-L1 IHC scores of 2+ or 3+. This treatment was well tolerated, with 4.4% of patients having grade 3 adverse events. This led to a larger single-arm phase II study of 310 patients who had progressed during or following a platinum-based therapy, with ORR as the primary endpoint [40]. The objective response was 15% overall and 26% in those tumors with PD-L1 on 5% of tumor-infiltrating immune cells (n = 100). This led to FDA approval in May 2016, and a

confirmatory randomized phase III study is underway. There are also encouraging data from pembrolizumab, with an ORR of 25% (7/28 patients), and avelumab (an IgG1 anti PD-L1 antibody fully capable of ADCC; EMD Serono), with 8/44 patients having a response (18%) and 6/12 patients with   5% of tumor cells expressing PD-L1 having a response [41]. This has led to multiple ongoing studies with PD-1/PD-L1-targeting agents either alone or in combination with other agents in various stages of urothelial cancer, as recently reviewed [42,43].

Future Directions

Despite recent advances in immune checkpoint inhibition, the benefits are still limited to a minority of unselected patients (often < 20%) who likely have a pre-existing immune response that can be unconstrained by immune checkpoint inhibition [44,45]. A primary focus of future studies should be to evaluate strategies that enhance T-cell infiltration of the tumor microenvironment, thereby providing greater benefit to a broader population of cancer patients. Proof of concept comes from a neoadjuvant study in prostate cancer where sipuleucel-T demonstrated its ability to mobilize T cells to the tumor microenvironment when administered prior to radical prostatectomy [10,14]. In this manner, subsequent combination studies with checkpoint inhibitors could capitalize on this augmented local immune response. Future studies will investigate another vaccine, Prostvac, in combination with ipilimumab and nivolumab (anti-PD-1) in the neoadjuvant setting in prostate cancer.

Similar principles underlie a current study investigating anti-PD-1 (pembrolizumab) in patients with high-risk but localized bladder cancer who have already been treated with BCG (NCT02625961). It is likely that BCG's clinical benefit is based on nonspecific inflammation of the bladder that results in increased immune-cell infiltration, thereby potentiating an antitumor immune response [46]. In some patients where PD-1/PD-L1 interactions may inhibit benefit from BCG alone, concurrent or, as in this trial, subsequent PD-1/PD-L1 inhibition may potentiate improved clinical outcomes.

Another focus of future trials will likely be the deployment of multiple immunotherapies as part of a therapeutic immunologic platform. A previous study combined the vaccine Prostvac with ipilimumab, resulting in improved OS (37.2 months in patients treated with 10 mg/kg ipilimumab; 31.3 months in all doses) relative to previous studies with Prostvac alone [47]. A phase I study (NCT02616185) is combining a prostate cancer vaccine with locally administered anti-CTLA-4 therapy (to maximize immune activation with the vaccine but minimize toxicity), PD-1 inhibition, and sunitinib (at a low dose with intent to deplete T_{regs} [48]). Although results with anti-PD-1/PD-L1 in prostate cancer have been disappointing, trials like this aim to optimize immune mobilization with a vaccine and local anti-CTLA-4 therapy in a receptive immune environment (depleted of T_{regs}), thereby potentiating the benefits of PD-1 inhibition within the tumor microenvironment.

Additional studies will capitalize on the growing understanding of how cytotoxic therapies or radiation may immunologically modulate tumors, enabling immune recognition and immune-mediated tumor-cell killing [49]. This has been demonstrated in preliminary studies with radiation as well as chemotherapy [50,51]. A previous trial compared the

radiopharmaceutical samarium 153 with Prostvac to samarium 153 alone [52]. The results of the study suggested a substantial improvement in time to progression (3.7 vs. 1.7 months; p = 0.03) as well as PSA responses in patients who had received the combination. The advent of an alpha-emitting radiopharmaceutical with less toxicity (radium 223) has led to studies combining that agent with sipuleucel-T (NCT02463799). In addition, an ongoing trial is evaluating Prostvac in combination with docetaxel in patients with newly diagnosed metastatic castration-sensitive prostate cancer (NCT02649855).

Conclusion

The use of immune checkpoint therapy for the treatment of GU malignancies is an exciting area of active research. Available trials demonstrate checkpoint inhibitor efficacy in both RCC and bladder cancer. However, trials in prostate cancer have not yet shown clinical benefit. The reasons behind this are likely multifactorial and include host and tumor factors as well as timing and dosing of checkpoint inhibitor therapy. The combination of checkpoint inhibitor therapy with standard-of-care therapies and alternative immunotherapies is another area of active research that may improve ORRs. Despite evidence of long-term response to checkpoint blockade, relatively low ORRs are consistently seen in clinical trials evaluating treatment effect in GU malignancies. Biomarker development is needed to inform selection of patients who will benefit most from this arm of cancer immunotherapy. However, patient selection is not enough. Ultimately, the goal is to achieve clinical benefit in a large majority of patients with GU malignancy. This will only be achieved through continued exploration of cancer immunotherapy mechanisms of action.

Acknowledgments

References

1. Tivol EA, Borriello F, Schweitzer AN, et al. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity. 1995; 3:541–547. [PubMed: 7584144]

2. Wei XX, Fong L, Small EJ. Prospects for the use of ipilimumab in treating advanced prostate cancer. Expert Opin Biol Ther. 2016; 16:421–432. [PubMed: 26698365]

3. Lee KM, Chuang E, Griffin M, et al. Molecular basis of T cell inactivation by CTLA-4. Science. 1998; 282:2263–2266. [PubMed: 9856951]

4. Peggs KS, Quezada SA, Chambers CA, et al. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. J Exp Med. 2009; 206:1717–1725. [PubMed: 19581407]

5. Hoos A. Development of immuno-oncology drugs - from CTLA4 to PD1 to the next generations. Nat Rev Drug Discov. 2016; 15:235–247. [PubMed: 26965203]

6. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363:711–723. [PubMed: 20525992] *Study that led to the approval of the first immune checkpoint inhibitor by the FDA.

7. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011; 364:2517–2526. [PubMed: 21639810]

8. Wolchok JD, Weber JS, Maio M, et al. Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials. Ann Oncol. 2013; 24:2174–2180. [PubMed: 23666915]

9. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 2015; 33:1191–1196. [PubMed: 25713437]

10. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363:411–422. [PubMed: 20818862] **Study that led to the approval of the first therapeutic vaccine for any cancer by the FDA.

11. George DJ, Nabhan C, DeVries T, et al. Survival Outcomes of Sipuleucel-T Phase III Studies: Impact of Control-Arm Cross-Over to Salvage Immunotherapy. Cancer Immunol Res. 2015; 3:1063–1069. [PubMed: 25943532]

12. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010; 28:1099–1105. [PubMed: 20100959]

13. GuhaThakurta D, Sheikh NA, Fan LQ, et al. Humoral Immune Response against Nontargeted Tumor Antigens after Treatment with Sipuleucel-T and Its Association with Improved Clinical Outcome. Clin Cancer Res. 2015; 21:3619–3630. [PubMed: 25649018]

14. Fong L, Carroll P, Weinberg V, et al. Activated lymphocyte recruitment into the tumor microenvironment following preoperative sipuleucel-T for localized prostate cancer. J Natl Cancer Inst. 2014; 106 *Study that suggested immune infiltrate in the tumor following sipuleucel-T.

15. Schellhammer PF, Chodak G, Whitmore JB, et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. Urology. 2013; 81:1297–1302. [PubMed: 23582482]

16. Small EJ, Lance RS, Gardner TA, et al. A Randomized Phase II Trial of Sipuleucel-T with Concurrent versus Sequential Abiraterone Acetate plus Prednisone in Metastatic Castration-Resistant Prostate Cancer. Clin Cancer Res. 2015; 21:3862–3869. [PubMed: 25925891]

17. Kwon ED, Hurwitz AA, Foster BA, et al. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. Proc Natl Acad Sci U S A. 1997; 94:8099–8103. [PubMed: 9223321]

18. Kwon ED, Foster BA, Hurwitz AA, et al. Elimination of residual metastatic prostate cancer after surgery and adjunctive cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade immunotherapy. Proc Natl Acad Sci U S A. 1999; 96:15074–15079. [PubMed: 10611340]

19. Klyushnenkova EN, Riabov VB, Kouiavskaia DV, et al. Breaking immune tolerance by targeting CD25+ regulatory T cells is essential for the anti-tumor effect of the CTLA-4 blockade in an HLA-DR transgenic mouse model of prostate cancer. Prostate. 2014; 74:1423–1432. [PubMed: 25111463]

20. Fan X, Quezada SA, Sepulveda MA, et al. Engagement of the ICOS pathway markedly enhances efficacy of CTLA-4 blockade in cancer immunotherapy. J Exp Med. 2014; 211:715–725. [PubMed: 24687957]

21. Linch SN, Kasiewicz MJ, McNamara MJ, et al. Combination OX40 agonism/CTLA-4 blockade with HER2 vaccination reverses T-cell anergy and promotes survival in tumor-bearing mice. Proc Natl Acad Sci U S A. 2016; 113:E319–E327. [PubMed: 26729864]

22. van den Eertwegh AJ, Versluis J, van den Berg HP, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol. 2012; 13:509–517. [PubMed: 22326922]

23. Madan RA, Mohebtash M, Arlen PM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol. 2012; 13:501–508. [PubMed: 22326924] *A study combining a therapeutic vaccine (currently in phase III testing) and an immune checkpoint modulator in prostate cancer.

24. Kwek SS, Lewis J, Zhang L, et al. Preexisting Levels of CD4 T Cells Expressing PD-1 Are Related to Overall Survival in Prostate Cancer Patients Treated with Ipilimumab. Cancer Immunol Res. 2015; 3:1008–1016. [PubMed: 25968455]

25. Fong L, Kwek SS, O'Brien S, et al. Potentiating endogenous antitumor immunity to prostate cancer through combination immunotherapy with CTLA4 blockade and GM-CSF. Cancer Res. 2009; 69:609–615. [PubMed: 19147575]

26. Kwek SS, Dao V, Roy R, et al. Diversity of antigen-specific responses induced in vivo with CTLA-4 blockade in prostate cancer patients. J Immunol. 2012; 189:3759–3766. [PubMed: 22956585]

27. Slovin SF, Higano CS, Hamid O, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. Ann Oncol. 2013; 24:1813–1821. [PubMed: 23535954]

28. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014; 15:700–712. [PubMed: 24831977]

29. Fizazi K, Drake CG, Kwon ED, et al. Updated Overall Survival (OS) From the Phase 3 Trial, CA184-043: Ipilimumab (Ipi) vs Placebo (PBO) in Patients with Post-Docetaxel Metastatic Castration-Resistant Prostate Cancer (MCRPC). Annals of Oncology. 2014; 25

30. Martin AM, Nirschl TR, Nirschl CJ, et al. Paucity of PD-L1 expression in prostate cancer: innate and adaptive immune resistance. Prostate Cancer Prostatic Dis. 2015; 18:325–332. [PubMed: 26260996]

31. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010; 28:3167–3175. [PubMed: 20516446]

32. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015; 372:2509–2520. [PubMed: 26028255]

33. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015; 161:1215–1228. [PubMed: 26000489]

34. Vaccine Therapy and Pembrolizumab in Treating Patients With Hormone-Resistant, Metastatic Prostate Cancer. [Available from: https://clinicaltrials.gov/ct2/show/NCT02499835?term=vaccine+prostate+pembrolizumab&rank=1

35. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015; 373:1803–1813. [PubMed: 26406148] **Study that led to approval of nivolumab for renal cell cancer.

36. Lan KH, Liu YC, Shih YS, et al. A DNA vaccine against cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) prevents tumor growth. Biochem Biophys Res Commun. 2013; 440:222–228. [PubMed: 24041689]

37. Beck KE, Blansfield JA, Tran KQ, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. J Clin Oncol. 2006; 24:2283–2289. [PubMed: 16710025]

38. Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother. 2007; 30:825–830. [PubMed: 18049334]

39. Rini BI, Stein M, Shannon P, et al. Phase 1 dose-escalation trial of tremelimumab plus sunitinib in patients with metastatic renal cell carcinoma. Cancer. 2011; 117:758–767. [PubMed: 20922784]

40. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016; 387:1909–1920. [PubMed: 26952546] **Study that led to approval for atezolizumab for advanced urothelial cancer.

41. Apolo AB, Infante J, Hamid O, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic urothelial carcinoma from the JAVELIN solid tumor phase 1b trial: Analysis of safety, clinical activity, and PD-L1 expression. J Clin Oncol. 2016; 34S abstr 4514.

42. Fakhrejahani F, Tomita Y, Maj-Hes A, et al. Immunotherapies for bladder cancer: a new hope. Curr Opin Urol. 2015; 25:586–596. [PubMed: 26372038]

43. Sundararajan S, Vogelzang NJ. Anti-PD-1 and PD-L1 therapy for bladder cancer: what is on the horizon? Future Oncol. 2015; 11:2299–2306. [PubMed: 26260808]

44. Mahoney KM, Atkins MB. Prognostic and predictive markers for the new immunotherapies. Oncology (Williston Park). 2014; 28(Suppl 3):39–48. [PubMed: 25384886]

45. Gajewski TF, Woo SR, Zha Y, et al. Cancer immunotherapy strategies based on overcoming barriers within the tumor microenvironment. Curr Opin Immunol. 2013; 25:268–276. [PubMed: 23579075]

46. Honda S, Sakamoto Y, Fujime M, et al. Immunohistochemical study of tumor-infiltrating lymphocytes before and after intravesical bacillus Calmette-Guerin treatment for superficial bladder cancer. Int J Urol. 1997; 4:68–73. [PubMed: 9179670]

47. Singh H, Madan RA, Dahut WL, et al. Combining active immunotherapy and immune checkpoint inhibitors in prostate cancer. J Clin Oncol. 2015; 33(suppl 7) abstr 172.

48. Farsaci B, Higgins JP, Hodge JW. Consequence of dose scheduling of sunitinib on host immune response elements and vaccine combination therapy. Int J Cancer. 2012; 130:1948–1959. [PubMed: 21633954]

49. Kepp O, Galluzzi L, Martins I, et al. Molecular determinants of immunogenic cell death elicited by anticancer chemotherapy. Cancer Metastasis Rev. 2011; 30:61–69. [PubMed: 21249425]

50. Gameiro SR, Jammeh ML, Wattenberg MM, et al. Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing. Oncotarget. 2014; 5:403–416. [PubMed: 24480782]

51. Hodge JW, Garnett CT, Farsaci B, et al. Chemotherapy-induced immunogenic modulation of tumor cells enhances killing by cytotoxic T lymphocytes and is distinct from immunogenic cell death. Int J Cancer. 2013; 133:624–636. [PubMed: 23364915]

52. Heery C, Madan RA, Bilusic M, et al. A phase II randomized clinical trial of samarium-153 EDTMP (Sm-153) with or without PSA-tricom vaccine in metastatic castration-resistant prostate cancer (mCRPC) after docetaxel. Oncotarget. 2016 *in press*.

Bullet points

1. Genitourinary cancers have been among the first to be responsive to immunotherapies, leading to FDA approval of the first anticancer therapeutic vaccine (for prostate cancer) and the use of PD-1/PD-L1 checkpoint inhibitors (for renal cell and bladder cancer).

2. Multiple studies are ongoing in genitourinary malignancies using immunotherapy in combination with other agents; some studies are using immunotherapies in earlier disease states to expand the impact of these agents.

3. Overall survival appears to be the best discriminator of efficacy for immunotherapies and predictive and prognostic biomarkers are urgently needed.

mAb	Indication	Phase	Status	Notes	Ref.
Ipilimumab	Prostate cancer	I	Active	In combination with Sargramostim	NCT00064129
		I	Active	In combination with Sipuleucel-T; evaluating safety and immune monitoring	NCT01832870
		I	Completed	In combination with PROSTVAC/TRICOM	NCT00113984
		II	Recruiting	In combination with Sipuleucel-T; evaluating sequence	NCT01804465
		II	Active	In combination with androgen deprevation therapy; patient's who had progression on ART as defined by measurable PSA	NCT01498978
		II	Recruiting	In combination with niovlumab; tumors expressing androgen receptor-variant-7	NCT02601014
		II	Recruiting	Evaluation of T-cell response to neoantigens	NCT02113657
		II	Completed	In combination with leuprolide acetate prior to radical prostectomy	NCT01194271
		II	Recruiting	In combination with Degarelix; prior to radical prostectomy or patients with biochemical or metastatic recurrence	NCT02020070
		II	Completed	In combination with docetaxel	NCT00050596
		II	Active	Comparison of Ipilimumab 3 mg/kg versus 10 mg/kg	NCT02279862
		III	Completed	Ipilimumab versus placebo for mCRPC chemonaive patients	NCT01057810
	Renal cell	I	Recruiting	In combination with Nivolumab	NCT02210117
		II	Completed	Monotherapy in metastatic RCC patients who progressed on IL2	NCT00057889
	Bladder cancer	II	Recruiting	In combination with Nivolumab after progression on Nivolumab	NCT02553642
		II	Active	In combination with Gemcitabine and Cisplatin	NCT01524991
	GU cancers	I	Recruiting	In combination with cabozantinib and nivolumab	NCT02496208
	Prostate cancer Renal cell Solid tumors	I	Recruiting	In combination with MGA271 (anti-B7-H3)	NCT02381314
Tremelimumab	Colorectal Melanoma Prostate Renal cell Melanoma	II	Active	Provides access for patients who have received tremelimumab to continue to receive tremelimumab	NCT00378482