Blocking the PD-1/PD-L1 axis in advanced prostate cancer: are we moving in the right direction?

Andre P. Fay[1,2], Emmanuel S. Antonarakis[3,4]

[1]PUCRS School of Medicine, Sao Lucas Hospital at PUCRS, Porto Alegre, Brazil; [2]Oncoclinicas Institute, Sao Paulo, Brazil; [3]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, [4]Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA

Correspondence to: Emmanuel S. Antonarakis MD. Associate Professor of Oncology and Urology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Skip Viragh Building, Room 9129, 201 N. Broadway, Baltimore, MD 21287, USA. Email: eantona1@jhmi.edu.

Provenance: This is an invited article commissioned by Section Editor Kaiping Zhang (Academic Director, AME Publishing Company, China).

Comment on: Hansen AR, Massard C, Ott PA, *et al.* Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann Oncol 2018;29:1807-13.

Submitted Jan 07, 2019. Accepted for publication Jan 14, 2019.

doi: 10.21037/atm.2019.01.37

View this article at: http://dx.doi.org/10.21037/atm.2019.01.37

Prostate cancer is the most common malignant neoplasm in men, other than non-melanoma skin cancer (1). Although a great proportion of patients may be cured with local therapies, a significant fraction will develop recurrent and metastatic disease. Unfortunately, patients with distant spread will ultimately develop metastatic castrate-resistant prostate cancer (mCRPC) and subsequent therapeutic resistance leading to lethal disease despite therapies with different mechanisms of action. During the last 8 years, six new agents—including one immunotherapy drug—have been FDA-approved for the treatment of mCRPC resulting in significant improvements in overall survival (OS) (2-7). However, the clinical benefit with each individual agent is rarely durable and the median OS in the castrate-resistant phase of the disease is only approximately 2–3 years.

Sipuleucel-T, an autologous active cellular immunotherapy, was approved by the FDA in 2010 for asymptomatic or minimally symptomatic patients with mCRPC, resulting in a 4.1-month improvement in median OS (3). The exact mechanism of action of sipuleucel-T is unclear, and several questions remain unanswered such as the optimal timing of administration, combinations, or biomarkers of sensitivity (8). Despite the relatively modest clinical benefit and these open questions, the development of sipuleucel-T provided the foundation to further investigate immunotherapy in prostate cancer. Since the emergence of sipuleucel-T, there have been few successes and many failures in terms of further improving OS in men with advanced disease using the immune system to eliminate cancer. For example, cell-based and viral-based vaccines have shown largely disappointing results in patients with mCRPC (9).

In 2018, Drs. James Allison and Tasuku Honjo were awarded the Noble Prize in Physiology or Medicine for their research on immune checkpoints and uncovering ways to activate the immune system to attack cancer. These breakthrough discoveries have resulted in the development of several clinical immune checkpoint inhibitors that are changing the natural history of various malignancies including melanoma, lung cancer, renal cell carcinoma, urothelial carcinoma, among others (10). Since immune checkpoint blockade has emerged as a promising treatment strategy for several tumor types, it has also been tested recently in patients with prostate cancer.

The first immune checkpoint to be studied in prostate cancer, thanks primarily to Dr. Allison, was cytotoxic T lymphocyte-associated protein-4 (CTLA-4) which led to the development of a fully human monoclonal antibody blocking the CTLA-4 pathway, called ipilimumab (11). This agent was first developed for metastatic melanoma and dramatically altered the natural history of that disease, opening new avenues to investigate this immune checkpoint inhibitor in other tumor types. As a result, two large phase III clinical trials were conducted to investigate the role of ipilimumab in mCRPC (pre- and post-docetaxel chemotherapy) (12,13). Unfortunately, these trials did not meet their primary endpoint of improving OS compared to placebo. Interestingly, a prespecified "*post hoc*" analysis of the

post-chemotherapy trial suggested a potential improvement in OS for a subgroup of patients with favorable prognosis defined by two baseline stratification factors (low alkaline phosphatase and high hemoglobin) and the absence of visceral metastasis. Efforts to develop biomarkers to select specific prostate cancer patients who may benefit from this treatment strategy are needed.

Dr. Honjo's research has investigated the role of the programmed death-1 (PD-1) T-cell receptor and its ligand PD-L1 in maintaining an immunosuppressive tumor microenvironment (14). Overcoming this adaptive mechanism of immune escape using agents inhibiting the PD-1/PD-L1 axis may result in effective T-cell responses against cancer cells (15). The PD-1/PD-L1 pathway is known to be activated in many tumor types including lung, head and neck, kidney, and bladder cancers (16). However, in the first phase I study to investigate the role of a PD-1 inhibitor (nivolumab) in multiple malignancies, no encouraging responses were observed in seven prostate cancer patients enrolled in that study (17).

Recently, a phase II trial evaluated the role of a different PD-1 blocker, pembrolizumab, in prostate cancer patients who had failed enzalutamide. Four of 20 patients treated with pembrolizumab plus ongoing enzalutamide therapy had significant radiographic or prostate-specific antigen (PSA) responses. Interestingly, biomarker analysis revealed that one responder had DNA mismatch-repair deficiency and microsatellite instability (18), supporting the hypothesis that a high mutational (and neoantigen) load may be associated with better responses to immune checkpoint inhibition (19).

More recently, results from the phase Ib KEYNOTE-028 trial of pembrolizumab in advanced cancers were published, suggesting antitumor activity in a subset of patients with prostate cancer. In this multicenter open-label basket trial, the efficacy and safety of pembrolizumab in patients with PD-L1-positive advanced cancers was investigated. In the prostate cancer cohort, 245 mCRPC patients were screened for PD-L1 expression in tumor cells or immune cells, and 35 men (14%) were considered PD-L1-positive, forming the evaluable study population. It is important to note that previous pathology studies exploring PD-L1 expression in prostate cancer have reported variable frequencies of PD-L1 positivity. The largest study evaluated PD-L1 expression in 539 primary prostate cancer specimens and 57 cases of mCRPC. That study showed that PD-L1 expression in primary prostate cancers was observed in 8% of cases, while 32% of mCRPC samples were considered PD-L1-positive (20), suggesting that advanced castrate-resistant prostate cancer (CRPC) clones may use this pathway to escape immune system surveillance.

Returning to the results of the prostate cancer cohort of the KEYNOTE-028 study, 23 out of the 35 PD-L1-positive patients received pembrolizumab at a dose of 10 mg/kg intravenously every 2 weeks, for 24 months or until disease progression or unacceptable adverse events. The overall response rate (ORR) was 17% (4 patients), and no complete responses (CR) were identified. Stable disease (SD) was observed in 8 patients (35%). One patient had an unconfirmed partial response (PR), which may increase the ORR to 22%. Median duration of benefit (among responding patients) was 13 months. Importantly, progressive disease (PD) was the best response in 9 patients (39%), suggesting that many prostate cancer patients do no derive any benefit from pembrolizumab. Median OS for the entire prostate cancer population was 8 months, which is in the expected range of OS for this patient population.

Even more recently, at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, results from the KEYNOTE-199 study were presented. This large phase II study evaluated the role of pembrolizumab in 258 patients with mCRPC following docetaxel treatment. Patients were enrolled into 3 cohorts based on disease and PD-L1 characteristics (cohort 1: soft-tissue disease and PD-L1-positive; cohort 2: soft-tissue disease and PD-L1-negative; cohort 3: bone-predominant disease irrespective of PD-L1 status) to evaluate antitumor activity with this PD-1 inhibitor. Patients enrolled in all cohorts received pembrolizumab 200 mg intravenously every 3 weeks, for 35 cycles or until disease progression or unacceptable toxicity (21). In this trial, pembrolizumab showed equivalent activity in PD-L1-positive and PD-L1-negative soft-tissue cohorts, and also looked promising in patients with bone-predominant disease. Although the ORR was only approximately 4%, about 9% of patients had durable response or SD (lasting >6 months). Importantly, 2 patients achieved a CR in the PD-L1-positive cohort. At the time of cut off analysis, approximately 10% of patients were still on treatment and the main cause of treatment discontinuation was PD. No treatment-related discontinuations or deaths were observed, and the safety profile of pembrolizumab was consistent with previous use of this agent in other tumor types. Therefore, the combined results of the KEYNOTE-028 and -199 studies suggest that a small but meaningful proportion of mCRPC patients do benefit from single-agent PD-1 inhibitor treatment, and that these antitumor responses may be very durable in some patients.

The challenge that lies before us now is to develop molecular and genomic biomarkers that may help to predict immunotherapy benefit among mCRPC populations. Some hints are already beginning to emerge (22,23). To this end, in addition to DNA mismatch-repair deficiency as discussed above, there may be other genomic markers of immune checkpoint inhibitor sensitivity. Some of these may include inactivating mutations in the *CDK12* gene that lead to increased gene fusion-associated neoantigens (24,25), exonuclease-domain mutations in the DNA polymerase genes *POLE* and *POLD1* that lead to ultra-mutation without underlying microsatellite instability (26,27), deletion of the 3'-untranslated region of the *CD274* (*PD-L1*) locus resulting in stabilization of PD-L1 transcripts (28), and perhaps inactivation of homologous-recombination DNA repair genes (e.g., *BRCA2*, *ATM*) (29). Finally, an interesting hypothesis is that patients harboring circulating tumor cells with greater phenotypic and genomic heterogeneity may respond preferentially to immune checkpoint inhibitor treatments, but this concept remains to be tested (30).

In conclusion, PD-1/PD-L1 inhibitors represent a breakthrough advance in cancer treatment. Attempts to improve immunotherapy efficacy in prostate cancer are warranted and remain actively investigated. Pembrolizumab demonstrates antitumor activity in a subset of patients with treatment-refractory mCRPC, with an acceptable safety profile. Although it is unlikely that immune checkpoint inhibitors will result in durable responses in the overall unselected prostate cancer population, there may be a subset of patients who may experience remarkable clinical benefit. Efforts to develop predictive genomic biomarkers should be encouraged and will hopefully drive future trial designs moving forward. Finally, understanding the mechanisms of resistance to PD-1/PD-L1 inhibitor therapy may help to optimize treatment decisions and guide the next steps in the development of immunotherapy for advanced prostate cancer.

Acknowledgements

Funding: Dr. Antonarakis is partially supported by National Institutes of Health Cancer Center Support Grant P30 CA006973, and U.S. Department of Defense Grant W81XWH-16-PCRP-CCRSA.

Footnote

Conflicts of interest: Dr. Fay: advisory role for Novartis, Roche, Ipsen and MSD; honoraria from Astrazeneca, Bristol-Myers Squibb, Pfizer, Novartis, Roche, Astellas, MSD; Clinical research funding: Bristol-Myers Squibb, Roche, Astrazeneca, MSD, Pfizer. Dr. Antonarakis: consultant/advisor to Janssen, Astellas, Sanofi, Dendreon, Medivation, ESSA, AstraZeneca, Amgen, Clovis, and Merck; has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Tokai, Bristol Myers-Squibb, AstraZeneca, Celgene, Clovis, and Merck; and is the co-inventor of a biomarker technology that has been licensed to Qiagen.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
2. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138-48.
3. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
4. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-54.
5. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-97.
6. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213-23.
7. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12.
8. Crawford ED, Petrylak DP, Higano CS, et al. Optimal timing of sipuleucel-T treatment in metastatic castration-resistant prostate cancer. Can J Urol 2015;22:8048-55.
9. Patel A, Fong L. Immunotherapy for Prostate Cancer: Where Do We Go From Here?-PART 1: Prostate Cancer Vaccines. Oncology (Williston Park) 2018;32:112-20.
10. Topalian SL. Targeting Immune Checkpoints in Cancer Therapy. JAMA 2017;318:1647-8.
11. Egen JG, Kuhns MS, Allison JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. Nat Immunol 2002;3:611-8.
12. 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;24:1813-21.
13. 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;15:700-12.
14. Iwai Y, Ishida M, Tanaka Y, et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 2002;99:12293-7.
15. Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer. Nat Rev Clin Oncol 2014;11:24-37.
16. McDermott DF, Atkins MB. PD-1 as a potential target in cancer therapy. Cancer Med 2013;2:662-73.
17. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
18. Graff JN, Alumkal JJ, Drake CG, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 2016;7:52810-7.
19. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
20. Haffner MC, Guner G, Taheri D, et al. Comprehensive Evaluation of Programmed Death-Ligand 1 Expression in Primary and Metastatic Prostate Cancer. Am J Pathol 2018;188:1478-85.
21. De Bono JS, Goh JC, Ojamaa K, et al. KEYNOTE-199: Pembrolizumab (pembro) for docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2018;36:5007.
22. Manogue C, Cotogno P, Ledet E, et al. Biomarkers for Programmed Death-1 Inhibition in Prostate Cancer. Oncologist 2018. [Epub ahead of print].
23. Nuhn P, De Bono JS, Fizazi K, et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology. Eur Urol 2019;75:88-99.
24. Wu YM, Cieslik M, Lonigro RJ, et al. Inactivation of CDK12 Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer. Cell 2018;173:1770-82.e14.
25. Antonarakis ES. Cyclin-Dependent Kinase 12, Immunity, and Prostate Cancer. N Engl J Med 2018;379:1087-9.
26. Campbell BB, Light N, Fabrizio D, et al. Comprehensive Analysis of Hypermutation in Human Cancer. Cell 2017;171:1042-56.e10.
27. Lee L, Ali S, Genega E, et al. Aggressive-Variant Microsatellite-Stable POLE Mutant Prostate Cancer With High Mutation Burden and Durable Response to Immune Checkpoint Inhibitor Therapy. JCO Precis Oncol 2018. doi: 10.1200/PO.17.00097
28. Kataoka K, Shiraishi Y, Takeda Y, et al. Aberrant PD-L1 expression through 3'-UTR disruption in multiple cancers. Nature 2016;534:402-6.
29. Boudadi K, Suzman DL, Anagnostou V, et al. Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer. Oncotarget 2018;9:28561-71.
30. Scher HI, Graf RP, Schreiber NA, et al. Phenotypic Heterogeneity of Circulating Tumor Cells Informs Clinical Decisions between AR Signaling Inhibitors and Taxanes in Metastatic Prostate Cancer. Cancer Res 2017;77:5687-98.

Cite this article as: Fay AP, Antonarakis ES. Blocking the PD-1/PD-L1 axis in advanced prostate cancer: are we moving in the right direction? Ann Transl Med 2019;7(Suppl 1):S7. doi: 10.21037/atm.2019.01.37

