Introduction

Compared with intravesical chemotherapy, immunotherapy, such as intravesical bacillus Calmette–Guérin, decreases local recurrence in early bladder urothelial carcinoma (UC) patients. High-dose interleukin-2 also achieved durable response in parts of advanced renal cell carcinoma (RCC) patients. Both examples underscore the effectiveness of immunotherapy in the treatment of genitourinary (GU) cancer. Recently, a renaissance in immunotherapy, especially immune checkpoint blockade treatment, has caused a paradigm shift in anticancer therapy. The T-cell receptor programmed cell death-1 (PD-1) and its ligand programmed cell-death ligand 1 (PD-L1) perform an important role in maintaining peripheral tolerance (maintaining the quiescence of autoreactive T-cells that have already matured and escaped central tolerance during development in the thymus). Tumors can use this pathway to escape T-cell–mediated tumor-specific immunity.

The PD-1/PD-L1 blockade alone has demonstrated its clinical efficacy in GU cancer. CheckMate 025, a phase III trial focusing on patients with advanced clear cell RCC (ccRCC), has demonstrated superior efficacy to sunitinib in advanced RCC patients with International Metastatic RCC Database Consortium intermediate and poor risk. This mini-review article focuses on the rational combination with the PD-1/PD-L1 blockade in GU cancers.

Keywords: Genitourinary cancer, immune checkpoint, programmed death-1, programmed death-ligand 1

Abstract

Immunotherapy, especially immune checkpoint blockade treatment, has changed the landscape of anticancer therapy. In genitourinary (GU) cancer, the programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) blockade alone has resulted in improved outcomes compared with conventional therapies, such as chemotherapy and targeted therapy in advanced urothelial carcinoma and renal cell carcinoma (RCC), respectively. To improve the efficacy of the PD-1/PD-L1 blockade, a combination of this blockade with other therapeutic modalities has been explored in the earnest. In a recent study, ipilimumab, an anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody, combined with nivolumab, an anti-PD-1 monoclonal antibody as the first-line therapy, has demonstrated superior efficacy to sunitinib in advanced RCC patients with International Metastatic RCC Database Consortium intermediate and poor risk. This mini-review article focuses on the rational combination with the PD-1/PD-L1 blockade in GU cancers.

Keywords: Genitourinary cancer, immune checkpoint, programmed death-1, programmed death-ligand 1

Access this article online

Quick Response Code:  
Website: www.e-urol-sci.com  
DOI: 10.4103/UROS.UROS_11_19

How to cite this article: Guo JC, Lin CC. Rational combination with an immunotherapy backbone in genitourinary cancers. Urol Sci 2020;31:4-7.
failed vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) compared nivolumab with everolimus, and nivolumab demonstrated superior efficacy.[4] In KEYNOTE-045, another Phase III trial, pembrolizumab also, demonstrated superior efficacy, compared with chemotherapy, in patients with advanced UC failed platinum-based chemotherapy.[5] However, the response rate of PD-1/PD-L1 blockade alone only ranges from 20% to 30%. To improve the efficacy of the blockade, a combination of the PD-1/PD-L1 blockade with other therapeutic modalities has been explored in the earnest.

Several strategies have been developed to improve the efficacy of the PD-1/PD-L1 blockade. A combination of the blockade with conventional therapeutic agents for GU cancers, either chemotherapy (UC) or targeted therapy (RCC), is being tested.[6] A combination of the PD-1/PD-L1 blockade with other immune checkpoint inhibitors (ICIs), such as the anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody, as well as with other not-yet-approved agents, is also under rigorous investigation.[7] In this mini-review article, we focus on the combinations of the blockade with conventional therapeutic agents and ICIs.

**Combination of the Programmed Cell Death-1/Programmed Cell Death-Ligand 1 Blockade with Conventional Therapeutic Agents**

**Renal cell carcinoma**

Angiogenesis is associated with the pathophysiology of ccRCC.[8] Anti-angiogenesis therapies, especially those targeting the vascular endothelial growth factor (VEGF)/VEGFR pathway, have become standard therapy for patients with advanced ccRCC.[9] Beyond targeting cancer cells, anti-angiogenesis also has an immunomodulatory effect.

Angiogenesis affects the immune system (immunosuppression) in three ways. First, angiogenesis has direct effects on immune cells, such as increasing the proliferation of regulatory T-cells (immunosuppressive cells), decreasing the maturation of dendritic cells, and increasing PD-L1 expression on macrophages. Second, angiogenesis regulates the expression of adhesion molecules on endothelial cells, such as PD-L1 and Fas ligand (causing apoptosis of effector immune cells). Third, angiogenesis induces hypoxia and physically decreases the filtration of immune cells due to high intratumoral pressure.[10] Collectively, anti-angiogenesis may reverse the immunosuppressive tumor microenvironment and may enhance the efficacy of the PD-1/PD-L1 blockade in advanced ccRCC.

Three recent, large-scale, Phase III studies evaluating a combination of the PD-L1 blockade and VEGF/VEGFR blockade (either via VEGF monoclonal antibody or VEGFR TKI) have been publicized. IMmotion151, a Phase III trial focusing on treatment-naïve advanced ccRCC, compared atezolizumab plus bevacizumab with sunitinib as the first-line therapy. The combination therapy exhibited superior progression-free survival (PFS) for PD-L1-positive (≥1%) patients (11.2 vs. 7.7 months, hazard ratio [HR]: 0.74, *P* = 0.02).[11] JAVELIN Renal 101, another phase III trial targeting the same patient population, compared avelumab plus axitinib with sunitinib as the first-line therapy. The combination therapy also exhibited superior PFS for PD-L1-positive (≥1%) patients (13.8 vs. 7.2 months, HR: 0.61, *P* < 0.0001).[12,13] Although a longer follow-up period is required to determine overall survival (OS) in both studies, promising preliminary results indicate that this combination may become one option of the standard therapies for ccRCC. KEYNOTE-426, a recently published trial, compared pembrolizumab plus axitinib with sunitinib as the first-line therapy. The combination therapy demonstrated superior PFS (15.1 vs. 11.1 months, HR: 0.69, *P* < 0.001), 1-year OS rate (89.9% vs. 78.3%, HR: 0.53, *P* < 0.001), and objective response rate (59.3% vs. 35.7%, HR: 0.53, *P* < 0.001).[14] Although the improvement in anticancer efficacy was significant, the occurrence and severity of the accompanying adverse events increased. Other ongoing, selective Phase III studies are summarized in Table 1.

**Urothelial carcinoma**

Chemotherapy is a long-established standard systemic therapy for advanced UC.[15] In addition to the cytotoxic effect on cancer cells, immunogenic cell death induced by chemotherapy could improve antigen presentation by antigen-presenting cells and prime the immune system.[16,17] As pembrolizumab is demonstrably superior to chemotherapy with paclitaxel, docetaxel, or vinflunine for advanced UC patients who failed platinum-based chemotherapy,[18] evaluating the combination of the PD-1/PD-L1 blockade with the standard first-line chemotherapy, such as with cisplatin/gemcitabine or carboplatin/gemcitabine, becomes animated. Four large-scale Phase III trials (IMvigor 130 [NCT02807636], KEYNOTE-361 [NCT02853305], CheckMate 901 [NCT03036098], and NILE [NCT03682068]) are ongoing to test how much better the combination of the PD-1/PD-L1 blockade plus chemotherapy and that of the PD-1/PD-L1 blockade plus the CTLA-4 blockade are relative to the standard first-line chemotherapy (with platinum plus gemcitabine). These trials are also summarized in Table 1.

**Combination of the Programmed Cell Death-1/Programmed Cell Death-Ligand 1 Blockade with the CTLA-4 Blockade**

With the exception of stimulatory signal 1 (antigen on major histocompatibility binding with the T-cell receptor), CD80 and CD86 bind to CD28 expressed by T-cells, thus leading to the expression of stimulatory signal 2 and activation of naïve T-cells. The immune checkpoint molecule CTLA-4 (an inhibitory signal) expressed by T-cells binds CD80 and CD86 expressed by antigen-presenting cells. Signaling via CD28 or CTLA-4 results in the opposite outcomes: stimulation and inhibition of T-cells, respectively.[18] Moreover, the
Table 1: Combination of programmed cell death-1/programmed cell death ligand-1 blockade in advanced genitourinary cancers

| Cancer types         | Rationale                                                                 | Selected phase 3 trials               |
|----------------------|---------------------------------------------------------------------------|---------------------------------------|
| Targeted therapy     |                                                                           |                                       |
| VEGF/VEGFR inhibitor | VEGF/VEGFR blockade is a standard therapy for ccRCC Anti-angiogenesis has immunomodulatory effect (direct effects on immune cells, direct effects on endothelial cells and indirect effects on hypoxia) | IMMmotion 151 (NCT02420821) JAVELIN renal 101 (NCT02684006) KEYNOTE-426 (NCT02853331) CLEAR (NCT02811861) CheckMate 9ER (NCT03141177) NCI trial (NCT03793166) |
| Chemotherapy         |                                                                           |                                       |
| Platinum/gemcitabine| Platinum plus gemcitabine is the standard therapy for UC Induce immunogenic death of cancer cells and antigen presentation by antigen-presenting cells | IMvigor 130 (NCT02807636) KEYNOTE-361 (NCT02853305) CheckMate 901 (NCT03036098) NILE (NCT03682068) |
| Immune checkpoint blockade |                                                                  |                                       |
| CTLA-4 blockade      | Different immune checkpoint blockades to enhance anticancer immunity     | CheckMate 214 (NCT02231749) NCI trial (NCT03793166) DANUBE (NCT02516241) CheckMate 901 (NCT03036098) |

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4, VEGF/VEGFR: Vascular endothelial growth factor/VEGF receptor, ccRCC: Clear cell renal cell carcinoma, UC: Urothelial carcinoma

A combination of ipilimumab and nivolumab was then evaluated in advanced melanoma patients. In CheckMate 067, a large Phase III study evaluated nivolumab plus ipilimumab in comparison to ipilimumab alone. Nivolumab plus ipilimumab achieved a higher response rate and longer PFS and OS, in CheckMate 067 making this a promising combination.[20,21] CheckMate 214, a Phase III study, compared nivolumab plus ipilimumab with sunitinib for treatment-naïve advanced ccRCC patients. Nivolumab plus ipilimumab was superior to sunitinib with regard to the response rate (42% vs. 27%, P < 0.0001) and OS (not reached vs. 26.0 months, HR: 0.63, P < 0.0001) in advanced ccRCC patients with International Metastatic RCC Database Consortium intermediate and poor risk. Clinically meaningful improvements in PFS were observed, although the improvements were not statistically significant (11.6 vs. 8.4 months, HR: 0.82, P = 0.0331).[22] With the success of this combination, nivolumab plus ipilimumab was subsequently approved by regulatory agents and was tested in many other cancer types, including advanced UC and prostate cancer. Another similar combination of durvalumab plus tremelimumab was also tested in advanced UC patients. These trials are summarized in Table 1.

CONCLUSION

A combination of the PD-1/PD-L1 blockade with either the VEGF/VEGFR blockade or CTLA-4 blockade has demonstrated promising efficacy in advanced GU cancers.

Several large-scale trials evaluating different combinations will be publicized in the near future. However, the accompanying financial issues and higher rates of adverse events are causes of concern. These novel combinations should only be used in clinical trials setting if there is no evidence from large clinical trials available.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Lamm DL, Blumenstein BA, Crawford ED, Montie JE, Scardino P, Grossman HB, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille calmette-guérin for transitional-cell carcinoma of the bladder. N Engl J Med 1991;325:1205-9.
2. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d’immunothérapie. N Engl J Med 1998;338:1272-8.
3. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med 2016;375:1767-78.
4. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
5. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26.
6. Gotwals P, Cameron S, Cipolletta D, Cremasco V, Crystal A, Hewes B, et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat Rev Cancer 2017;17:286-301.
7. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov 2019;18:197-218.
8. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005;353:2477-90.
9. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376:354-66.

10. Khan KA, Kerbel RS. Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. Nat Rev Clin Oncol 2018;15:310-24.

11. Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): A multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393:2404-15.

12. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. LBA6 PRJAVELIN renal 101: A randomized, phase III study of avelumab+axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma (aRCC). Ann Oncol 2018;29:Suppl. 8.

13. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103-15.

14. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116-27.

15. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602-8.

16. Ménard C, Martin F, Apetoh L, Bouyer F, Ghiringhelli F. Cancer chemotherapy: Not only a direct cytotoxic effect, but also an adjuvant for antitumor immunity. Cancer Immunol Immunother 2008;57:1579-87.

17. Hannani D, Sistigu A, Kepp O, Galluzzi L, Kroemer G, Zitvogel L, et al. Prerequisites for the antitumor vaccine-like effect of chemotherapy and radiotherapy. Cancer J 2011;17:351-8.

18. Krammel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995;182:459-65.

19. Oleinika K, Nibbs RJ, Graham GJ, Fraser AR. Suppression, subversion and escape: The role of regulatory T cells in cancer progression. Clin Exp Immunol 2013;171:35-45.

20. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345-56.

21. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480-92.

22. Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90.