Review Article

Immunotherapy for genitourinary tumors

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Abstract: The present review provides an update about the major achievements and recent advances of immunotherapy in renal cell carcinoma, urothelial carcinoma, and prostate cancer. Although the treatment strategy for renal cell carcinoma and urothelial carcinoma includes traditional cancer immunotherapies, such as interleukin-2 and interferon-alfa, the clinical outcomes of these therapies are unsatisfactory. In recent years, the development of immune checkpoint inhibitors has drastically changed the treatment strategy for various cancers, including genitourinary cancer. The present review summarizes the approved cancer immunotherapies for renal cell carcinoma, urothelial carcinoma and prostate cancer. Furthermore, we review the response evaluation and biomarkers for immune checkpoint inhibitors with a distinctive mode of action that is different from cytotoxic agents. Finally, future perspectives for cancer immunotherapy are discussed.

Key words: cancer immunotherapy, immune checkpoint inhibitor, prostate cancer, renal cell carcinoma, urothelial carcinoma.

Introduction

The development of ICIs has caused a paradigm shift in cancer treatment. Immunotherapy has become one of the fundamental cancer therapies, alongside surgery, chemotherapy and radiation. In genitourinary cancers, several ICIs have been approved for RCC and UC by the US FDA (Fig. 1). Both cancers have been considered to be immunogenic because immunotherapy with IFN-α1,2 or IL-23,4 was generally successful for RCC, and therapy with bacillus Calmette–Guérin was successful in the case of bladder cancer. However, traditional immunotherapy has shown an unsatisfactory response rate and survival benefit. Immunotherapy with a monoclonal antibody against the PD-1/PD-L1 has presented a high response rate of approximately 15–40% for various cancers. Approval of new drugs for cancer immunotherapy is expected to continue for some time. However, the use of ICIs in cancer therapy faces several challenges. First, an established biomarker that distinguishes between ICI responders and non-responders has not been detected. Second, ICIs can trigger specific adverse events called irAEs. Although most irAEs occur during treatment, some occur several months after treatment. Third, the high cost of ICIs could have a negative impact on the economy.

The present review summarizes the clinical development of immunotherapy in RCC, UC and PCa, and discusses the future perspectives of immunotherapy in relation to these cancers.

Immunotherapy in RCC

In the treatment of advanced RCC, cytokine therapies (IFN-α and IL-2) have been widely used as first-line therapy for a long time before the approval of antiangiogenic and molecularly targeted therapies that mainly inhibit the vascular endothelial growth factor and the mammalian target of rapamycin pathways.1–4 However, the survival benefit of these therapies has been limited. Although targeted therapies have improved the response rate and OS for advanced RCC patients, the drugs have rarely (<3%) achieved a CR.5–8 Thus, the recent advent of ICI holds promise in the field of cancer therapy. In this section, we discuss two ICIs (nivolumab and ipilimumab), which were developed as the first in class anti-CTLA-4 antibody and anti-PD-1 antibody approved for RCC by the FDA. Table 1 lists the FDA-approved ICIs for RCC.
**Nivolumab**

Nivolumab, a monoclonal antibody that inhibits PD-1, was approved by the FDA in 2015 for advanced RCC patients who had received antiangiogenic therapy. This approval was based on the result of the phase III CheckMate-025 trial. In total, 821 advanced clear cell RCC patients who had received one or two antiangiogenic therapy sessions were administered 3 mg/kg nivolumab every 2 weeks \((n = 406)\) or 10 mg everolimus daily \((n = 397)\). Nivolumab significantly improved the OS compared with everolimus (median 25.0 vs 19.6 months, HR 0.73, \(P = 0.002\)). The ORR with nivolumab was also superior compared with everolimus (25% vs 5%, \(P < 0.001\)). In 103 objective responses with nivolumab, four (1%) achieved a CR. PD-L1 expression on tumor cells by IHC was not correlated with OS benefit by nivolumab. Fewer patients taking nivolumab experienced grade \(\geq 3\) adverse events compared with those taking everolimus (19% vs 37%). The most frequent grade \(\geq 3\) adverse event was fatigue (2%).

**Nivolumab plus ipilimumab**

Many clinical trials with combination therapy including ICIs have been shown to exceed the clinical effect of ICI monotherapy. In this setting, the FDA approved nivolumab plus ipilimumab for intermediate and poor-risk advanced RCC patients based on data from the phase III CheckMate-214 study. Advanced clear cell RCC patients who were previously untreated were randomly assigned to nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks for four doses, followed by nivolumab at 3 mg/kg every 2 weeks \((n = 550)\), or to sunitinib at 50 mg daily for 4 weeks, followed by 2 weeks off before continuation of treatment \((n = 546)\). At a median follow-up period of 25.2 months for 847 patients with intermediate- or poor-risk disease, nivolumab plus ipilimumab showed significant improvement compared with sunitinib in the ORR (42% vs 27%, \(P < 0.001\)), PFS (median 11.6 vs 8.4 months, HR 0.82, \(P = 0.03\)) and OS (median not reached vs 26 months, HR 0.63, \(P < 0.001\)). In contrast, exploratory end-point analysis for 249 patients from a favorable-risk group showed that
nivolumab plus ipilimumab was inferior to sunitinib in ORR (29% vs 52%, \( P < 0.001 \)) and PFS (median 15.3 vs 25.1 months, HR 2.18, \( P < 0.001 \)). However, the CR rates for the favorable-risk group were higher with nivolumab plus ipilimumab than with sunitinib (11% vs 6%). Grade \( \geq 3 \) adverse events occurred in 46% of patients treated with nivolumab and ipilimumab, and in 63% with sunitinib.

### Immunotherapy in UC

mUC is a lethal disease with poor survival outcomes. MVAC chemotherapy has improved the clinical outcome for mUC patients,\(^{11,12} \) and has been the standard first-line therapy for a long time. Although GC treatment has the advantage of being less toxic compared with MVAC, the effect of GC is similar to that of MVAC.\(^{13} \) Thus, the development of new therapies that show a superior outcome in terms of survival benefit compared with platinum-based combination chemotherapies is expected. In this context, the appearance of ICIs has changed the treatment strategy for mUC patients. To date, five antibodies (pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab) have been approved by the FDA for UC patients. Table 1 lists the FDA-approved ICIs for UC. This section provides a brief overview of these ICIs for UC.

### Pembrolizumab

Pembrolizumab, an anti-PD-1 antibody, was approved by the FDA for UC in the second-line setting based on the results of the phase III KEYNOTE-045 study.\(^{14} \) In that study, 542 patients with advanced UC who had recurred after or progressed on a platinum-based chemotherapy were randomly assigned to pembrolizumab at 200 mg every 3 weeks for 24 months or with the investigator’s choice of chemotherapy (paclitaxel, docetaxel and vinflunine). Pembrolizumab was found to be superior to chemotherapy in OS (median 10.3 vs 7.4 months, HR 0.73, \( P = 0.002 \)) and ORR (21.1% vs 11.4%, \( P = 0.001 \)), whereas there was no statistically significant difference in PFS (median 2.1 vs 3.3 months, HR 0.98, \( P = 0.42 \)). Fewer adverse events greater than grade 3 occurred in the pembrolizumab group than in the chemotherapy group (15.0% vs 49.4%).

Pembrolizumab also received accelerated approval for patients with advanced or mUC who are not eligible for platinum-based chemotherapy based on the data from the phase II KEYNOTE-052 study.\(^{15} \) In this ongoing, single-arm, open-label trial, 370 cisplatin- ineligible UC patients who had not previously undergone systemic chemotherapy were treated with pembrolizumab at 200 mg every 3 weeks for up to 2 years. At the median follow-up period of 5 months, 89 patients (29%) achieved an objective response and 17 patients (5%) showed a CR.

### Nivolumab

The phase II, single-arm, CheckMate 275 study led to the FDA approval for nivolumab.\(^{16} \) In the trial, 270 patients with UC, who had received at least one platinum-based regimen, were enrolled. At the median follow-up period of 7 months, the ORR was 19.6%. Among all patients, six patients (2%) achieved CR. Grade \( \geq 3 \) adverse events occurred in 18% of patients, and the most frequent grade \( \geq 3 \) adverse event was diarrhea (2%).

### Atezolizumab

In 2016, atezolizumab, an anti-PD-L1 antibody, became the first FDA-approved drug for the second-line treatment of advanced UC. The single-arm, phase II, IMvigor210 study was pivotal for FDA approval.\(^{17,18} \) The study comprised two cohorts of locally advanced and mUC. Cohort 1 included patients who were treatment-naïve and cisplatin-ineligible patients, and cohort 2 included patients who were previously treated with platinum-based chemotherapy. The ORR of all cohorts was 15%. Cohort 1 included 119 patients with advanced UC who were treated with atezolizumab in the first-line setting. In these patients, ORR was 23%, and 11 patients (9%) experienced a CR. Based on these results, atezolizumab received accelerated approval as a first-line treatment for cisplatin-ineligible patients with locally advanced or mUC. However, the result of a randomized, open-label, phase III trial (IMvigor211; \( n = 931 \)) showed that atezolizumab use in platinum-refractory mUC patients (\( n = 234 [25\%] \)) with \( \geq 5\% \) expression of PD-L1 on tumor infiltrating immune cells did not show statistically significant benefits in OS as compared with the OS benefits after chemotherapy.\(^{19} \) Grade \( \geq 3 \) adverse events occurred in 20% with atezolizumab and in 43% with chemotherapy. The most frequent grade \( \geq 3 \) adverse event with atezolizumab was fatigue (2%). In the first-line setting, the result of the currently ongoing phase III trial (IMvigor130: NCT02807636) comparing atezolizumab monotherapy with atezolizumab combined with platinum-based chemotherapy in previously untreated locally advanced or mUC will be important.

### Durvalumab

Durvalumab, an anti-PD-L1 antibody, received accelerated FDA approval for UC patients in a second-line setting after platinum-based chemotherapy. The approval was based on the data of a phase I/II open-label study in which 191 UC

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**Table 1** FDA-approved ICIs for RCC and UC

| Cancer type | Drug    | Target   | Object          | Approved in Japan |
|------------|---------|----------|-----------------|-------------------|
| RCC        | Nivolumab | PD-1      | 2nd line        | Yes               |
| RCC        | Nivolumab + ipilimumab | PD-1 + CTLA-4 | 1st line        | Yes               |
| UC         | Pembrolizumab | PD-1     | 1st line (not eligible for cisplatin containing therapy) | Yes               |
| UC         | Nivolumab | PD-1      | 2nd line        | No                |
| UC         | Atezolizumab | PD-L1   | 2nd line        | No                |
| UC         | Durvalumab | PD-L1    | 2nd line        | No                |
| UC         | Avelumab | PD-L1     | 2nd line        | No                |
patients who experienced disease progression during, were ineligible for or had refused chemotherapy were treated with durvalumab.20 The ORR was 17.8%, and 3.7% of patients achieved a CR. Grade ≥3 treatment adverse events occurred in 6.8% of the patients.

Avelumab
Avelumab, an anti-PD-L1 antibody, received accelerated FDA approval for UC patients in the second-line setting after platinum-based chemotherapy. The approval was based on the data from the open-label, single-arm, phase I dose-expansion JAVERIN Solid Tumor study.21 The study analyzed 249 UC patients who had experienced progression after at least one previous platinum-based chemotherapy or who were cisplatin-ineligible patients. In 161 post-platinum-based chemotherapy patients, who had been followed up after 6 months, 27 patients (17%) showed an objective response and nine (6%) showed a CR. Grade ≥3 adverse events occurred in 8%, the most frequent of which was fatigue (2%).

Immunotherapy in PCa
Sipuleucel-T
Sipuleucel-T, a dendritic cell vaccine activated using prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor, was approved by the FDA for asymptomatic or minimally symptomatic metastatic castration-resistant PCa in 2010 as the first cancer vaccine based on the results of a double-blind, placebo-controlled, multicenter, phase III trial (IMPACT study).22 In that study, 512 patients were randomly assigned in a 2:1 ratio to receive sipuleucel-T (n = 341) or placebo (n = 171) intravenously every 2 weeks for three cycles. At the median follow-up periods of 34.1 months, the OS was superior in the sipuleucel-T group than in the placebo group (median 25.8 vs 21.7 months, HR 0.78, P = 0.03). There was no significant difference between the sipuleucel-T group and placebo group in the time to objective disease progression (median 3.7 vs 3.6 months, HR 0.95, P = 0.63). These results suggested that sipuleucel-T showed delayed antitumor effects after administration of the drug. Grade ≥3 adverse events occurred in 31.7%, the most common of which was back pain (3.6%).

Immune checkpoint inhibitors
Several clinical trials have been carried out to assess the impact of ICIs on PCa. However, no ICI has been approved for PCa. In two phase III trials in metastatic PCa patients, ipilimumab showed no significant improvement in OS compared with a placebo, although PFS was significantly longer in both trials.23,24 Those results suggest that ipilimumab has an antitumor effect for PCa. In contrast, ICIs targeting the PD-1/PD-L1 axis are also under study in PCa. In the phase Ib KEYNOTE-028 study, pembrolizumab showed an ORR of 17.4% for advanced PCa patients whose PD-L1 expressed in ≥1% of tumor or stromal cells.25 To improve the clinical outcome of ICIs, appropriate patients’ selection is one of the key factors. PD-L1 expression has been assessed in predictive ability for response of ICIs in various cancers. However, PD-L1 expression in PCa is low and not prognostic.26 In contrast, high PD-L2 expression was correlated with worse prognosis (distant metastasis-free survival, PCa-specific survival and OS), and was also associated with immune-related pathways in the study of gene expression from 9393 PCa samples.27 Thus, PD-L2 might be a potential target for immunotherapy in PCa.

Response evaluation for immunotherapy
ICIs induce characteristic responses different from cytotoxic agents. In particular, pseudo progression, which is considered to occur as a result of infiltration of immune cells into tumors, must be considered when evaluating the treatment response to ICI.28,29 RECIST version 1.1 (RECIST v1.1) are widely used for assessing treatment responses in patients with advanced malignancies.30 In general, especially in daily practice, once tumor progression is indicative of a progressive disease according to RECIST v1.1, the drug is terminated in most cases. Thus, RECIST v1.1 cannot assess pseudo progression and leads to immature discontinuance of immunotherapy. In this context, irRC were proposed for a more precise assessment of immunotherapy.31 One of the important differences between those two criteria is that irRC require reconfirmation at least 4 weeks irPD. This might help prevent overlooking of pseudo progression cases. In the comparison between RECIST v1.1 and irRC in patients with advanced melanoma treated with pembrolizumab (KEYNOTE-001 study), approximately 15% of these patients experienced pseudo progression, and RECIST v1.1 showed a risk of underestimating the effect of pembrolizumab.32 Similarly, irRECIST have been proposed.33 Although progressive disease in irRECIST also requires reconfirmation after the first evaluation of progression, the definition of confirmed progressive disease largely differs among studies.34 In this setting, the RECIST working group modified RECIST v1.1 for immune-based therapeutics (iRECIST) as criteria intended for the precise evaluation of ICI treatment.35 A notable characteristic of iRECIST is that treatment responses are classified as immune CR, iUPD, iCPD and iSD. The development of new lesions during treatment is classified as iUPD. iCPD is only assigned if additional new lesions appear or an increase in the size of new lesions is seen (≥5 mm for the sum of new lesion targets or any increase in a new lesion non-target) at the next assessment; appearance of new lesions when none have previously been recorded can also confirm iCPD. In addition, imiRECIST criteria were recently proposed.36 The imiRECIST have been developed to utilize a unidimensional measurement system, and might provide advantages over RECIST v1.1 by recognizing the potential benefits from cancer immunotherapy in patients who experience pseudo progression after initiation of treatment. These new criteria are more stringent for progressive disease than the conventional RECIST v1.1 (Table 2). Consequently, the new criteria can decrease the chance of missing late responses to ICI. At present, there are several criteria for assessing the response to ICI and clinicians are conflicted in which criteria should be used. A prospective
study to evaluate these criteria will thus be required for the optimal management of immunotherapy.

**Biomarkers for immunotherapy**

Searches for biomarkers that predict clinical response to cancer immunotherapy and irAEs have been actively carried out in recent days. However, no established biomarker, except for PD-L1 expression by IHC for advanced lung cancer (ex. PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 22C3 pharmDx; DACO, Glostrup, Denmark), has been determined. This might be so because the treatment response is related to many complicated factors including both tumor and immunological factors. Detection of precise biomarkers will reduce overtreatment in patients with no clinical benefit and the frequency of severe irAEs, finally leading to economic cost benefit. In this section, potential biomarkers for cancer immunotherapy are summarized.

**PD-L1 expression**

Anti-PD-1/PD-L1 inhibitors, PD-L1 expression on tumors or on immune cells has been expected to be a predictive biomarker for the ICI. In a phase I trial of nivolumab for melanoma, non-small cell lung cancer, RCC, PCa or colorectal cancer patients, nine (36%) of 25 patients with PD-L1-positive tumors showed an objective response, whereas none of the patients with a PD-L1-negative tumor showed an objective response. According to this result, several companies have developed an anti-PD-L1 antibody toward the establishment of companion diagnostics. Although a subsequent study reported that more patients with PD-L1-positive tumors tend to show beneficial effects by ICI than patients with PD-L1-negative tumors, many patients with PD-L1-negative tumors experience clinical benefits from ICI. In fact, in a phase II trial of nivolumab for metastatic RCC, 18% of patients with PD-L1 expression (5% cut-off) showed an objective response. There are several possible reasons for discordance between PD-L1 positivity and the efficacy of anti-PD-1/PD-L1 antibody. First, several clones of anti-PD-L1 antibodies for IHC exist and their cut-off values are variable. Second, PD-L1 is dynamic marker affected by concentration of IFN-γ in the tumor microenvironment,
which could change according to time course and treatment. Third, the investigation target of PD-L1 expression is variable with the studies because PD-L1 is expressed in both tumor cells and immune cells. Fourth, PD-L1 expression level is discordant between the primary tumors and metastatic sites, and is heterogeneous even in tumors. The discordance rate for PD-L1 expression between primary clear cell RCC and metastases is 20.8% and, in primary RCC, PD-L1 showed stronger expression in high nuclear grade areas than in low nuclear grade areas. Given these situations, it is difficult to precisely evaluate PD-L1 expression in cancer patients. Further study is, therefore, required to establish the method for evaluating PD-L1 expression to predict the ICI response.

**Tumor mutation burden**

Many somatic mutations are accumulated in cancer cells during the tumorigenic process. Proteins derived from these cancer-specific non-synonymous mutations are possibly recognized by the host immune system as non-self proteins. Among these, proteins recognized by the immune system are called neoantigens. Neoantigens have been a focus of great attention as the target of cancer immunotherapy. Several studies have reported that ICIs are more effective for cancers that have high levels of TMB, such as melanoma and non-small cell lung cancer, than for those that have low levels. Although RCC that is relatively sensitive for ICI is considered an immunogenic tumor, the TMB of RCC is lower than that of cancers with high TMB. For this discrepancy, Turajlic et al. reported that RCC showed the highest proportion and number of insertion and deletion mutations (indels). Most studies about the correlation between the effect of ICI and TMB focus on SNVs. In general, a frameshift caused by indels has a greater impact on generating non-self amino acids recognized by the host immune system than SNVs. Thus, frameshift can create neoantigens in an efficient way. Taking TMB into account as a biomarker for cancer immunotherapy, it is preferable to consider the mutation type.

**TILs**

TILs, especially CD8+ cytotoxic T cells, play a key role in cancer immunity. In various cancers, including bladder cancer, infiltration of cytotoxic T cells into tumors was associated with good prognosis after treatment. In a study of 69 patients with advanced UC, patients with strong invasion of cytotoxic T cell into the tumor showed better disease-free survival and OS than those without it. Conversely, several reports showed that strong infiltration of cytotoxic T cell was correlated with poor survival in RCC patients. In a study on 135 clear cell RCC and 51 clear cell RCC lung metastasis patients, high tumor infiltration of CD8+

| Table 3 | Ongoing phase III trials evaluating combination immunotherapy in RCC, UC and PCa |
|---------|--------------------------------------------------------------------------|
| Cancer type | ClinicalTrials.gov. identifier | Trial | Treatment arm | Object | Primary end-point |
| RCC | NCT02231749 | CheckMate 214 | ① Nivolumab + ipilimumab | 1st line | PFS, OS and ORR |
| | | | ② Sunitinib | | |
| | NCT02420821 | IMmotion151 | ① Atezolizumab + bevacizumab | 1st line | PFS and OS |
| | | | ② Sunitinib | | |
| | NCT02684006 | JAVELIN Renal 101 | ① Avelumab + axitinib | 1st line | PFS in PD-L1 positive patients |
| | | | ② Sunitinib | OS in PD-L1 positive patients |
| | NCT02811861 | ① Lenvatinib + everolimus | 1st line | PFS |
| | | | ② Lenvatinib + pembrolizumab | | |
| | | | ③ Sunitinib | | |
| | NCT02853331 | KEYNOTE-426 | ① Pembrolizumab + axitinib | 1st line | PFS and OS |
| | | | ② Sunitinib | | |
| | NCT03141177 | CheckMate 9ER | ① Nivolumab + cabozantinib | 1st line | PFS |
| | | | ② Sunitinib | | |
| | NCT03260894 | KEYNOTE-679 | ① Pembrolizumab + epacadostat | 1st line | PFS and OS |
| | | | ② Sunitinib or pazopanib | | |
| UC | NCT02807636 | IMvigor130 | ① Atezolizumab + gencatibine + carboplatin/cisplatin | 1st line | PFS, OS and percentage of participants with AEs |
| | | | ② Placebo + gencatibine + carboplatin/cisplatin | | |
| | | | ③ Atezolizumab | | |
| | NCT02853305 | KEYNOTE-361 | ① Pembrolizumab | 1st line | PFS and OS |
| | | | ② Pembrolizumab + chemotherapy | | |
| | | | ③ Chemotherapy | | |
| | NCT03361865 | KEYNOTE-672 | ① Pembrolizumab + epacadostat | 1st line | PFS and OS |
| | | | ② Pembrolizumab + placebo | | |
| | | | ③ Pembrolizumab + placebo | | |
| | NCT03374488 | KEYNOTE-698 | ① Pembrolizumab + epacadostat | 2nd line | PFS and OS |
| | | | ② Pembrolizumab + placebo | | |
| | PCa | NCT03016312 | IMbassador250 | ① Atezolizumab + enzalutamide | 3rd line | OS |
T lymphocytes was correlated with poor survival. Interestingly, among patients with high CD8+ T lymphocyte infiltration, the group with mature dendritic cells in tertiary lymphoid structures showed improved risk of disease progression. The authors thus suggested that mature dendritic cells in a local area might educate cytotoxic T cells. Exploring the mechanism of the prognostic impact of TILs in various cancers might thus lead to an improved clinical performance of cancer immunotherapy.

**Future perspectives**

As broad-based attempts to improve the clinical effect of ICI, many clinical trials for combination therapies including ICIs are being carried out. Ongoing phase III studies for combination therapy including ICI in RCC, UC and PCa are listed in Table 3. During the clinical application of combination therapy, adverse events should be carefully analyzed. In the phase Ib study for axitinib and pembrolizumab, the latter showing a multikinase inhibitor, 52 patients were included for advanced RCC in the first-line setting. Although 38 (73%) patients achieved an objective response, grade ≥3 adverse events occurred in 34 (65%) patients. In the study, although the adverse events seemed to be largely caused by axitinib, some adverse events were related with pembrolizumab. In the ongoing phase Ib study for avelumab and axitinib, 55 RCC patients were enrolled. A total of 32 (58%) patients achieved an objective response at the cut-off date. However, one (2%) patient died of treatment-related autoimmune myocarditis. The management of irAEs differed from that of the adverse events caused by cytotoxic agents. For example, severe irAEs required immunosuppressive agents to ease the activated immune system. Thus, confronting adverse events for patients receiving combination therapy with ICI and cytotoxic agents, physicians need to discriminate which drug is responsible for the adverse events.

**Conclusions**

In the present review, we outlined the FDA-approved immunotherapies for genitourinary cancers and covered some important aspects regarding ICI use. The recently observed promising effects of ICIs will hopefully lead to the development of a strategy for cancer immunotherapy.

Many phase III studies on ICI treatment in various cancers are being carried out. Furthermore, the development of other antibody therapies that regulate activation of T cells is well practiced. Clinical trials on combination therapy with these drugs are now ongoing. Although expansion of ICI use confers benefits for advanced cancer patients, it also causes economic problems. Thus, it is important to detect biomarkers to enable the appropriate use of ICIs. With the current technology, including genetic analysis using next-generation sequencers, mass cytometers, multicolor flow cytometers, protein assays and multiplex IHC, detection of useful biomarkers that reflect the immune status of cancer and/or the host and provide important clues for personalized medicine is desired.

**Conflict of interest**

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