PD-1/PD-L1 Blockade in Cancer Immunotherapy: Clinical Benefits, Limitations and Beyond

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Abstract. Compared with traditional chemotherapy and radiation therapy, immune checkpoint inhibitors (ICIs) exhibit better efficacy and lower side effects on many cancers, especially monoclonal antibodies (mAbs) targeting programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1). At present, many related drugs such as nivolumab, pembrolizumab, cemiplimab-rwlc, atezolizumab, avelumab and durvalumab have been widely used in clinic, while drug resistance and toxicity are the two major factors that have limited their use. For this case, the results of several clinical trials have shown significant improvements with combination treatment strategies compared to monotherapy.

Keywords: Cancer Immunotherapy, Checkpoint Inhibitors, Anti-PD-1, Anti-PD-L1, Toxicity.

1. Introduction

Cancer is one of human’s biggest health challenges. In recent years, it has exceeded cardiovascular disease and takes up the biggest share as the leading cause of death in the population of developed countries. Chemotherapy, as a traditional cancer treatment that is most widely used, has its limitations. Apart from limited benefits and severe side effects, there is evidence showing that chemotherapy can cause genetic changes in the patients’ offspring after the initial exposure of the patients. Therefore, more effort should be made into new therapies like immunotherapies, and immune checkpoint inhibitors (ICIs) are good alterations for conventional chemotherapy.

ICI therapies take effect by blocking the pathways of immune checkpoint proteins that suppress T-cell mediated immunity, thereby boosting the patients’ immune system to fight against cancer and reducing the activity of immune escape of cancer cells. Two of the promising immunosuppressive molecules that have been serving as targets of ICI therapies are PD-1 and PD-L1.

PD-1 (PDCD1 or CD279), was discovered in 1992 by Dr. Honjo from a mouse T cell hybridoma [1]. It is mainly expressed in activated T cells and B cells. Sustained activation of the PD-1 pathway results in the suppression of T cell function, especially in peripheral tissues. PD-L1 (CD274 or B7-H1) is the major binding partner of PD-1, which can be expressed by antigen-presenting cells and induced on nonimmune cells, including tumor cells [2].

The interaction between PD-1 and PD-L1 takes an essential role in suppressing the function of tumor T cells. The binding of PD-1 to both ligands can lead to phosphorylation of ITIMs and ITSMs, recruits and activates tyrosine phosphatase 2 (SHP-2), which can dephosphorylate several key proteins in the TCR signaling pathway, thereby inhibiting the activation of phosphoinositide 3-kinase (PI3K), protein kinase B (AKT) and extracellular-signal-regulated kinase (ERK), further inducing CD8 + T cells and CD4 + T cells to be in an inactive state, and finally inhibiting the secretion of related cytokines and the proliferation of T lymphocytes [3].

In addition, interferon induces adaptive immune resistance through PD-1: PD-L1 interaction. T cells recognize tumor antigens, release interferon-γ (IFN-γ), and activate Janus kinases (JAKs), leading to the recruitment and phosphorylation of STAT1 and STAT3. It activates interferon regulatory factor 1 (IRF1), which induces upregulation of PD-L1 expression, allowing cancer cells to evade T cell attack [4]. Antibodies against PD-1/PD-L1 disrupt this pathway, thereby enhancing antitumor immune activity.
Focusing on a systematic review of clinical trials, we notice that checkpoint inhibitors targeting PD-1 and PD-L1 have yielded promising and lasting responses in a considerable proportion of cancer patients in recent years. Nivolumab, as a PD-1-targeting ICB therapy, shows survival benefits over other traditional therapies in advanced renal cell carcinoma (RCC), small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Some PD-L1-targeting drugs, such as avelumab, atezolizumab and durvalumab, have also been approved in various settings and achieved good curative effects. Also, there is an increasing number of potential combination therapies which may induce tumor regressions in patients who would not have responded to either treatment alone.

In this paper, we summarize a variety of anti-PD-1/PD-L1 monoclonal antibodies (mAbs) in terms of application, efficacy, and clarify the clinical benefits and limitations of the therapy, with a view to providing helpful insights.

2. ICI Monotherapy in Cancer Treatment

ICIIs have emerged as a central pillar of cancer therapy. Antibodies against PD-1/PD-L1 have been approved by the Food and Drug Administration (FDA) for the second-line or first-line treatment of various types of cancer, including NSCLC, melanoma, SCLC, RCC, classical Hodgkin’s lymphoma, urothelial carcinoma (UC), colorectal carcinoma and so on.

For the treatment of NSCLC, the most prominent agents are two PD-1 inhibitors, namely nivolumab (Opdivo) and pembrolizumab (Keytruda), and two PD-L1 inhibitors, namely atezolizumab (Tecentriq) and durvalumab (Infinzi). Compared with chemotherapy, they can markedly improve the response rate, prolong patient survival and have relatively low toxicity.

Zayas-Soriano M et al. conducted a 4-year retrospective observational study and focused on the overall survival (OS) and progression-free survival (PFS) of NSCLC patients treated with nivolumab, pembrolizumab, and atezolizumab in one hospital. The OS rate at 6 to 49 months for patients receiving nivolumab ranged from 65% to 80%; the OS rate at 2 to 24 months for patients receiving pembrolizumab was 70.9% (second-line therapy or beyond); the OS rate at 3 to 7 months for patients receiving atezolizumab was 75.8% [5].

Unfortunately, only a minor share of patients with NSCLC respond positively to monotherapy with this class of drugs, taking up approximately 20% [6]. Combination approaches based on anti-PD-1/PD-L1 therapy, have shown better survival benefits in patients with advanced NSCLC.

It is worth mentioning that Conforti F, et al. found a gender difference in the efficacy of anti-PD-1/PD-L1 monotherapy in patients with advanced NSCLC expressing high PD-L1 levels, with a greater survival benefit in men than women who received immunotherapy [7].

There are studies showing that anti-PD-1 monotherapy also has modest efficacy in gastroesophageal adenocarcinoma (GEA) and squamous esophageal carcinoma (ESCC) [8]. While the experimental results of Laercio Lopes da Silva et al. suggest that anti-PD-1 monotherapy improves the safety profile of advanced gastroesophageal cancers, especially pembrolizumab monotherapy, which is the safest first-line treatment but without a significant survival benefit [9]. What is more, anti-PD-1 monotherapy can also be used for immunotherapy of advanced nasopharyngeal cancer, and metastatic triple negative breast cancer, but less effective for pancreatic cancer [10].

In addition, several new PD-1 / PD-L1 inhibitors, such as PDR001 (spartalizumab) and BPI-371153, have entered preclinical or clinical trials.

3. ICI Combination Therapy in Cancer Treatment

3.1. Why Combination Therapy?

Prior to the use of ICI in multiple tumor types, chemotherapy, radiotherapy and molecularly targeted therapies were the main modalities employed. Even though the therapies that are mentioned above are proved to be effective in early-stage cancers, they have somehow received little curative effect in advanced stage ones. And despite the positive progress made by monotherapy of PD-1/PDL1
inhibitors, only a small fraction of patients responded, many of whom were relapsing. Also, the resistance to anti-PD-1/PD-L1 therapy has limited a broader application in clinical practices. Emerging evidence indicates that rational strategies combining anti-PD-1/PD-L1 agents with conventional cancer therapies and many novel immune techniques could hopefully increase the immune response and overcome resistance, thus showing a higher efficacy, as compared to using these therapies alone.

3.2. Other Immune Checkpoint Inhibitors

It is proved that the combination of PD-1/PD-L1 and CTLA-4 blockade could increase antigen-specific inflammatory cytokine production, as well as tumor-infiltrating lymphocyte (TIL) activation. Such dual blockade has shown its anti-tumor effect in NSCLC, melanoma, RCC, bladder cancer, etc. The combination of ipilimumab and nivolumab was the first approved double checkpoint inhibitor in unresectable or metastatic melanoma (NCT01844505). In a recent trial using durvalumab with or without tremelimumab in metastatic NSCLC (NCT02352948), longer OS and PFS (progression-free survival) for durvalumab + tremelimumab versus SoC (standard of care) were found, along with a consistent safety profile in previous studies. Still, there are clinical trials showing no additional benefit (NCT02516241) (NCT03043872), some of which even lead to aggravated irAEs [11], suggesting more well-designed studies with different doses and proper patient selection.

3.3. Chemotherapy

Evidence has indicated that chemotherapy can help form a favorable immune microenvironment by mechanisms including increasing tumor antigen exposure, reducing the number and activity of immune-suppressive cells and inducing molecules that can further activate effector immune cells [12, 13], thus showing encouraging response when combining with ICI therapy. The approval of the pembrolizumab-chemotherapy combination therapy in NSCLC inspired more studies to evaluate the efficacy of such a strategy in other cancers. The combination of atezolizumab and chemotherapy was evaluated in extensive-stage SCLC, where 403 patients were enrolled. Compared with the standard platinum-doublet chemotherapy, the combination therapy showed impressively longer OS, with the median raising from 10.3 to 12.3 months. Yet in advanced NSCLC, a phase 1b trial of platinum-doublet chemotherapy combined with nivolumab has reported the development of treatment-related AEs (NCT01454102), suggesting a further investigation on this topic. Luckily, more randomized, double-blind, large cohort studies are on their way (NCT02578680) (NCT02366143).

3.4. Radiotherapy

Radiotherapy has been proved to induce cell death and thus initiate systemic antitumor effects, which is known as the abscopal effect [14]. This intriguing clinical phenomenon represents the synergistic antitumor effects of the combination of radiotherapy and PD-1/PD-L1 inhibitors. A phase 3 clinical trial showed that durvalumab significantly increased the OS and PFS of locally advanced, unresectable NSCLC patients undergoing chemoradiotherapy (NCT02125461). Similarly, a study on radiation plus ipilimumab showed prolonged survival from 5 to 21 months compared with radiation alone with metastatic malignant melanoma [15].

3.5. Molecular Targeted Therapies

3.5.1. BRAF / MEK Inhibitors

Mitogen-activated protein kinase (MAPK) pathway inhibitors, including BRAF and MAPK/ERK kinase (MEK) inhibitors, for instance, indicated improved outcomes in NSCLC, colorectal cancer, pancreatic cancer, etc. However, a significant proportion of patients experienced tumor recurrence, largely associated with resistance. Fortunately, on the other hand, ICI ensures a relatively durable tumor regression in patients, despite its limited clinical performance. Studies have shown synergetic outcomes when combining BRAF / MEK Inhibitors with PD-1/PD-L1 inhibitors. NCT03374254 is a phase 1b study testing the efficacy of pembrolizumab plus binimetinib (MEK inhibitor) and
pembrolizumab plus chemotherapy, with or without binimetinib in metastatic CRC, and there hasn’t been a result yet. A phase I study demonstrated an acceptable safety profile for a PD-L1 inhibitor combined with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in certain types of melanoma [16], and more trials are undergoing to optimize the efficacy.

3.5.2. Poly ADP-ribose Polymerase (PARP) Inhibitors

PARP can repair single-strand DNA break, and PARP inhibition is able to improve the genomic instability, thus enhancing tumor antigenicity and sensitizing tumors to ICI therapies. In a phase I/II TOPACIO trial, niraparib combined with pembrolizumab was evaluated in platinum-resistant ovarian cancer, which showed increased ORR with no new safety concerns (NCT02657889).

3.5.3. Angiogenesis Inhibitors

In previous preclinical studies, angiogenesis inhibitors combined with PD-1/PD-L1 inhibitors have improved efficacy by blocking proangiogenic pathways, normalizing vessel formation and reshaping TME [17, 18]. In the phase III IMbrave150 trial, HCC patients who underwent the treatment of atezolizumab plus bevacizumab (anti-VEGF-A) showed improved PFS, OS and ORR compared to the sorafenib group. According to the results of KEYNOTE-426, pembrolizumab combined with axitinib was approved by the FDA for treating advanced RCC in 2019 (NCT02853331).

3.6. Chimeric Antigen Receptor T (CAR-T) Cell Therapy

Certain cancers can remain tricky because of the immunosuppressive tumor microenvironment. Interestingly, the combination of CAR-T cell therapy and PD-1/PD-L1 inhibitors can boost the therapeutic efficacy through rescuing CAR-T cells from immune exhaustion, thus jointly overcoming immunosuppression [19]. Notably, such a technique may achieve enhanced immunotherapeutic efficacy by CRISPR-Cas9-mediated gene-editing, providing a promising future where precise genome editing synergizes with immunotherapies [20].

3.7. Other Combination Strategies

3.7.1. IDO Inhibitors

Indoleamine 2,3-dioxygenase (IDO), produced by tumor cells, TAMs and MDSCs, is expressed in certain tumors and often led to poor prognosis. A phase III trial using epacadostat (IDO inhibitor) plus pembrolizumab in unresectable or metastatic melanoma (NCT02752074) was designed to test the efficacy but failed to find obvious enhancement using the IDO1 selective inhibitor.

3.7.2. Neoantigen Tumor Vaccines

The combined use of neoantigen tumor vaccines and PD-1/PD-L1 inhibitors is also under active investigation, considering an effective innate immune response could be initiated, thus forming a virtuous immune cycle. The efficacy of this combination is being investigated in melanoma (NCT01176474) (NCT01176461), and it is positively hypothesized that ICI may become the ideal combination choice for neoantigen tumor vaccines against malignant cells, such synergistic effect can be observed in some preclinical studies [21, 22].

4. The Efficacy of Anti-PD-1/PD-L1 ICIs: What lies behind?

Efficacy is one of the major factors that have limited the use of anti-PD-1/PD-L1 drugs. Even though the application of PD-1-targeted mAbs has greatly improved the treatment of melanoma and some other types of cancer, the outcomes can be very different between various malignancies. In a 5-year cohort study of patients with different malignancies receiving nivolumab monotherapy, a remarkable gap was shown in disease control rate, with 53.3% in melanoma, 70.6% in RCC and 41.9% in NSCLC (NCT00730639). The differences that are mentioned above can be partly explained by the impact of Fcγ receptors (FcγRs) and tumor microenvironment (TME).
Immune cells express FcγRs on their surface, which are responsible for the regulation of immune response. FcγRs can be subdivided into two IgG classes, activating, which includes FcγRI, FcγRIIa, and FcγRIIIa, and inhibitory, which is FcγRIIb, and the ratio between activating and inhibitory receptor binding (A/I) can help to predict the anti-tumor immune response of the ICIIs [23]. Despite the extensive use of anti-PD-1/PD-L1 drugs in cancer treatment, the interaction between the Fc portion on mAbs and FcγRs hasn’t been fully elucidated. Recent studies suggest that the engagement of activating FcγR can result in a lower anti-tumor response in anti-PD-1 therapy, and the explanation for this might be the elimination of activated infiltrated CD8+ T Cells. Lower efficacy of anti-PD-1 therapy was also found when FcγRIIb activities were engaged [24].

At the stage right now, the mostly used anti-PD-1 drugs (e.g., nivolumab and pembrolizumab), are of the IgG4 subtype, which has a much lower affinity to activating FcγRs but is still able to bind to FcγRIIb, resulting in a relatively low A/I ratio that can impact the efficacy of these drugs. Therefore, developing anti-PD-1 mAbs that do not contain Fc portion has been a promising field in ICI therapy. However, evidence from animal experiments suggests that in cold tumors (e.g., neuroblastoma) which have fewer infiltrated immune cells, the Fc portion is still required when using anti-PD-1 drugs, despite the fact that it may result in a decrease in efficacy [25].

Changes driven by oncogenes in TME are also an important cause of ICI resistance. Apart from disruption of cell responses to IFN-γ that eventually leads to blockade of the induction of PD-L1 and therefore makes anti-PD-1/PD-L1 mAbs ineffective, changes in cell metabolism inside the tumor can also set barriers to ICI therapy. Because of the poor differentiation of blood vessels inside the neoplasm, immune cells usually have to compete with tumor cells for nutrients and oxygen. This can lead to metabolic adaptation of immune cells, which will eventually cause a decrease in anti-tumor cytotoxicity and therefore lead to dismal outcomes [26].

Cancer cell proliferation may lead to changes in the level of different components in the TME. For instance, a drop in the content of glucose, amino acids, as well as fatty acids, and a surge in the level of lactate in the surrounding microenvironment. An increase in immune checkpoint expression may occur as an adaptation to lower glucose and acidity, causing immunosuppression. Recently, many studies have shown that PD-1/PD-L1 has the ability to suppress metabolic reprogramming of immune cells and inhibit the process of glycolysis, therefore anti-PD-1/PD-L1 mAbs may enhance the antitumor immune response by promoting the effector function of tumor infiltrating lymphocytes (TILs) [27]. Usually, each amino acid plays multiple roles in modulating both immunity and tumor proliferation. Glutamine is the most consumed nutrient in the TME after glucose, and the blockade of either glutamine or glutaminase is a rather hot field in recent years. Leone et al. applied glutamine blockade in mice with tumors using 6-Diazo-5-oxo-L-norleucine (DON), which showed its ability to suppress cancer cell metabolism and thus decrease acidosis, hypoxia and shortage of nutrients in TME. Notably, anti-PD-1 combined with DON has shown a significantly improved antitumor response in the study compared with using anti-PD-1 alone [28], presenting great potential in ICI combination therapy.

5. Toxicity of Anti-PD-1/PD-L1 mAbs

Apart from drug resistance, toxicity is also one of the major concerns that have, to some extent, limited the use of anti-PD-1/PD-L1 drugs and other forms of immunotherapies as well. Many toxicities have manifestations similar to autoimmune diseases, which are defined as immune-related adverse events (irAEs). According to the Common Terminology Criteria for Adverse Events (CTCAE), irAE severity can be graded into five ascending grades, with grade 1 referring to mild symptoms and grade 5 representing death. Usually, grade 3-5 are considered severe.
Table 1. Immune-related adverse effects (irAEs) in anti-PD-1/PD-L1 therapy

| irAEs                  | Intervention | Incidence rate (%) | Conditions                          | References          |
|------------------------|--------------|--------------------|-------------------------------------|---------------------|
| **Dermatologic**       |              |                    |                                     |                     |
| Rash                   | Nivolumab    | 4.17%              | NSCLC                               | NCT033829 12       |
|                        | Pembrolizum ab| 17.48%             | Melanoma                            | NCT028210 00       |
| Vitiligo               | Pembrolizum ab| 7.14%              | Melanoma                            | NCT021800 61       |
| Pruritus               | Nivolumab    | 19.00%             | Fallopian Tube Carcinoma            | NCT024986 00       |
|                        | Pembrolizum ab| 9.52%              | Ovarian Carcinoma                   | NCT028356 90       |
| **Gastrointestinal**   |              |                    |                                     |                     |
| Diarrhea               | Nivolumab    | 2.09%              | -                                   | NCT028321 67       |
|                        | Atezolizumab | 1.28% (severe)     | Carcinoma                           | NCT024503 31       |
|                        | Durvalumab   | 23.64%             | Mesothelioma                        | NCT028991 95       |
| **Hepatitis**          | Nivolumab    | 2.72%              | RCC                                 | NCT025960 35       |
| **Colitis**            | Nivolumab    | 0.78%              | NSCLC                               | NCT030907 37       |
|                        | Atezolizumab | 1.97%              | NSCLC                               | NCT028486 51       |
| **Endocrine**          |              |                    |                                     |                     |
| Hypothyroidism         | Nivolumab    | 2.94%              | Melanoma                            | NCT036186 41       |
|                        | Atezolizumab | 7.81%              | Advanced Solid Tumors               | NCT024586 38       |
| Hypophysitis           | Nivolumab    | 0.42%              | -                                   | NCT028321 67       |
|                        | Atezolizumab | 0.26%              | Carcinoma                           | NCT024503 31       |
| **Pulmonary**          |              |                    |                                     |                     |
| Pneumonitis            | Nivolumab    | 2.29%              | Prostate Cancer                     | NCT007306 39       |
|                        | Pembrolizum ab| 7.53%              | RCC                                 | NCT023439 52       |
|                        |               |                    | Metastatic Melanoma                 |                     |
|                        |               |                    | NSCLC                               |                     |

**References:**
- NSCLC: Non-Small Cell Lung Cancer
- RCC: Renal Cell Carcinoma
- Melanoma
According to the statistical analysis done by Michot et al., anti-PD-L1 drugs have the least severe irAEs, followed by anti-PD-1 drugs. Overall, anti-PD-1/PD-L1 mAbs are less frequently to develop irAEs than anti-CTLA-4 mAbs, which are also widely used in ICI therapy [29].

Immune-related toxicities of anti-PD-L1 drugs can affect almost every organ system. Some of the most commonly seen irAEs and their incidence rates are listed in Table 1. Dermatologic adverse effects include dry mouth, mucositis, rash, pruritus, vitiligo, etc. It is worth mentioning that in patients suffering from melanoma, vitiligo is the most frequent irAE when applying anti-PD-1 therapy. Gastrointestinal adverse effects (e.g., colitis, diarrhea) can possibly occur in every part of the digestive tract, and the small intestine and colon are usually more affected than the rest of the tract [29]. Severe colitis which grades higher than 3 is not very common in anti-PD-1/PD-L1 monotherapy, accounting for 0.78% and 1.97% in the use of nivolumab and atezolizumab respectively (NCT03090737) (NCT02848651) (Table 1), but it is a frequent reason for the discontinuation of treatment. Hepatitis is also rare, accounting for approximately 3% in patients with RCC (NCT02596035) (Table 1). Symptoms of endocrine adverse events can be severe, with hypothyroidism and hypophysitis affecting patients the most, and can be managed by supplementing hormones that are missing. As for irAEs in the pulmonary system, pneumonitis can be seen in 2.29% of patients using Nivolumab (NCT00730639), and is potentially fatal if not under proper control.

Many current studies are focusing on identifying the biomarkers of response to ICIs, and clinical observations have hinted at the potential correlation between developing irAEs and better outcomes for patients [30]. As is shown in a retrospective study of 157 patients with a variety of malignancies treated with pembrolizumab, atezolizumab and nivolumab, patients who developed irAEs had improved progression-free survival (PFS) according to Kaplan–Meier estimate, and multivariate Cox regression have suggested that irAEs were related a remarkable improvement of PFS in patients with cancer. Notably, this improvement persisted even in patients under the control of these irAEs receiving glucocorticoids [31]. In another retrospective study in patients taking anti-PD-1 therapy for metastatic melanoma, 59% of patients developed irAEs, and the mOS was 12.2 months longer in patients who developed irAEs (not including vitiligo) compared with patients without irAEs, indicating that the development of irAEs is associated with improved survival rate and more favorable outcome [32].

| Pleural effusion | Pembrolizumab | 2.63% | Mediastinal Large B-cell Lymphoma | NCT025769 90 |
| Renal | Nivolumab | 2.11% | RCC | NCT025960 35 |
| | Pembrolizumab | 1.30% | Lung Cancer | NCT033225 40 |
| Medistinal Large B-cell Lymphoma | Durvalumab | 5.45% | Mesothelioma | NCT028991 95 |
| Cardiovascular | Pembrolizumab | 2.04% | UC | NCT033618 65 |
| | Avelumab | 0.43% | Carcinoma | NCT021556 47 |
| Infections | Nivolumab | 4.65% | NSCLC | NCT030907 37 |
| Nervous | Avelumab | 2.72% | NSCLC | NCT017720 04 |
An explanation of the findings above is antigen cross activity. Antigens presented on healthy tissues and tumor cells, to some extent, have similarities, which enable T-cell mediated response in both sites. Therefore, when activated, the immune system could possibly target non-tumor sites as well. Vitiligo is a perfect example of this hypothesis, with CD8+ T-cell attacking both melanocytes and melanoma cells [30].

6. Conclusions

Studies have shown that anti-PD-1/PD-L1 monotherapy can all be used for a huge variety of malignancies, especially in the treatment of NSCLC, which can significantly prolong patients’ overall survival. However, the proportion of patients with drug response is not favorable enough, and there should be more attention on bringing up the response rate through developing ICIs with better efficacy.

The limited efficacy shown in anti-PD-1/PD-L1 monotherapy has also led to a large-scale discussion about its combination with other therapies, which include other ICIs, conventional therapies, molecular targeted therapies, neoantigen tumor vaccines, to name a few. It must be noted that many of the combination strategies are still under investigation to clarify the efficacy and toxicity, but such rationale is without doubt a symbol of a new age in cancer immunotherapy.

Even though efficacy and toxicity have, to some extent, limited the use of anti-PD-1/PD-L1 mAbs in cancer treatment, many studies have illustrated the suspected reasons behind these two aspects, mostly towards the impacts of immune receptors, TME, and antigen cross-activities. It is also worth mentioning that irAEs can possibly be used as a biomarker for drug response, which might be of great help in future clinical practice.

References

[1] Ishida Y., Agata Y., Shibahara K., et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. [J]. The EMBO Journal, 1992, 11(11): 3887–3895.
[2] Buchbinder Elizabeth I., Desai Anupam. CTLA-4 and PD-1 Pathways[J]. American Journal of Clinical Oncology, 2016, 39(1): 98–106.
[3] Baumeister Susanne H., Freeman Gordon J., Dranoff Glenn, et al. Coinhibitory Pathways in Immunotherapy for Cancer [J]. Annual Review of Immunology, 2016, 34(1): 539–573.
[4] Kalbasi Anusha, Ribas Antoni. Tumour-intrinsic resistance to immune checkpoint blockade [J]. Nature Reviews Immunology, 2020, 20(1): 25–39.
[5] Zayas-Soriano Marta, Bonete-Sánchez Manuel, Campillo-López Juan, et al. Clinical efficacy and safety of anti PD-1/PD-L1 antibodies as monotherapy in patients with non-small-cell lung cancer [J]. Farmacia Hospitalaria: Organoficial De Expresion Cientifica De La Sociedad Espanola De Farmacia Hospitalaria, 2020, 45(1): 22–27.
[6] Sui Hongshu, Ma Ningxia, Wang Ying, et al. Anti-PD-1/PD-L1 Therapy for Non-Small-Cell Lung Cancer: Toward Personalized Medicine and Combination Strategies [J]. Journal of Immunology Research, 2018, 2018: 6984948.
[7] Conforti F., Pala L., Pagan E., et al. Sex-based differences in response to anti-PD-1 or PD-L1 treatment in patients with non-small-cell lung cancer expressing high PD-L1 levels. A systematic review and meta-analysis of randomized clinical trials [J]. ESMO open, 2021, 6(5): 100251.
[8] Smyth E. C., Gambardella V., Cervantes A., et al. Checkpoint inhibitors for gastroesophageal cancers: dissecting heterogeneity to better understand their role in first-line and adjuvant therapy [J]. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 2021, 32(5): 590–599.
[9] Da Silva Laercio Lopes, Aguiar Pedro Nazareth, Park Robin, et al. Comparative Efficacy and Safety of Programmed Death-1 Pathway Inhibitors in Advanced Gastroesophageal Cancers: A Systematic Review and Network Meta-Analysis of Phase III Clinical Trials [J]. Cancers, 2021, 13(11): 2614.
[10] Feng Mengyu, Xiong Guangbing, Cao Zhe, et al. PD-1/PD-L1 and immunotherapy for pancreatic cancer [J]. Cancer Letters, 2017, 407: 57–65.
[11] Postow Michael A., Sidlow Robert, Hellmann Matthew D. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade [J]. The New England Journal of Medicine, 2018, 378(2): 158–168.

[12] Apetoh L., Ladoire S., Coukos G., et al. Combining immunotherapy and anticancer agents: the right path to achieve cancer cure? [J]. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 2015, 26(9): 1813–1823.

[13] Galluzzi Lorenzo, Buqué Aitziber, Kepp Oliver, et al. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents [J]. Cancer Cell, 2015, 28(6): 690–714.

[14] Asna N., Livoff A., Batash R., et al. Radiation therapy and immunotherapy—a potential combination in cancer treatment[J]. Current Oncology, 2018, 25(5): e454–e460.

[15] Knisely Jonathan P. S., Yu James B., Flanigan Jaclyn, et al. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival [J]. Journal of Neurosurgery, 2012, 117(2): 227–233.

[16] Atkins Michael B., Larkin James. Immunotherapy Combined or Sequenced With Targeted Therapy in the Treatment of Solid Tumors: Current Perspectives [J]. Journal of the National Cancer Institute, 2016, 108(6): djv414.

[17] Huang Yuhui, Yuan Jianping, Righi Elda, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy [J]. Proceedings of the National Academy of Sciences of the United States of America, 2012, 109(43): 17561–17566.

[18] Pan Chongxian, Liu Hongtao, Robins Elizabeth, et al. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy [J]. Journal of Hematology & Oncology, 2020, 13(1): 29.

[19] Lai Junyun, Beavis Paul A., Li Jasmine, et al. Augmenting Adoptive T-cell Immunotherapy by Targeting the PD-1/PD-L1 Axis [J]. Cancer Research, 2021, 81(23): 5803–5805.

[20] Rupp Levi J., Schumann Kathrin, Roybal Kole T., et al. CRISPR/Cas9-mediated PD-1 disruption enhances anti-tumor efficacy of human chimeric antigen receptor T cells [J]. Scientific Reports, 2017, 7(1): 737.

[21] Shi Xiaojun, Zhang Xinji, Li Jinlong, et al. PD-1 blockade enhances the antitumor efficacy of GM-CSF surface-modified bladder cancer stem cells vaccine [J]. International Journal of Cancer, 2018, 142(10): 2106–2117.

[22] Fu Juan, Kanne David B., Leong Meredith, et al. STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade [J]. Science Translational Medicine, 2015, 7(283): 283ra52.

[23] Furness Andrew J.S., Vargas Frederick Arce, Peggs Karl S., et al. Impact of tumour microenvironment and Fc receptors on the activity of immunomodulatory antibodies [J]. Trends in Immunology, 2014, 35(7): 290–298.

[24] Dahan Rony, Sega Emanuela, Engelhardt John, et al. FcγRs Modulate the Anti-tumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis [J]. Cancer Cell, 2015, 28(3): 285–295.

[25] Moreno-Vicente Julia, Willoughby Jane E, Taylor Martin C, et al. Fc-null anti-PD-1 monoclonal antibodies deliver optimal checkpoint blockade in diverse immune environments[J]. Journal for Immunotherapy of Cancer, 2022, 10(1): e003735.

[26] Pavlova Natalya N., Thompson Craig B. The Emerging Hallmarks of Cancer Metabolism [J]. Cell Metabolism, 2016, 23(1): 27–47.

[27] Bader Jackie E., Voss Kelsey, Rathmell Jeffrey C. Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy[J]. Molecular cell, 2020, 78(6): 1019–1033.

[28] Leone Robert D., Zhao Liang, Englert Judson M., et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion [J]. Science, 2019, 366(6468): 1013–1021.

[29] Michot J.M., Bigenwald C., Champiat S., et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review [J]. European Journal of Cancer, 2016, 54: 139–148.

[30] Hussaini Syed, Chehade Rania, Boldt Ronald Gabriel, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors – A systematic review and meta-analysis [J]. Cancer Treatment Reviews, 2021, 92: 102134.
[31] Shafqat Hammad, Gourdin Theodore, Sion Amy. Immune-related adverse events are linked with improved progression-free survival in patients receiving anti-PD-1/PD-L1 therapy [J]. Seminars in Oncology, 2018, 45(3): 156–163.

[32] Indini Alice, Di Guardo Lorenza, Cimminiello Carolina, et al. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma [J]. Journal of Cancer Research and Clinical Oncology, 2019, 145(2): 511–521.