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REVIEW

Research Status and Outlook of PD-1/PD-L1 Inhibitors for Cancer Therapy

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Abstract: PD-1/PD-L1 inhibitors are a group of immune checkpoint inhibitors as front-line treatment of multiple types of cancer. However, the serious immune-related adverse reactions limited the clinical application of PD-1/PD-L1 monoclonal antibodies, despite the promising curative effects. Therefore, it is urgent to develop novel inhibitors, such as small molecules, peptides or macrocycles, targeting the PD-1/PD-L1 axis to meet the increasing clinical demands. Our review discussed the mechanism of action of PD-1/PD-L1 inhibitors and presented clinical trials of currently approved PD-1/PD-L1 targeted drugs and the incidence of related adverse reactions, helping clinicians pay more attention to them, better formulate their intervention and resolution strategies. At last, some new inhibitors whose patent have been published are listed, which provide development ideas and judgment basis for the efficacy and safety of novel PD-1/PD-L1 inhibitors.

Keywords: PD-1, PD-L1, immune checkpoint inhibitors, clinical trials, adverse events, monoclonal antibody

Introduction

Programmed cell death protein-1 (PD-1, Pdcd1), an inhibitory receptor in the immune response phase, was first identified in the early 1990s as a member of the CD28/CTLA-4 family of immunoglobulin (lg) superfamily.[1–8] PD-1 is a type I transmembrane protein with a size of 50–55 kDa, induced in a variety of hematopoietic cells in the peripheral blood and widely expressed in immune cells (T cells, B cells, macrophages, and certain types of dendritic cells, etc.) and tumor cells by antigen receptor signaling and cytokines (Figure 1).[2,4,5,7,9-11]

There are two main immunoregulatory ligands of PD-1, programmed cell death ligand 1 and 2 (PD-L1/PD-L2).[10] PD-L1 is a type I transmembrane protein with a size of 40 kDa, which was identified as PD-1 ligands in 2000. It is widely expressed in both lymphoid tissue and non-lymphoid tissue, and in antigen-presenting cells (macrophages, dendritic cells, etc.) and all kinds of tumor cells (Figure 1).[1,2,6,10-13] Both PD-1 and PD-L1 belong to the immune checkpoint protein family. As co-inhibitors, they can regulate the tolerance of central and peripheral T cells and reduce the proliferation of $CD8^+$ T cells in lymph nodes by combining and conducting inhibitory signals (Figure 2).[2,5,8,11,14-21]

PD-1 and PD-L1 inhibitors are important immune checkpoint inhibitors (ICIs) for the treatment of cancer after the discovery of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4).[22] A study using antibodies in a mouse model published by Dong et al in 2002 showed that local immunosuppression could be eliminated by

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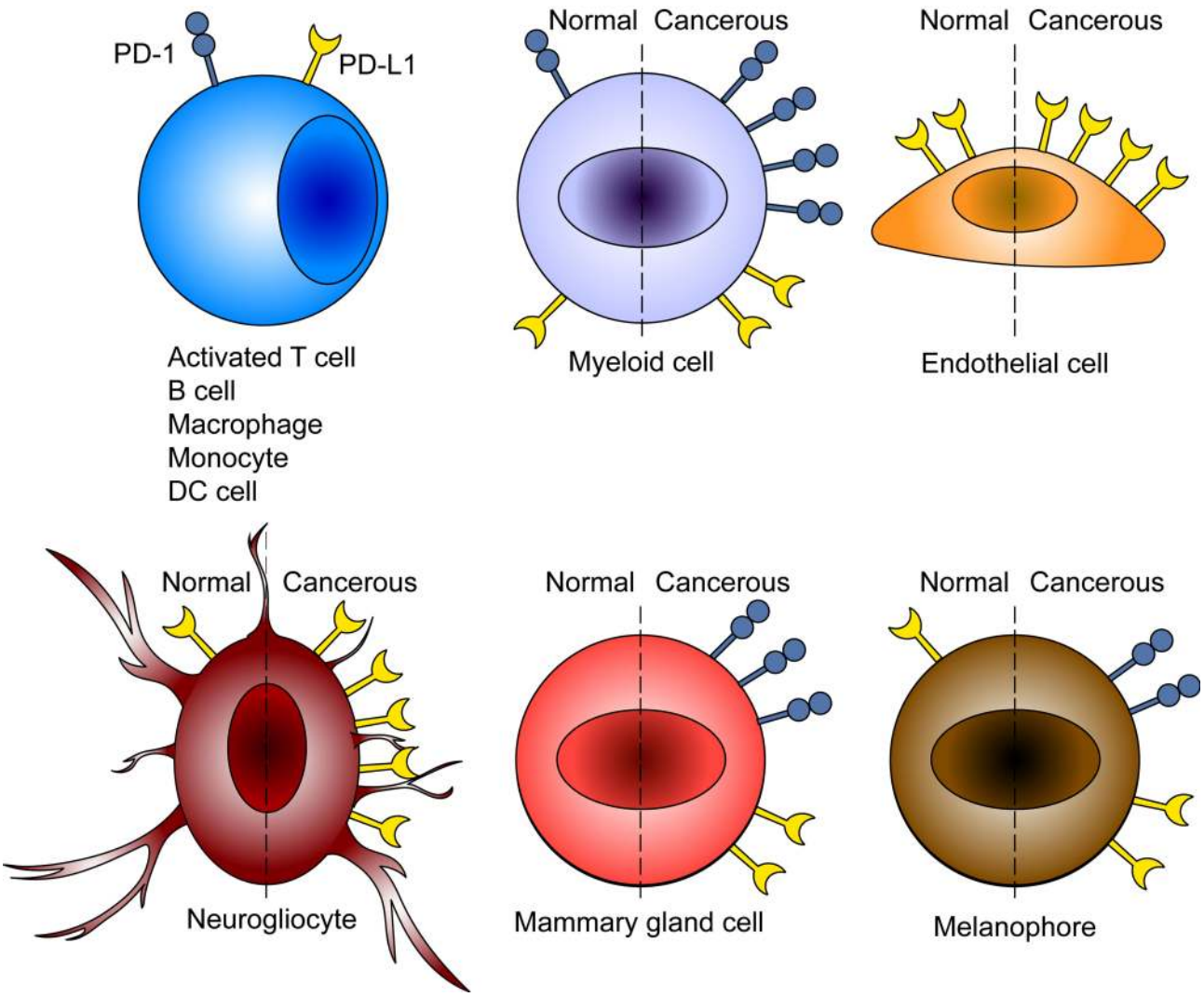


Figure 1 The expression of PD-1 and PD-L1 at different cell types at physiological condition and in tumors.

blocking the binding of PD-1 and PD-L1. The discovery laid the foundation for later immunotherapy for cancer based on T cells.[14] In the same year, Carter et al proposed the concept of treating cancer by blocking PD-1 and PD-L1.[15] Subsequently, pharmaceutical companies began trying to develop PD-1/PD-L1 inhibitors, and the first clinical trial to evaluate nivolumab was launched in 2006. A proof-of-concept clinical study using PD-1 inhibitors in the treatment of refractory solid tumors was conducted in the United States in the same year.[6] Since then, the potential of ICIs in the field of cancer treatment has come to the attention of researchers.

Under normal circumstances, the immune system produces an anti-cancer immune response by executing cancer immunity cycle that kills cancer cells. And yet, the PD-1/PD-L1 pathway is an adaptive immune resistance mechanism of tumor cells to endogenous immune anti-tumor activity.[2,3,6,11,14,23,24] PD-1/PD-ligand interaction down-regulates the immune response during the regression of infection or tumor or the development of self-tolerance. PD-L1 is usually over-expressed in tumor cells or untransformed cells in tumor microenvironment and inhibits cytotoxic T cells by binding to PD-1 receptor on activated T cells, resulting in immune escape. The inhibitors of PD-1 and PD-L1 inhibit the interaction between PD-L1 and PD-1 receptor, preventing cancer cells from evading the immune system in this way and acting as ICIs by reactivating the T-cell-mediated tumor cell death process (Figure 2).[1,3,6,10,22,25-30] With the development of PD-1/PD-L1 inhibitors, immunotherapy has made great progress in the treatment of cancer.[6,9,10,22,25-29,31–41]

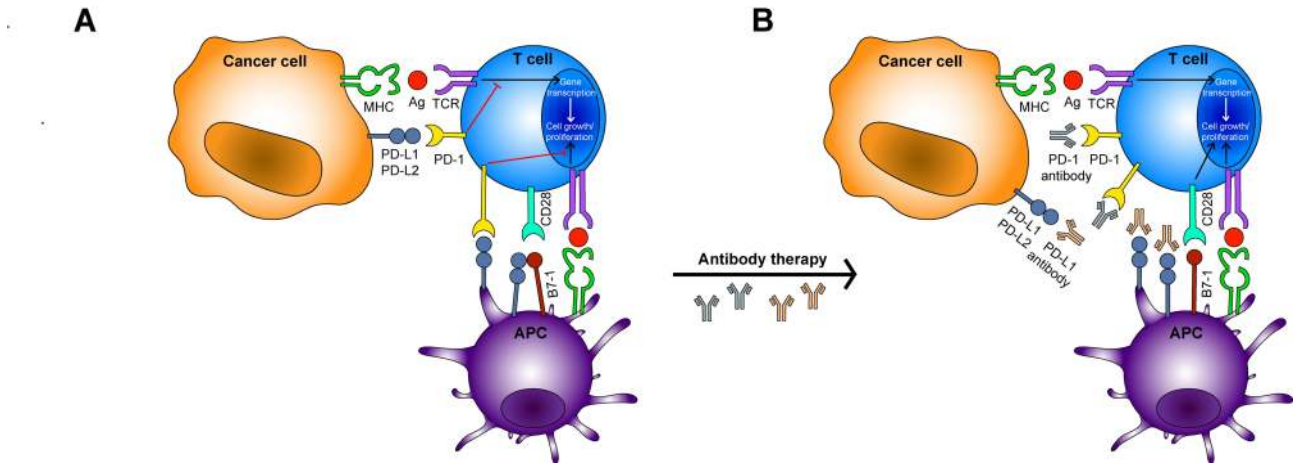


Figure 2 Mechanism of anti-tumor immune surveillance and PD-1/PD-L1 inhibitors. (**A**) Shows that PD-L1 is highly expressed in tumor cells and tumor-related APCs, while PD-1 is highly expressed in tumor-infiltrating lymphocytes. The combination of PD-L1 and PD-1 can inhibit the activation, proliferation and anti-tumor function of $CD8^+$ T cells and realize tumor immune escape. (**B**) Shows that after antibody treatment, anti-PD-1 will bind to PD-1, preventing PD-1 from binding to PD-L1 or PD-L2, and anti-PD-L1 will bind to PD-L1, blocking the binding of PD-L1 to PD-1 and B7-1, releasing the tumor-specific killing ability of T cells.

Approved Drugs

Since May 2006, the FDA has approved six immune checkpoint inhibitors for the PD-1/PD-L1 pathway, including three for PD-1 (pembrolizumab, nivolumab and cemiplimab) and three for PD-L1 (atezolizumab, avelumab and durvalumab).

Pembrolizumab

Introduction

Pembrolizumab (MK-3475 or lambrolizumab, Keytruda) is a full-length-humanized IgG4κ monoclonal antibody against PD-1, which was developed by Merck.[1,5,10,11,33] Pembrolizumab can block the pathway of PD-1 receptor by binding to the PD-1 receptor, leading to a physiological shift to immune reactivity and anti-tumor effect, so as to restore the anti-tumor immune response of T cells to play an anti-tumor role.[1,5,10,42]

Clinical Trials

Studies on pembrolizumab usually begin with KEYNOTE. At present, clinical trials of pembrolizumab for a variety of tumors are ongoing, including monotherapy or combination therapy for almost all types of cancer.[1]

Melanoma The first clinical trial of pembrolizumab in the treatment of melanoma was published by Hamid et al in 2013. The researchers tested lambrolizumab (also known as pembrolizumab) in 135 patients with advanced melanoma and found that lambrolizumab treatment can lead to a high incidence of continued tumor regression, and the toxicity caused by it is also acceptable.[43] In the KEYNOTE-001 expansion group published in July 2014, Robert et al compared the efficacy and safety of pembrolizumab at the dose of 2 mg/kg and 10 mg/kg every 3 weeks in patients with ipilimumab-refractory advanced melanoma. The results showed that pembrolizumab at the dose of 2 mg/kg or 10 mg/kg every 3 weeks might be an effective treatment for those patients who had almost no effective treatment.[44] Based on these data, pembrolizumab was the first accelerated approval drug by FDA in September 2014 for the treatment of patients with unresectable or metastatic advanced melanoma and disease progression following ipilimumab and, if BRAF V600 mutation is positive, a BRAF inhibitor.[11]

The KEYNOTE-002 study published in 2015 evaluated the efficacy and safety of two pembrolizumab doses and investigator-selected chemotherapy in patients with ipilimumab-refractory melanoma, making pembrolizumab the new standard for treatment of ipilimumab-refractory melanoma.[45] An open-label, multicenter, randomized controlled, Phase 3 study, KEYNOTE-006, demonstrated that pembrolizumab was still superior to ipilimumab in efficacy, independent of BRAF status. These results are in line with the expectations of previous studies and provide further support for the use of pembrolizumab in patients with advanced melanoma.[1,46] As a result, the FDA approval was expanded in December 2015 to treat patients with unresectable or metastatic melanoma, including the initial treatment of patients with unresectable or metastatic melanoma with pembrolizumab.[11]

Eggermont et al published a phase 3 double-blind trial KEYNOTE-054 in 2018 to assess the efficacy of pembrolizumab as adjuvant therapy for high-risk stage III melanoma. At a median follow-up of 15 months, pembrolizumab had a recurrence-free survival rate of 75.4% in the overall intention-to-treat population, significantly higher than 61.0% in placebo. Recurrence-free survival was 77.1% in the pembrolizumab group and 62.6% in the placebo group. Grade 3–5 adverse events associated with the trial regimen accounted for 14.7% in the pembrolizumab group and 3.4% in the placebo group. This study proved that as adjuvant treatment of high-risk stage III melanoma, using 200 mg pembrolizumab every three weeks for up to one year, the recurrence-free survival rate of patients was significantly higher than that of placebo, with no unknown side effects identified.[47] Based on this trial, the US FDA accepted a Supplemental Biologics License Application (sBLA) to use pembrolizumab for adjuvant treatment for patients with melanoma with involvement of lymph node(s) following complete resection.[1]

Lung Cancer

NSCLC. In a large international Phase 1 trial, KEYNOTE-001 (clinicaltrials.gov identifier NCT01295827), the researchers evaluated the side effects, safety, and antitumor activity of pembrolizumab in patients with advanced non-small cell lung cancer, and verified that the expression of PD-L1 in at least 50% of tumors was associated with the improvement of pembrolizumab efficacy.[11,48,49] Based on this trial, pembrolizumab was approved by FDA in 2015 for second-line treatment of PD-L1 positive (Tumor proportion score (TPS) ≥1%) metastatic NSCLC with prior chemotherapy or pretreated with tyrosine kinase inhibitors (TKI) if EGFR mutated or (ALK) rearranged.[1,11]

KEYNOTE-024, an open-label, phase 3 clinical trial published in 2016, randomly selected 305 patients with advanced NSCLC who were previously untreated and with PD-L1 expressed in at least 50% cancer cells and without epidermal growth factor receptor gene mutation or anaplastic lymphoma kinase gene translocation, to compare the efficacy and safety of pembrolizumab and platinum-based chemotherapy.[33] KEYNOTE-010 is a randomized, open-label, Phase 2/3 study involving 1034 previously treated patients with advanced non-small cell lung cancer (NSCLC) with PD-L1 positive. This study is the first to report that PD-L1 can be used as a biomarker in the treatment of lung cancer, and establish pembrolizumab as a treatment option for previously treated PD-L1-positive patients with advanced non-small cell lung cancer.[50]

Based on the results of these two trials, the FDA-approved pembrolizumab in October 2016 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test. FDA-approved addition of the following indications for pembrolizumab: Patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] greater than or equal to 50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC; Patients with metastatic NSCLC whose tumors express PD-L1 (TPS greater than or equal to 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. This is the first time the FDA has approved a checkpoint inhibitor for the first-line treatment of lung cancer treatment. And it extends the indications for pembrolizumab to include all NSCLC patients expressing PD-L1 in the second-line treatment of lung cancer.[1,33]

KEYNOTE-021 is an open-label, multicenter, multicohort trial involving 123 patients with locally advanced or metastatic non-squamous cell lung cancer. The results showed improvements in both ORR and PFS in patients randomly assigned to pembrolizumab + PC group.[51] Following the research results of the KEYNOTE-021, the FDA granted accelerated approval of pembrolizumab combined with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC) in May 2017.

KEYNOTE-189 is a randomized, multicenter, double-blind, active, controlled study of 616 patients receiving the first-line treatment of metastatic NSqNSCLC. The estimated rate of overall survival at 12 months was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab-combination group and 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group [Hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64; $P < 0.001$]. Overall survival rates improved in all assessed PD-L1 classifications. Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group [Hazard Ratio for disease progression or

death, 0.52; 95% CI, 0.43 to 0.64; P < 0.001].[52] Based on this, on August 20, 2018, the FDA-approved pembrolizumab in combination with pemetrexed and platinum as first-line treatment of patients with metastatic NSqNSCLC, without EGFR or ALK genomic tumor aberrations.

In addition, KEYNOTE-042, a randomized, open-label, controlled, phase 3 trial published in April 2019, further studied the overall survival rate of pembrolizumab in PD-L1 + (TPS≥1%) patients (all other conditions being equal). The results show that compared with platinum-based chemotherapy, the first-line pembrolizumab monotherapy significantly improved the overall survival in locally advanced or metastatic non-small-cell lung cancer patients with at least 1% of the cancer cells expressing PD-L1 without sensitizing EGFR mutation or ALK translocation. Fewer adverse events were also observed. This suggests that pembrolizumab monotherapy appears to be a reasonable treatment option for patients with low expression level of PD-L1, but a series of subsequent evaluations are required.[53] Following this trial, the FDA-approved pembrolizumab in April 2019 for the first-line treatment of patients with stage III non-small cell lung cancer (NSCLC), who are not candidates for surgical resection or definitive chemoradiotherapy or metastatic NSCLC. And patients must have tumors without EGFR or ALK genomic aberrations and that express PD-L1 (Tumor Proportion Score [TPS]≥1%) determined by an FDA-approved test.

Squamous Cell NSCLC. In the double-blind, phase 3 clinical trial KEYNOTE-407, 559 untreated patients with metastatic squamous non-small cell lung cancer were randomized at a 1:1 ratio to compare overall survival and progression-free survival of pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel to chemotherapy alone. The results demonstrated that in previously untreated patients with metastatic squamous non-small cell lung cancer, pembrolizumab-combination notably prolonged overall survival and progression-free survival compared to chemotherapy alone, and the benefit was independent of PD-L1 expression, but the degree of benefit was related to PD-L1 TPS expression.[1,54] Thus, the FDA-approved pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC) on October 30, 2018.

Urothelial Carcinoma KEYNOTE-045 is an open-label, international phase 3 trial published in 2017, covering 542 patients with advanced urothelial cancer who had recurred or progressed following platinum-based chemotherapy. Based on the experimental results that pembrolizumab significantly prolonged overall survival (about 3 months) of platinum-refractory advanced urothelial carcinoma, the FDA regularly approved pembrolizumab used in the treatment for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy regardless of PD-L1 status.[1,10] KEYNOTE-052, published in the same year, evaluated the activity and safety of first-line pembrolizumab in patients with cisplatin-ineligible, locally advanced, unresectable or metastatic urothelial carcinoma. According to this, pembrolizumab has also been accelerated for approval in patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, providing a new treatment option.[1,55]

HNSCC In August 2016, the FDA accelerated the approval of pembrolizumab for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. The approval is based on KEYNOTE-012, an international, multicenter, non-randomized, open-label, multi-cohort study. The objective response rate (ORR) for these 174 patients with HNSCC with disease progression on or after platinum-containing chemotherapy was 16% (95% confidence interval [CI] 11, 22).[1,56] Subsequently, based on the results of a randomized, multicenter, three-arm, open-label, active-controlled trial, KEYNOTE-048, pembrolizumab was approved by FDA in June 2019 as the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC).

MSI-H or dMMR Tumors FDA accelerated the approval of pembrolizumab in May 2017 for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed after prior treatment and those with no satisfactory alternative therapy or MSI-H or dMMR colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. This is the FDA's first tissue/site-agnostic approval. It was based on the results of five

uncontrolled, multi-cohort, multi-center, single-arm clinical trials involving a total of 149 MSI-H or dMMR cancer patients, which were KEYNOTE-016 (NCT01876511).[57] KEYNOTE-164 (NCT02460198).[58,59] KEYNOTE-012 (NCT01848834), KEYNOTE-028 (NCT02054806), KEYNOTE-158 (NCT02628067). Overall, the ORR of pembrolizumab group was 39.6% (95% CI: 31.7, 47.9), and 78% of the responses lasted ≥6 months.[1,11]

Other Indications Pembrolizumab has been approved for the treatment of 17 types of cancer. Table 1 summarizes the other approved indications and related studies of pembrolizumab.

Adverse Events

The adverse reactions of Pembrolizumab can be roughly divided into two types: immune-related adverse effects (irAEs) and infusion-related reactions. The most common AE (reported in ≥20% of patients) with pembrolizumab as a single drug were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. But the more worrisome AE is the immune-related Adverse Events (irAEs) associated with pembrolizumab treatment, which are generally consistent across different tumor types.[1] It has been reported that some rare but life-threatening AE includes encephalopathy, pneumonia, nephritis, hepatitis, myocarditis and colitis.[11] Their treatment includes discontinuation of medication, alternative therapy, and immunosuppression with high doses of corticosteroids or potent immunosuppressive agents, such as tumor necrosis factor antagonists or mycophenolate mofetil.[22]

Nivolumab

Introduction

Nivolumab (Opdivo, ONO4538, MDX-1106 or BMS-936,558) is a genetically engineered fully humanized IgG4 monoclonal antibody against PD-1 developed by Bristol-Myers Squibb, which is the first time using transgenic mice carrying the human immunoglobulin gene.[6,60] Nivolumab selectively blocks the interaction between the PD-1 receptor and its two known programmed death ligands, PD-L1 and PD-L2, by binding to the PD-1 receptor, thereby interfering with the negative signal regulating the activation and proliferation of T cells, and releasing the immune response inhibition mediated by PD-1 pathway, including anti-tumor immune response.[25,61,62]

Clinical Trials

Nivolumab, whose research usually begins with CheckMate, is currently undergoing clinical trials for a variety of tumors, including head and neck cancer (NCT03355560), Hodgkin's lymphoma (NCT03337919), renal cancer (NCT03203473), lung cancer (NCT03325816), hematologic malignancies (NCT02985554), prostate cancer (NCT04019964), glioma (NCT03557359), and so on. Phase 1 clinical trials of nivolumab began in the United States in 2006 and in Japan in 2009.[9] Studies have shown that the response rate to nivolumab in advanced cancers is approximately 20% to 30%, among which the incidence of malignant melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma are 28%, 18%, and 27%, respectively.[63,64]

Melanoma In December 2014, the FDA accelerated the approval of nivolumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The approval was based on a randomized (2:1), multicenter, non-blind trial CA209037, which compared the efficacy and safety of nivolumab with chemotherapy in patients with unresectable or metastatic melanoma and disease progression on or after anti-CTLA-4 treatment and BRAF V600 mutations whose disease progressed on or after BRAE inhibitors. The results showed that in 120 patients who were given 3mg/kg nivolumab every 2 weeks and followed for at least six months, the ORR was 31.7% (95% CI: 23.5, 40.8) with 4 (3.3%) complete responses (SR) and 34 (28.3%) partial responses (PR). Five responding patients had progress, and the other 33 patients (87%) had ongoing responses (range 2.6+ to 10+ months). Thirteen patients had ongoing responses of 6 months or longer.

Then, according to the results of an international, multicenter, double-blind, randomized, double-arm, active-controlled, phase 3 clinical trial, CheckMate 067, that the ORR increased, response duration prolonged and PFS progressed, the FDA accelerated approved on September 30, 2015, nivolumab combined with ipilimumab in the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.

Checkmate 238 (NCT02388906) is a randomized, double-blind, phase 3 clinical trial involving 906 patients (≥15 years old) who have undergone complete resection of stage IIIb/c or stage IV melanoma. In this trial, the recurrence rate/mortality rate of the patients in nivolumab group was 34% (n=154), while that in ipilimumab group was 45.5% (n=206) [Hazard Ratio 0.65, 95% CI: 0.53, 0.80,

Table 1 Main Clinical Trials Leading to Other Indications FDA Approved for Pembrolizumab

Disease Site	Study	n	Major Efficacy Outcome Measures	ORR	Median Response Duration (Months)	Median PFS (Months)	HR (95% CI)	Median OS (Months)	HR (95% CI)	FDA Approval
cHL	KEYNOTE-087[144]	210	ORR, Complete Response Rate, and DoR	69% (95% CI: 62, 75)	11.1 (0+, 11.1) (for the 145 patients)	–	–	–	-	03/2017
Gastrointestinal cancers	KEYNOTE-059[1,145,146]	259	ORR and DoR	13.3% (95% CI: 8.2, 20.0) (for the 143 patients)	8.4 (1.6+, 17.3+)	2.0 (95% CI: 2.0, 2.1)	–	5.6 (95% CI: 4.3, 6.9)	–	09/2017
Cervical cancer	KEYNOTE-158[147]	98	ORR and DoR	14.3% (95% CI: 7.4, 24.1) (for the 77 patients)	–	2.1	–	9.4	–	06/2018
PMBCL	KEYNOTE-170[148]	53	ORR and DoR	45% (95% CI: 32, 60)	NR (1.1+, 19.2+) (for the 24 patients)	–	–	–	–	06/2018
HCC	KEYNOTE-224[149]	104	ORR and DoR	17% (95% CI: 11, 26)	NR (3.1+, 14.6+)	4.9 (95% CI: 3.4, 7.2)	–	12.9 (95% CI: 9.7, 15.5)	–	11/2018
MCC	KEYNOTE-017[150]	50	ORR and DoR	56% (95% CI: 41, 70)	NR (5.9, 34.5+)	16.8 (95% CI: 4.6, not estimable)	–	NR (95% CI: 26.0, not estimable)	–	12/2018
RCC	KEYNOTE-426[151]	861	OS and PFS	59% (95% CI: 54, 64)	–	15.1 (95% CI: 12.6, 17.7)	0.69 (0.56, 0.84)	NR (NR, NR)	0.53 (0.38, 0.74)	04/2019
Esophageal squamous cell cancer	KEYNOTE-181[152]	628	OS	22% (95% CI: 14, 33)	9.3 (2.1+, 18.8+)	3.2 (95% CI: 2.1, 4.4)	0.66 (0.48, 0.92)	10.3 (95% CI: 7.0, 13.5)	0.64 (0.46, 0.90)	07/2019
	KEYNOTE-180[153]	121	ORR and DoR	20% (95% CI: 8, 37) (for the 35 patients)	–	–	–	–	–	
Endometrial carcinoma	KEYNOTE-146[154]	108	ORR and DOR	38.3% (95% CI, 29, 49)	NR (1.2+, 33.1+) (for the 36 patients)	–	–	–	–	09/2019
NMIBC	KEYNOTE-057[155]	148	Complete Response and DoR	-	16.2 (0.0+, 30.4+)	–	–	–	–	01/2020

p<0.0001]. The median duration of nivolumab exposure was 11.5 months and 74% of patients received nivolumab for greater than 6 months.[65] According to these results, the US FDA approved the anti-PD1 monoclonal antibody nivolumab for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection.

Lung Cancer

NSCLC. On March 4, 2015, the FDA granted approval to nivolumab for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. The approval was based on an open-label, multicenter, multinational, randomized, phase 3 trial CheckMate 017 showing better OS values in patients with metastatic squamous NSCLC who have experienced disease progression in or after a previous platinum chemotherapy regimen. Compared with docetaxel, nivolumab showed a statistically significant improvement in OS in the pre-specified interim analysis of the protocol. The median OS was 9.2 months (95% CI: 7.3, 13.3) in nivolumab group and 6 months (95% CI: 5.1, 7.3) in docetaxel group [Hazard Ratio 0.59, 95% CI: 0.44, 0.79, p=0.00025]. The results of CA209063 (CM063) study also support this approval. This is a single-arm, multinational, phase 2 trial of nivolumab (BMS-936,558) in patients with advanced or metastatic squamous non-small cell lung cancer. In 117 patients receiving intravenous injection of 3mg/kg of nivolumab every 2 weeks, ORR was 15% (95% CI: 9, 22), all of which were partial responses.[66]

In an international, multicenter, open-label, randomized, phase 3 clinical trial, CheckMate 057, 582 patients were randomly divided into two groups: those who received nivolumab 3 mg/kg every two weeks (n=292) and those who received docetaxel 75 mg/m^2 every three weeks (n=290). The median OS of nivolumab group was 12.2 months (95% CI, 9.7, 15.0) (n=292), and docetaxel group was 9.4 months (95% CI, 8.1, 10.7) [Hazard Ratio 0.73, 96% CI: 0.59, 0.89, p=0.002]. The median response duration was 17 months in the nivolumab arm and 6 months in the docetaxel arm. In addition, the overall response rates of nivolumab group and docetaxel group (19% vs 12%) were significantly improved, respectively.[67] On the basis of the above results, nivolumab was approved in October 2015 to treat patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression in FDA-approved treatment of these aberrations prior to receiving Opdivo. And this approval expands the indications of nivolumab in NSCLC with progression on or after platinum chemotherapy, including non-squamous tissue.

SCLC. Following CheckMate-032 (NCT01928394), a multicenter, open-label, multicohort study in patients with metastatic solid tumors, FDA accelerated approval of nivolumab for patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy in 2018. The ORR was 12% (95% CI: 6.5, 19.5). Of the 13 responding patients, 77% responded for 6 months or longer, 62% for 12 months or longer, and 39% for 18 months or longer.

Renal Cell Carcinoma On November 23, 2015, the US FDA granted approval of nivolumab for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy. The approval was based on CheckMate-025 (NCT01668784), a randomized, open-label, phase 3 study. Median overall survival was 25.0 and 19.6 months in the nivolumab and everolimus arms, respectively [HR 0.73 (95% CI: 0.60, 0.89); p=0.0018]. Median progression-free survival was 4.6 in the nivolumab arm and 4.4 months in the everolimus arm [HR 0.88 (95% CI: 0.75, 1.03); p=0.11].[68]

CheckMate 214 (NCT02231749) is a phase 3, randomized, open-label trial comparing the objective response rate, progression-free survival and the overall survival of nivolumab combined with ipilimumab to sunitinib monotherapy in patients with previously untreated renal cell cancer. Based on this study, the FDA-approved nivolumab and ipilimumab in combination to treat intermediate or poor risk, previously untreated advanced renal cell carcinoma in April 2018.[69,70]

Other Indications Table 2 summarizes other approved indications and related studies for nivolumab.

Adverse Events

The label of nivolumab includes warnings about the increased risk of severe immune-mediated inflammation in the lungs, the colon, the liver, and the kidneys (with renal dysfunction), as well as immune-mediated hypothyroidism and hyperthyroidism.[10,71,72] In addition, autoimmune diabetes, like type 1 diabetes, occurs in people treated with nivolumab.[6]

Table 2 Main Clinical Trials Leading to Other Indications FDA Approved for Nivolumab

Disease Site	Study	n	Major Efficacy Outcome Measures	ORR	Median Response Duration (Months)	Median PFS (Months)	HR (95% CI)	Median OS (Months)	HR (95% CI)	FDA Approval
cHL	CheckMate 205[156]	95	ORR	66% (95% CI: 56, 76)	13.1 (9.5, NE)	–	–	–	–	05/2016
	CheckMate 039[157]									
SCCHN	CheckMate 141[158]	361	OS	13.3% (95% CI: 9.3, 18.3)	–	2.0 (95% CI: 1.9, 2.1)	0.89 (0.70, 1.13)	7.5 (95% CI: 5.5, 9.1)	0.70 (0.53, 0.92)	11/2016
Urothelial carcinoma	CheckMate 275[159]	270	ORR	19.6% (95% CI: 15.1, 24.9) (for the 53 patients)	10.3 (1.9+, 12.0+)	–	–	–	–	02/2017
Colorectal cancer	CheckMate 142[160]	53	ORR	28% (95% CI: 17, 42)	NR (2.8+, 22.1+) (for the 53 patients)	–	–	–	–	07/2017
HCC	CheckMate 040[161]	154	ORR	14.3% (95% CI: 9.2, 20.8)	–	–	–	–	–	9/2017

Cemiplimab

Introduction

Cemiplimab (REGN2810, SAR439684, Libtayo) is a fully humanized IgG4 monoclonal antibody against PD-1 developed by Sanofi/Regeneron in suspension culture of hamster ovary cells in China using recombinant DNA technology. By binding to PD-1 receptor and blocking its interaction with PD-L1, cemiplimab up-regulates cytotoxic T cells and enhances the antitumor activity of the immune system.[73–75]

Clinical Trials

The research of cemiplimab mainly focuses on cutaneous squamous cell carcinoma, and now there are also ongoing researches to evaluate the curative effect of cemiplimab on various tumors, including metastatic pancreatic cancer (NCT04177810), malignant glioma (NCT03690869), hepatocellular carcinoma (NCT03916627), non-small cell lung cancer (NCT03580694), renal cancer (NCT03294083), lymphoma (NCT02651662), multiple myeloma (NCT03194867), prostate cancer (NCT03951831), ovarian cancer (NCT03564340), cervical cancer (NCT03257267) and so on.[75]

CSCC On September 28, 2018, the US FDA-approved cemiplimab-rwlc for patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. The approval is based on the results of two clinical trials, R2810-ONC-1423 and R2810-ONC-1540. R2810-ONC-1423 is an open-label, multicenter, ascending-dose escalation study of REGN2810 (cemiplimab) as a monotherapy and in combination with other anti-cancer therapies in patients with advanced malignancies which was first carried out in humans. R2810-ONC-1540 is an open-label, multicenter, non-randomized, multi-cohort, phase 2 study of REGN2810 (cemiplimab) in patients with advanced cutaneous squamous cell carcinoma. In 108 patients with advanced CSCC, including metastatic (n=75) or locally advanced (n=33), the ORR was 47% (95% CI: 38, 57), with 4% complete response rate and 44% partial response rate. The ORR was 47% (95% CI: 35, 59) in 75 patients with metastatic CSCC and 49% (95% CI: 31, 67) in patients with locally advanced disease. The median response duration was not reached (range: 1.0 to 15.2+ months), and 61% of the responses lasted 6 months or longer.[75–77]

Adverse Events

Cemiplimab can cause severe and fatal immune-mediated adverse reactions in any organ, system, or tissue, including pneumonia, colitis, hepatitis, endocrine disorders, skin adverse reactions, nephritis and renal dysfunction.[22,73,75] Additionally, severe infusion-related reactions (Grade 3) can also occur. The most common adverse reactions (incidence ≥20%) of cemiplimab were fatigue, rash, and diarrhea.

Atezolizumab

Introduction

Atezolizumab (MPDL3280A, Tecentriq) is a fully humanized, high-affinity, engineered monoclonal antibody of IgG1 isotype against PD-L1, developed by Roche Genentech.[78] By specifically binding to PD-L1, it prevents the interaction of PD-L1 with PD-1 and CD80 receptors (B7-1), eliminates the inhibitory effect on cytotoxic T cells, and meanwhile maintains the integrity of the interaction between PD-1 and its alternative receptors, PD-L2 (B7-DC, CD273).[10,78] Compared with patients with low PD-L1 expression level, patients with high PD-L1 expression level on tumor immune cells have higher response rate, that is, its anti-tumor effect would be affected by the PD-L1 expression status of tumor-infiltrating immune cells.[78,79]

Clinical Trials

Before the approval of atezolizumab by FDA, it showed preliminary anti-tumor activity in a variety of solid tumors.[27] At present, the clinical study of atezolizumab is mainly focused on non-small cell lung cancer, and related research on other tumors is also in progress, including small cell lung cancer (NCT03262454), DLBCL (NCT03463057), cutaneous melanoma (NCT04020809), solid tumor (NCT04196530), bladder cancer (NCT03620435), colorectal cancer (NCT02982694), etc.

Urothelial Carcinoma

The FDA gave accelerated approval to atezolizumab injection in May 2016 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or after platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This approval is based on a multicenter, single-arm, double-cohort, phase 2 trial IMvigor210 (Cohort 2) (NCT02108652) which evaluated the efficacy of atezolizumab to treat patients with locally advanced or metastatic urothelial bladder cancer. Among the 310 patients involved, the ORR confirmed by independent review was 14.8% (95% CI: 11.1, 19.3); the middle DoR was not reached, and the response time ranged from 2.1+ to 13.8 + months. Of the 46 (14%) responders, 37 (11%) patients had an ongoing response for greater than or equal to 6 months, and 6 (1%) for greater than or equal to 12 months.[79]

Lung Cancer

NSCLC. OAK (NCT02008227) is an international, multicenter, open-label, randomized, phase 3 clinical trial that assessed the efficacy of atezolizumab compared to docetaxel in patients with locally advanced or metastatic NSCLC who failed platinum chemotherapy. One thousand two hundred and twenty-five patients involved were randomly divided into two groups to receive atezolizumab or docetaxel. The results showed that the median OS of atezolizumab group was 13.8 months (95% confidence interval [CI] 11.8, 15.7), while that of docetaxel group was 9.6 months (95% confidence interval 8.6, 11.2) [Hazard Ratio 0.74, 95% CI: 0.63, 0.87, p=0.0004].

POPLAR (NCT01903993) is a multicenter, open-label, randomized, phase 2 study that investigates the efficacy and safety of MPDL3280A (atezolizumab) compared with docetaxel in patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum therapy. Two hundred and eighty-seven patients were 1:1 randomized to receive either atezolizumab or docetaxel. The experimental results showed that the mean OS was 12.6 months (95% CI: 9.7, 16.0) and 9.7 months (95% CI: 8.6, 12.0) [Hazard Ratio 0.69, 95% CI: 0.52, 0.92, p=0.0106] for the atezolizumab and docetaxel groups, respectively.

Based on the results of these two studies, on October 18, 2016, the FDA-approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should develop disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

NSq NSCLC. Following IMpower150 (NCT02366143), the FDA-approved atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer (NSq NSCLC) without EGFR or ALK genomic tumor aberrations in December 2018. The trial is a randomized (1:1:1), open-label, phase 3 study of

atezolizumab combined with carboplatin+paclitaxel with or without bevacizumab compared with carboplatin+paclitaxel+bevacizumab in chemotherapy-naive patients with stage IV non-squamous NSCLC, involving 1202 patients receiving first-line treatment for metastatic NSq NSCLC. In 1045 (87%) patients without EGFR or ALK tumor mutations, the estimated median OS was 19.2 months for those receiving the 4-drug regimen and 14.7 months for those receiving carboplatin, paclitaxel, and bevacizumab [Hazard Ratio 0.78, 95% CI: 0.64, 0.96, p=0.016]. The median PFS was estimated to be 8.5 months for patients receiving the 4-drug regimen and 7.0 months for those in the control arm [Hazard Ratio 0.71, 95% CI: 0.59, 0.85, p=0.0002]. The overall response rates were 55% in the 4-drug arm and 42% in the control arm.

On December 3, 2019, atezolizumab has been approved by the FDA in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. IMpower130 (NCT02367781) is a multicenter, randomized (2:1), open-label, phase 3 clinical trial in chemotherapy-naive patients with stage Ⅳ non-squamous NSCLC evaluating the safety as well as efficacy of atezolizumab in combination with carboplatin+nab-paclitaxel compared with treatment with carboplatin+nab-paclitaxel. In the primary analysis population (ITT-WT, n=681), the median PFS of atezolizumab group was estimated to be 7.2 months (95% CI: 6.7, 8.3), while that of the control group was 6.5 months (95% CI: 5.6, 7.4) [Hazard Ratio 0.75, 95% CI: 0.63, 0.91, p=0.0024]. The median OS was 18.6 months (95% CI: 15.7, 21.1) and 13.9 months (95% CI: 12.0, 18.7), respectively [Hazard Ratio 0.80, 95% CI: 0.64, 0.99, p=0.0384]. These results led to this FDA approval of atezolizumab.

TNBC In March 2019, atezolizumab was approved in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥1% of the tumor area), as determined by an FDA-approved test, based on data from Impassion130 (NCT02425891). Impassion130 (NCT02425891) is multicenter, randomized, double-blind, placebo-controlled, phase 3 trial enrolled 902 patients with unresectable locally advanced or metastatic TNBC who had not previously received chemotherapy for metastatic disease, evaluating the efficacy, safety, and pharmacokinetics of atezolizumab combined with nab-paclitaxel compared with placebo combined with nab-paclitaxel. Among patients with PD-L1 expression, median progression-free survival (PFS) was 7.4 months (6.6, 9.2) in those treated with atezolizumab combined with paclitaxel protein-bound and 4.8 months (3.8, 5.5) in those treated with placebo with paclitaxel protein-bound. The stratified hazard ratio for PFS was 0.60 (95% CI: 0.48, 0.77, p<0.0001), indicating that atezolizumab plus paclitaxel protein-bound arm was better. The objective response rate (ORR) was 53% in the atezolizumab group and 33% in the placebo group. Although the overall survival data were immature, with 43% of patients dying in the intent to treat (ITT), the current safety data showed that atezolizumab can be safely used in combination with standard chemotherapy drugs.

ES-SCLC Following Impower133 (NCT02763579), atezolizumab was approved in March 2019 for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with carboplatin and etoposide. IMpower133 (NCT02763579) is a randomized (1:1), phase 1/3, multicenter, double-blind, placebo-controlled trial included 403 patients with ES-SCLC. Median OS for patients receiving atezolizumab with chemotherapy was 12.3 months (10.8, 15.9), and that for patients receiving placebo with chemotherapy was 10.3 months (9.3, 11.3) [Hazard Ratio 0.70, 95% CI: 0.54, 0.91, p=0.0069]. In the atezolizumab and placebo arms, the median PFS was 5.2 months (4.4, 5.6) and 4.3 months (4.2, 4.5), respectively [Hazard Ratio 0.77, 0.62, 0.96, p=0.0170].

Adverse Events

Like other PD-1/PD-L1 inhibitors, atezolizumab can lead to severe and fatal immune-mediated adverse reactions. These immune reactions might be involved in any organ system, including lung, liver, colon, endocrine system, skin, etc. And immune-mediated adverse reactions may also occur after atezolizumab is discontinued. The most common adverse reactions to atezolizumab as a single drug (reported ≥20% of patients) were fatigue/weakness, nausea, cough, dyspnea, decreased appetite and infection.[78] Urinary tract infection is the most common severe infection caused by atezolizumab. Whether atezolizumab is used as a single drug in a variety of cancer patients or in combination with other anti-tumor drugs in NSCLC and SCLC, the frequency and severity of infusion-related reactions are similar within the recommended

dose range. In the clinic, the infusion should be interrupted, slowed down or permanently stopped according to the severity of the infusion reaction.

Avelumab

Introduction

Avelumab (MSB0010718C, Bavencio) is a fully natural human IgG1 monoclonal antibody targeting PD-L1 developed by Merck KGaA and Pfizer, which inhibits PD-1/PD-L1 interactions while maintaining the integrity of the PD-1/PD-L2 pathway and enhancing immune activation to tumor cells.[80,81] In addition, due to its inherent Fc domain, avelumab retains the ability to induce NK-mediated antibody-dependent cytotoxicity (ADCC) in vitro, and is the only therapeutic antibody that uses both immune checkpoint inhibition and ADCC-mediated killing of tumor cells.[81]

Clinical Trials

The JAVELIN study is a large multicenter phase 1 clinical trial and an international clinical development project for avelumab, including at least 30 clinical projects involving 4000 patients and 15 tumor types in order to explore the efficacy of avelumab in the first-line treatment of multiple solid tumors. Currently, clinical trials of avelumab in various kinds of tumors are underway, including Hodgkin lymphoma (NCT03617666), hepatocellular carcinoma (NCT03389126), colorectal cancer (NCT03150706), urothelial cancer (NCT03891238), bladder cancer (NCT03747419), solid tumors (NCT03815643) and so on.

MCC On March 23, 2017, the FDA granted accelerated approval to avelumab for the treatment of patients 12 years and older with metastatic Merkel cell carcinoma (MCC) due to JAVELIN Merkel 200 trial. It is also the first drug approved for metastatic MCC.[81] JAVELIN Merkel 200 is an open-label, international, prospective, single-arm, multicenter, phase 2 trial enrolled 88 patients with metastatic MCC. The ORR was 33% (95% [CI]: 23.3, 43.8), with 11% complete and 22% partial response rates. The response duration ranged from 2.8 to 23.3+ months among 29 responding patients, and 86% of the responses lasted 6 months or longer. In addition, patients were observed to respond regardless of tumor expression of PD-L1 or presence of Merkel cell polyomavirus.[81,82]

Urothelial Carcinoma JAVELIN Solid Tumor trial is a phase 1, open-label, single-arm, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biology and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. The results of UC cohorts involved 242 patients showed that the confirmed overall response rate (ORR) in patients who had been followed for at least 13 weeks was 13.3% (n=30) (95% CI: 9.1, 18.4), and 16.1% (n=26) (95% CI: 10.8, 22.8) among the patients who had been followed up for at least 6 months. Median time to response was 2.0 months (range 1.3–11.0). The median response duration was not reached in patients who were followed up for at least 13 weeks or 6 months, but ranged from 1.4+ and 17.4+ months in both groups.[10] Based on the results of this trial, the US FDA granted accelerated approval to avelumab for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy in May 2017.

RCC JAVELIN Renal 101 (NCT02684006) led to the FDA approval of avelumab in combination with axitinib for first-line treatment of patients with advanced RCC. This randomized, multinational, multicenter, open-label, parallel-arm, phase 3 study enrolled 886 untreated patients with advanced renal cell carcinoma regardless of tumor PD-L1 expression, evaluating the anti-tumor activity and safety of avelumab combined with axitinib and of sunitinib monotherapy as first-line therapy in patients with advanced renal cell carcinoma. The results showed that the progression-free survival (PFS) of patients receiving avelumab combined with axitinib was significantly longer than that of patients receiving sunitinib. Among the 560 patients with PD-L1-positive tumors (63.2%), the median progression-free survival of patients receiving avelumab combined with axitinib was 13.8 months, as compared with 7.2 months with sunitinib [hazard ratio for disease progression or death, 0.61, 95% CI: 0.47, 0.79, $p<0.001$]. In the overall population, the median progression-free survival was 13.8 months with avelumab plus axitinib, higher than 8.4 months with sunitinib [Hazard Ratio 0.69, 95% CI: 0.56, 0.84, $p<0.001$]. Among the patients with PD-L1-positive tumors, the objective response rate of patients receiving avelumab combined with axitinib was 55.2% and that of patients receiving sunitinib was 25.5%. The median follow-up for overall survival of the two groups was 11.6 months and 10.7 months, respectively.[83]

Adverse Events

The most common severe adverse reactions of avelumab are immune-mediated adverse reactions (pneumonia, hepatitis, colitis, adrenal insufficiency, hyperthyroidism, diabetes and nephritis) and life-threatening infusion reactions. The most common adverse reactions (>20%) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reactions, rash, decreased appetite, peripheral edema and urinary tract infections.[10,81,82]

Durvalumab

Introduction

Durvalumab (MEDI4736, Imfinzi) is a high-selective, high-affinity, fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody developed by Medimmune/AstraZenecak. It can block the binding of PD-L1 with PD-1 and CD80 by binding with PD-L1 and CD80 instead of PD-L2, so that T cells can recognize and kill tumor cells, which might potentially reduce the immunotoxicity associated with the PD-L2 interaction.[84–86]

Clinical Trials

There are many clinical trials of durvalumab on lung cancer (NCT03822351, NCT03589547, NCT03818776), which are expected to expand the indications for lung cancer. For now, relevant studies are being carried out to evaluate the efficacy of durvalumab single drug or combination of various drugs (immune checkpoint inhibitors, chemotherapy, targeted therapy) and radiotherapy for various tumors, including HNSCC (NCT03726775), bladder cancer (NCT03759496), hepatocellular carcinoma (NCT04294498), solid tumor (NCT04078152), esophageal cancer (NCT02639065), urothelial cancer (NCT03406650), etc.

Urothelial Carcinoma On May 1, 2017, durvalumab has been granted accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. The approval is based on the urothelial carcinoma cohort of Study 1108 (NCT01693562), a multicenter, multi-cohort, open-label clinical trial, including 182 patients with locally advanced or metastatic urothelial carcinoma whose disease progressed after prior platinum-containing chemotherapy. Results of this study showed that the confirmed objective response rate (ORR) determined by blind independent central evaluation (RECIST 1.1) was 17.0% (95% CI: 11.9, 23.3). ORR was also analyzed by the expression of PD-L1 by VENTANA PD-L1 (SP263) Assay. Among the 182 patients, the confirmed ORR diagnosed in 95 patients with high PD-L1 was 26.3% (95% CI: 17.8, 36.4), while the confirmed ORR diagnosed in 73 patients with low or negative PD-L1 score was 4.1% (95% CI: 0.9, 11.5). Of the 37 patients who received only neoadjuvant or adjuvant therapy before entering the study, 9 patients (24%) responded. Of the 31 responding patients, 14 patients (45%) had ongoing responses of 6 months or longer, and 5 patients (16%) had ongoing responses of 12 months or longer.

NSCLC Following PACIFIC (NCT02125461), durvalumab was approved in February 2018 for patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. PACIFIC (NCT02125461) is a multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of durvalumab in patients with unresectable stage III NSCLC. Among the 713 patients included, the median progression-free survival (PFS) was 16.8 months (95% CI: 13, 18.1) in the durvalumab group and 5.6 months (95% CI: 4.6, 7.8) in the placebo group [Hazard Ratio 0.52, 95% CI: 0.42, 0.65, $p<0.0001$]. The ORR was 26% in the durvalumab group (95% CI: 23, 31) and 14% in the placebo group (95% CI: 10, 19).

Adverse Events

The most common adverse reactions of durvalumab experienced (≥15%) were fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, urinary tract infection, cough, upper respiratory tract infection, dyspnea, and rash. The most common level 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general health deterioration.[84,85,87]

Table 3 compares the incidence of adverse events induced by these six PD-1/PD-L1 inhibitors.

New Drugs in Development

Although monoclonal antibody blocking PD-1/PD-L1 immune checkpoint shows good curative effect on cancer treatment, its disadvantages cause some limitations for clinical application, that is, low response rate of patients, high cost of antibody, long half-life, severe immune-

Table 3 The Incidence of Adverse Events Induced by PD-1/PD-L1 Inhibitors

		Pembrolizumab[162]	Nivolumab[163]	Cemiplimab[77]	Atezolizumab[164]	Avelumab[165]	Durvalumab[166]
Serious adverse events	Haemorrhage intracranial	1.42%	0.20%	–	–	–	–
	Syncope	0.57%	0.30%	1%	0.65%	0.25%	0.21%
	Pneumonitis	0.85%	0.99%	4%	–	1.27%	3.58%
	Acute kidney injury	0.85%	0.89%	–	1.61%	0.76%	0.42%
	Hypothyroidism	0.28%	0.30%	0	0.32%	–	–
	Hyperthyroidism	–	0.10%	–	–	–	–
	Acute myocardial infarction	0.28%	0.10%	–	–	0	0.42%
	Atrial fibrillation	0.28%	0.30%	–	0.32%	0.76%	1.05%
	Colitis	1.42%	0.69%	–	0.32%	0.76%	–
	Hypophysitis	0.85%	0.40%	–	–	–	–
	Autoimmune hepatitis	0.28%	0.79%	1%	Hepatitis (0.32%)	–	–
	Severe skin reactions	Drug reaction with eosinophilia and systemic symptoms (0.57%)	Skin ulcer (0.30%)	Skin infection (1%)	Rash maculo-papular (0.32%)	Angioedema (0.25%) Henoch-Schonlein purpura (0.25%)	–
	Type 1 diabetes mellitus	0.28%	0.10%	0.70%	–	–	0.21%
	Infections and infestations	Sepsis (0.57%)	Pneumonia (1.29%) Urinary tract infection (1.09%)	Urinary tract infection (3%)	Urinary tract infection (7.42%)	Pneumonia (2.04%)	Pneumo (5.68%)
Other (not including serious) adverse events	Fatigue	25.85%	29.27%	42%	50.65%	17.56%	24.00%
	Diarrhoea	26.14%	20.83%	27%	21.29%	10.43%	18.32%
	Nausea	23.30%	21.03%	22%	25.81%	13.49%	14.32%
	Rash	20.74%	5.36%	13%	11.61%	8.14%	12.21%
	Pruritus	26.99%	11.41%	15%	14.84%	6.36%	12.42%
	Myalgia	8.52%	6.15%	-	5.48%	4.07%%	8.00%
	Back pain	12.22%	11.51%	10%	16.45%	11.45%	10.53%
	Arthralgia	17.61%	14.68%	10%	17.42%	6.62%	12.42%
	Cough	16.19%	13.29%	-	16.45%	18.58%	35.16%
	Dyspnoea	7.10%	8.04%	9%	16.13%	18.07%	22.11%
	Oedema peripheral	6.25%	8.04%	-	14.19%	5.34%	7.79%
	Decreased appetite	11.65%	14.19%	10%	27.10%	19.85%	14.32%

related adverse reactions (poor immunogenicity), poor drug diffusion, intravenous administration (lack of oral bioavailability), etc.[88] Therefore, researchers gradually turn their attention to the development of inhibitors such as small molecules, peptides, or macrocycles targeting the PD-1/PD-L1 axis, hoping to reduce irAEs and lead to more responders and higher efficacy.[89] Compared with antibodies, they have the following advantages:

(1) High oral bioavailability: small volume, ideal physical and chemical properties.[90]
(2) Short half-life (adjustable half-life): flexible treatment, reduced irAEs.[91]
(3) High response rate: small size, better penetration of solid tumors and tissues (better tumor penetration) than antibodies. Improved pharmacokinetics and diffusion rate.[90–93]
(4) Low manufacturing cost.[94]
(5) Higher stability.[90,93]

Small Molecules

The following summarizes the patent development of small-molecule inhibitors targeting the PD-1/PD-L1 pathway from January 2018 to April 2020 (Figures 3–5).

Aurigene Discovery Technologies Limited disclosed 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives with general structure 1 in September 2018.[95]

Betta Pharmaceuticals Co., Ltd disclosed heterocyclic compounds with general structure 2 in October 2019, which can be used for the treatment of cancer and infectious diseases.[96] In addition, compounds with general structures 3, 4, and 5 regulating PD-1/PD-L1 protein/protein interaction were also disclosed in 2020.[97–99]

Researchers at Bristol-Myers Squibb (BMS) company reported 2,8-diacyl-2,8-diazaspiro [5.5] undecane compounds with general structure 6 in 2019.[100] Heterocyclic compounds with general structure 7 were also reported in the patent published in September 2019.[101]

In February 2020, researchers from Chemocentryx Inc. published indane-amines with general structure 8 as PD-L1 antagonists.[102]

Gilead Sciences Inc researchers reported small molecular compounds with general structures 9 and 10 that block or inhibit the interaction of PD-1, PD-L1 and/or PD-1/PD-L1.[103,104] Scientists from Gilead Sciences Inc also described small molecular compounds with general structures 11, 12, 13 and 14 as PD-1/PD-L1 inhibitors in 2019.[105–108] Moreover, general structures 15 and 16 were disclosed by Gilead Sciences Inc in 2020.[109]

Guangzhou Wellheath Biopharmaceutical Co., Ltd. has applied for compounds with general structures 17, 18 and 19 as safer and more efficient novel PD-1/PD-L1 inhibitors.[110,111]

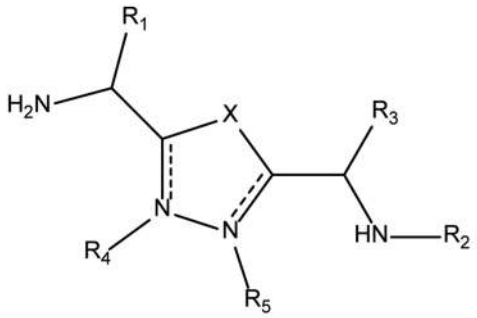
In 2019, Incyte Corporation disclosed heterocyclic compounds with general structures 20 and 21.[112,113]

Shanghai Haiyan Pharmaceutical Technology Co., Ltd. and Yangtze River Pharmaceutical Group Co., Ltd. disclosed noncondensed pyridines with general structures 22 and 23 in 2019.[114,115]

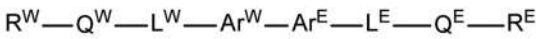
In 2020, Shanghai Ennovabio Pharmaceuticals Co., Ltd. published patents for three series of compounds with general structures 24, 25 and 26.[116–118]

Researchers from Shenyang Pharmaceutical University found that a class of indolines with general structure 27 could be used as immunomodulators.[119]

In 2020, Shenzhen Chipscreen Biosciences Co., Ltd. disclosed biphenyl compounds with general structure 28



General structure 1



General structure 9, 10

Figure 3 The general structures of small molecules in 2018: general structure 1 represents 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives.

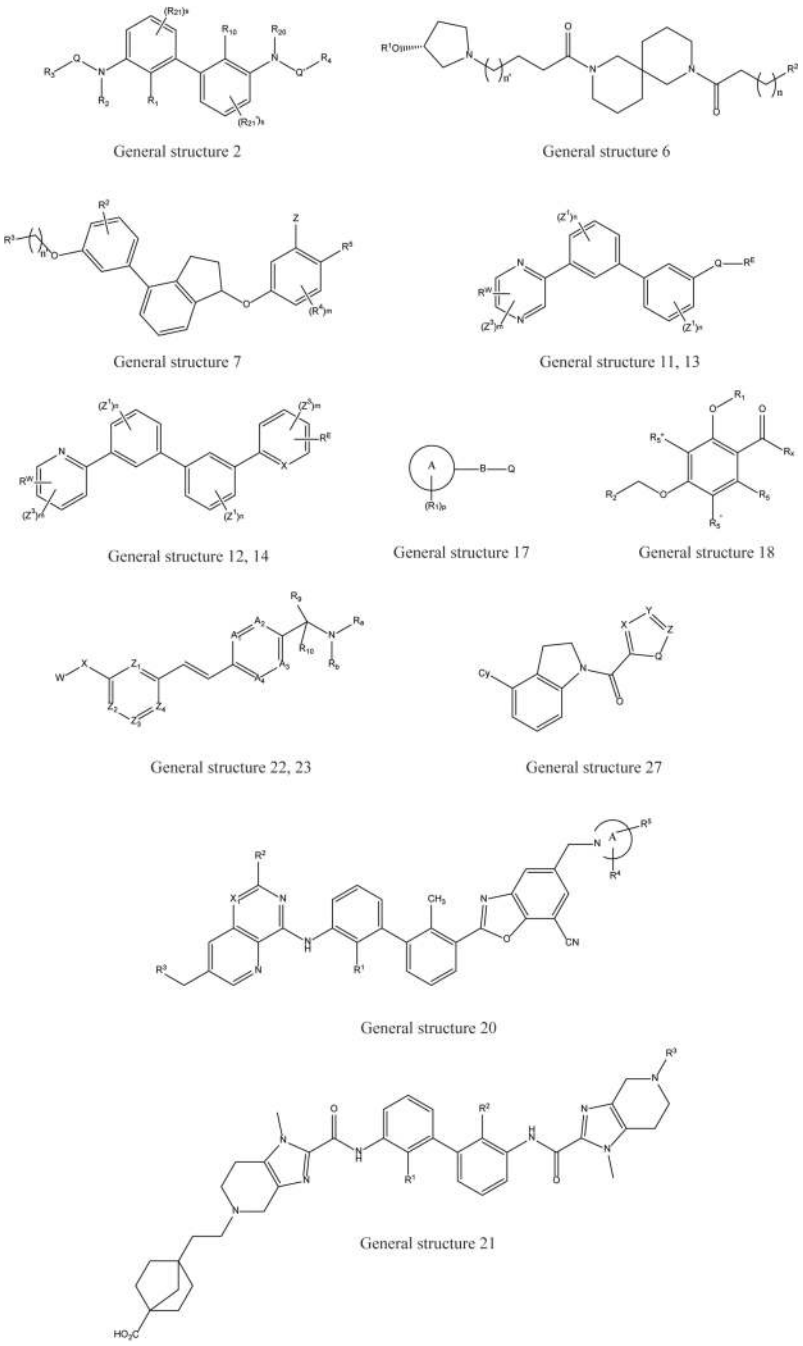


Figure 4 The general structures of small molecules in 2019: general structure 6 represents 2,8-diacyl-2,8-diazaspiro [5.5] undecane compounds; general structure 7, 20 and 21 represent heterocyclic compounds; general structure 22 and 23 represent noncondensed pyridines; general structure 27 represents a class of indolines.

that can block the interaction between PD-1/PD-L1 signaling pathway.[120]

Peptides

From 2015 to 2017, researchers from Aurigene Discovery Technologies Ltd. discovered multiple peptides and peptidomimetic compounds that inhibit the PD-1/PD-L1 pathway (Figure 6).

Synthetic peptide with general structure 29 was disclosed in March 2015.[121]

General structure 30 of peptidomimetic compounds was published in June 2015.[122]

In 2016, peptide compounds with general structure 31 were disclosed.[123]

Moreover, scientists from Aurigene Ltd. also published novel synthetic peptide and its derivatives as

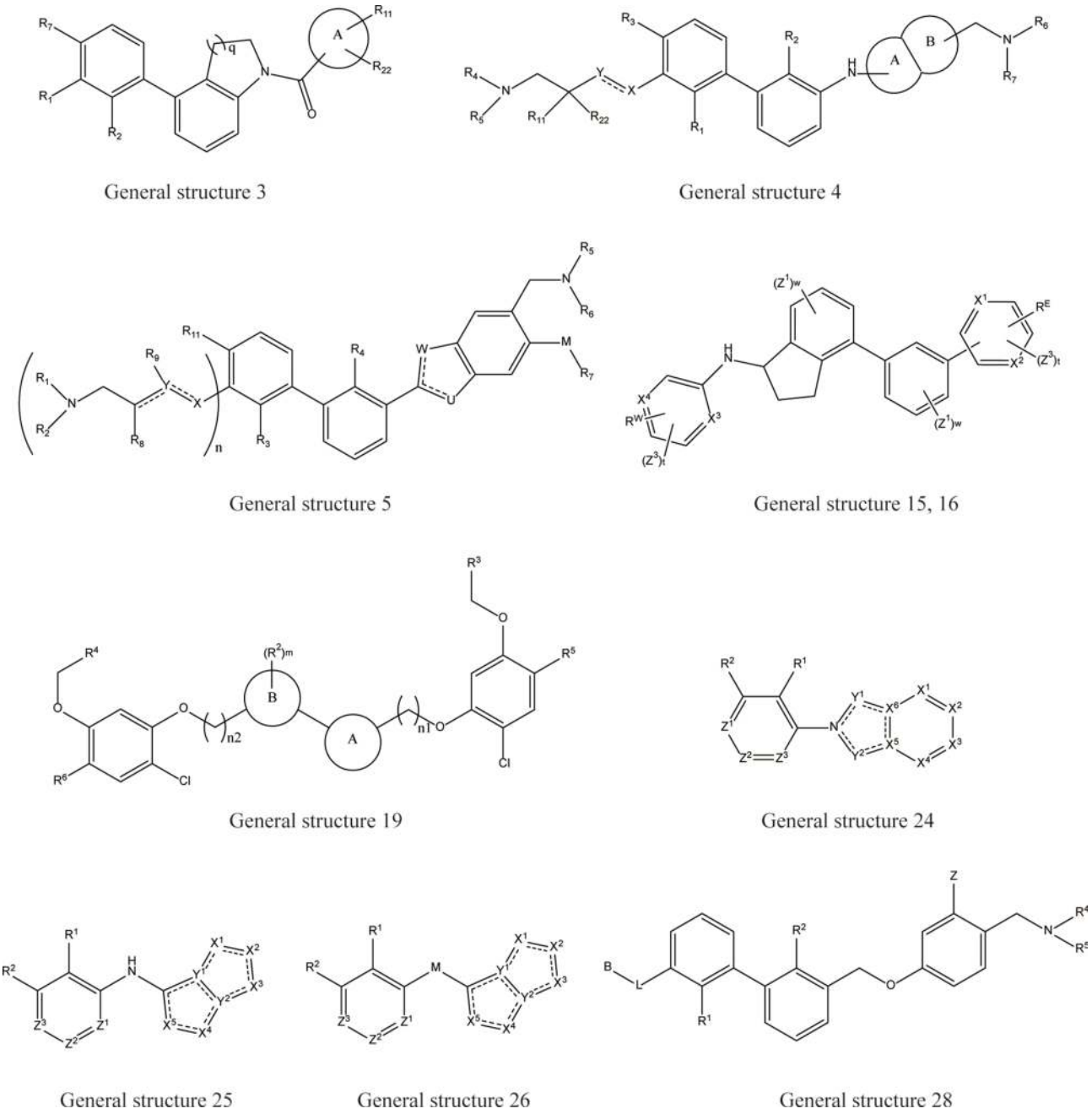


Figure 5 The general structures of small molecules in 2020: general structure 28 represents biphenyl compounds.

immunosuppression modulating compounds with general structure 32 (Figure 6).[124]

Macrocycles

Bristol-Myers Squibb company disclosed two novel macrocyclic compounds in 2017 and 2018, respectively, that inhibit the interaction of PD-1 with PD-L1 and with CD80, as shown in general structures 33 and 34 below.[125,126]

In 2018, BMS company also described novel macrocyclic peptides with general structures 35, 36, 37, 38 and 39, which are expected to improve various diseases including cancer and infectious diseases.[127–131]

Novel macrocyclic peptides with general structures 40, 41, 42, 43, 44, 45, and 46 were published in 2019.[132–138]

The macrocyclic peptides described in 2020 with general structure 47 have been proved to have the ability to block the interaction between PD-L1 and PD-1 in biochemical and cell-based experimental systems (Figure 7).[139]

At present, the development of small-molecule, peptide and macrocyclic PD-1/PD-L1 inhibitors is still in the early

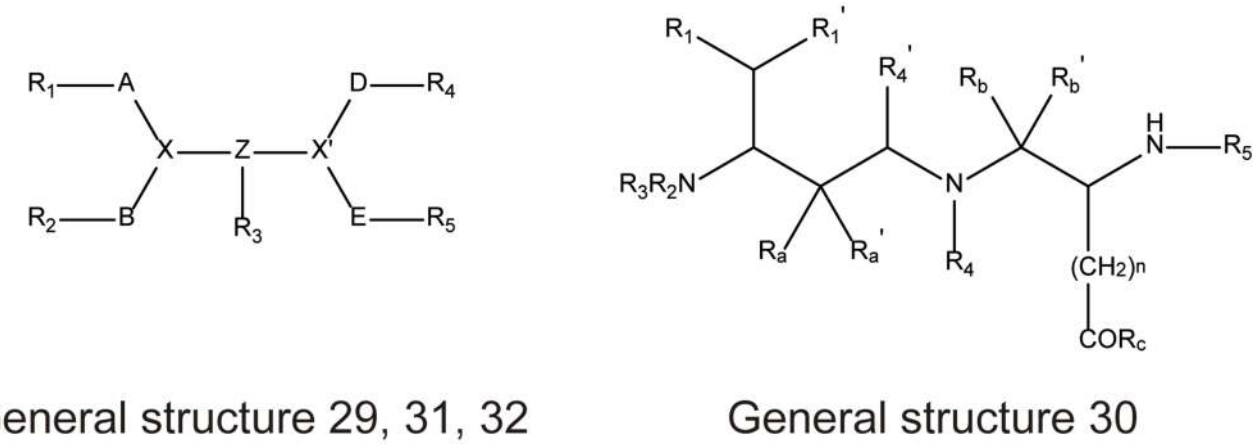


Figure 6 The general structures of peptides: general structure 29, 31 and 32 represent synthetic peptide; general structure 30 represents peptidomimetic compounds.

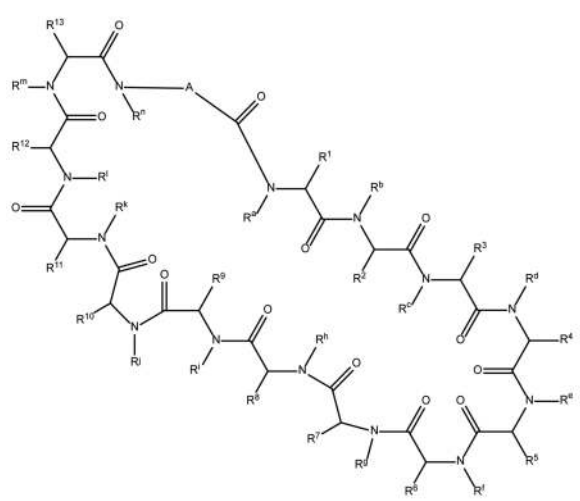
stage, but relevant studies on their mechanism of action and structure–activity relationship have been conducted. CA-170 is the only small-molecule modulator targeting PD-L1 and VISTA in clinical trials at present. However, research has shown that neither CA-170 nor its precursor, AUNP-12, has any binding with hPD-L1 that would destroy the hPD-1/hPD-L1 complex. The researchers speculated that these compounds may act on the downstream of the hPD-1 receptor or any other T-cell activation pathway, which provides a new idea for the development of small-molecule inhibitors later.[92] Qin et al developed a series of novel indoline-containing compounds, most of which can effectively inhibit the interaction of PD-1/PD-L1, and the IC50 value is at the nanoscale, which clearly shows that indoline is a suitable scaffold for the design of inhibitors. Among them, A13 is considered to be the most promising inhibitor of the PD-1/PD-L1 pathway which shows outstanding immunomodulation activity and no obvious toxic effect. Therefore, A13 can be used as a suitable lead compound to further design of non-peptide inhibitors for PD-1/PD-L1 interaction.[140] A novel PD-1/PD-L1 inhibitor was designed, which was provided with a C2-symmetric scaffold. Among them, the most effective compound 4 induced PD-L1 dimerization. Compared with the original monomer ligand, the binding affinity with hPD-L1 was significantly increased under physiological conditions, and the inhibitory activity of PD-1/PD-L1 interaction was significantly enhanced. This study contributes to the development of small-molecule modulators targeting the PD-1/PD-L1 pathway based on dimer scaffolds, and demonstrates the applicability of a symmetric ligand design as an attractive approach for targeting protein–protein interaction stabilizers.[94]

Conclusion

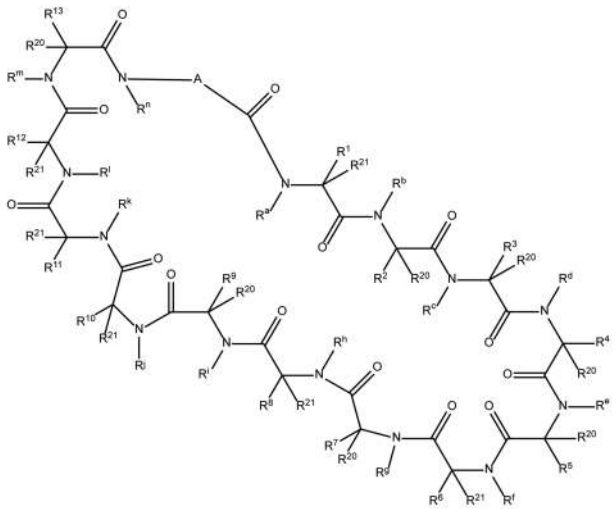
PD-1/PD-L1 inhibitors are a group of important immune checkpoint inhibitors (ICIs) for cancer treatment, following the discovery of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Since May 2006, the US FDA has approved six immune checkpoint inhibitors for PD-1/PD-L1 pathway, which are used to treat melanoma, lung cancer, urothelial carcinoma, cervical cancer, gastric or gastroesophageal cancer, solid tumors and so on. Adverse reactions induced by PD-1/PD-L1 inhibitors can be roughly divided into two types: immune-related adverse reactions (irAEs) and infusion-related reactions. Immune-related adverse reactions can involve the lungs, colon, liver, kidney, endocrine system and skin, and can be fatal in severe cases. Therefore, it is urgent to develop novel inhibitors such as small molecules, peptides or macrocycles targeting the PD-1/PD-L1 axis, so as to meet the increasing clinical needs for efficacy and safety.

Prospects

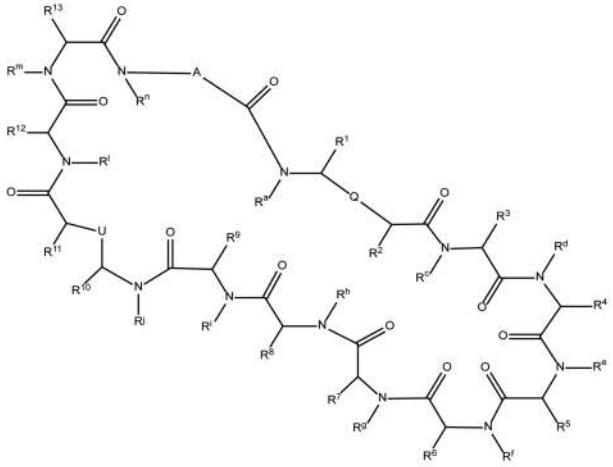
PD-1 and PD-L1 are membrane protein receptors with canonical immunoglobulin (Ig)-like extracellular domains on the cell surface, which are responsible for interaction and signal transduction to intracellular domains. The interaction between PD-L1 on tumor cells and PD-1 on T cells reduces the functional signal of T cells, thus preventing the immune system from attacking tumor cells. Cancer immunotherapy based on immune checkpoint PD-1/PD-L1 pathway has been proved to be effective in a wide range of tumor types and has lower toxicity level and long-lasting response compared with other immunotherapies.[141] So far, the US FDA has approved six immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway, including three for PD-1 (pembrolizumab,



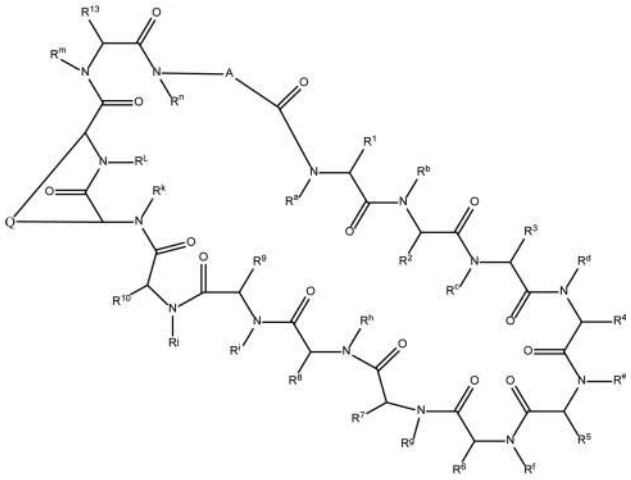
General structure 33, 34, 35, 36, 38, 39, 41, 43, 45, 47



General structure 37, 40, 42



General structure 44



General structure 46

Figure 7 The general structures of macrocycles: general structure 33 and 34 represent macrocyclic compounds; general structure 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 and 46 represent macrocyclic peptides.

nivolumab and cemiplimab) and three for PD-L1 (atezolizumab, avelumab and durvalumab). Pembrolizumab (Keytruda) was developed by Merck and first approved by the FDA for the treatment of melanoma in 2014. Nivolumab (Opdivo) was developed by Bristol-Myers Squibb and first approved by the FDA for the treatment of melanoma in 2014. Cemiplimab (Libtayo) was developed by Regeneron Pharmaceuticals and first approved by the FDA for the treatment of cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation in 2018. Atezolizumab (Tecentriq) was developed by Roche Genentech and first approved by the FDA for urothelial carcinoma and non-small cell lung cancer in 2016. Avelumab (Bavencio) was developed by Merck KGaA and Pfizer and first approved for the treatment of metastatic Merkel cell carcinoma. Durvalumab (Imfinzi) was developed by AstraZeneca and first approved by the FDA for the treatment of urothelial carcinoma and unresectable non-small cell lung cancer after chemoradiation.

However, there are some troubles in clinical application of monoclonal antibodies targeting PD-1/PD-L1, such as low response rate of patients, severe immune-related adverse reactions (poor immunogenicity), the need for intravenous

administration (lack of oral bioavailability), drug resistance, etc., which promote the development of small molecules, peptides, and macrocycles.[89,90,141] At present, a variety of PD-L1 inhibitors are under development. KN035 is the only PD-L1 with subcutaneous formulation antibody, which is currently in clinical trials in the United States, China and Japan.[142] CA-170, developed by Aurigene and Curis, is the only small-molecule antagonist for PD-L1 and VISTA in clinical trials so far. The compound is currently in phase 1 clinical trials in patients with mesothelioma.[91,143] In addition, many PD-1 inhibitors are also under study.

In our opinion, there are four main directions for the development of PD-1/PD-L1 inhibitors. Firstly, it is necessary to predict tumor response and tumor prognosis biomarkers through ICIs therapy to avoid overtreatment and minimize tumor progression. Secondly, formulate practical, effective, systematic and complete adverse reaction management strategy. Thirdly, there is great potential to develop novel drugs targeting PD-1/PD-L1, such as small molecules, peptides and macrocycles. Fourthly, the rational design and development of PD-1/PD-L1 inhibitors can be realized by studying the configuration and mechanism of the new compounds.

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Disclosure

The authors report no conflicts of interest in this work.

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