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REVIEW

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PD-1/PD-L1 pathway blockade works as an effective and practical therapy for cancer immunotherapy

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ABSTRACT Cancer immunotherapy has greatly advanced in recent years, and PD-1/PD-L1 blocking therapy has become a major pillar of immunotherapy. Successful clinical trials of PD-1/PD-L1 blocking therapies in cancer treatments have benefited many patients, which promoted the Food and Drug Administration (FDA) approval of PD-1/PD-L1 blocking drugs. In this review, we provide a detailed introduction of five PD-1/PD-L1 blocking drugs, with indications and studies, as a valuable reference for doctors and medical investigators. Moreover, the characteristics of PD-1/PD-L1 blocking therapies, including their universality and sustainability, are discussed in this review. Furthermore, we also discuss and predict the possibility of PD-L1 as an indication marker of PD-1/PD-L1 blocking therapy for pan-cancer treatment, and the current status of combination therapies.

KEYWORDS PD-1; PD-L1; cancer immunotherapy

Introduction

Programmed cell death-1 (PD-1) was first discovered in 1992 by Ishida et al. as a novel member of the immunoglobulin gene super family that plays a role in programmed cell death[1]. Moreover in the same year, Chen et al.[2] found that the interaction of the B7 molecule on antigen-presenting cells with its receptors, CD28 and CTLA-4, could change antitumor immunity, which may be a useful strategy for cancer treatment. These discoveries initiated a new era for cancer immunotherapy. Since then, more immune checkpoints have been discovered and further studies have been conducted. PD-1 is one of the most useful immune checkpoints, and many drugs that target PD-1/PD-L1 pathway have been approved for clinical cancer treatment. PD-1 belongs to the CD28 family and is expressed on T lymphocytes, B lymphocytes, dendritic cells, macrophages, and natural killer cells, with a predominance on activated $CD8^+$T cells, $CD4^+$T cells, and B cells in peripheral tissues[3-5].

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Programmed cell death ligand-1 (PD-L1) is the ligand of PD-1 and is expressed by antigen-presenting cells and tissue cells, including cancer cells[6-8]. The PD-1/PD-L1 pathway negatively regulates the immune response by inhibiting the activation and proliferation of T lymphocytes, reducing the production of cytokines, and enhancing the exhaustion of $CD8^+$ T lymphocytes[5,9,10]. The PD-1/PD-L1 pathway helps to mediate immune tolerance in peripheral tissues[11]. Moreover, for tumor cells, the PD-1/PD-L1 pathway plays an important role in dampening anti-tumor immunity[12,13]. Increasing number of clinical studies have indicated that the expression of PD-L1 on tumor cells is positively correlated with poor prognosis[14-19]. Furthermore, many studies have testified that the inhibition of PD-1/PD-L1 pathway provides a very effective tumor treatment[20,21]. Many drugs that target the PD-1/PD-L1 pathway have been developed, and many clinical trials have been conducted. Some of these clinical trials were so successful that the FDA approved several PD-1/PD-L1 pathway blocking drugs for clinical cancer treatment.

Clinical studies of PD-1/PD-L1 blocking drugs

So far, the FDA has approved five drugs that target the

PD-1/PD-L1 pathway for cancer treatment. These five drugs are Keytruda (pembrolizumab), Opdivo (nivolumab), Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab). Pembrolizumab, nivolumab, and durvalumab are PD-1 antibodies, while atezolizumab and avelumab are PD-L1 antibodies. The clinical studies that gained the FDA approval of pembrolizumab are listed in **Table 1**. As shown in **Table 1**, pembrolizumab has been approved for the treatment of seven different types of cancer. Particularly, the approval of pembrolizumab for the treatment of microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) solid tumors is the first time that the FDA has approved a drug for cancer treatment based on the marker rather than the location of cancer origin, which also reveals the extensive applicability of cancer immunotherapy.

DNA mismatch repair (MMR) is a highly conserved process that plays an important role in DNA repair, meiotic and mitotic recombination, DNA-damage signaling, apoptosis, and cell-type-specific processes, such as class-switch recombination, somatic hypermutation, and triplet-repeat expansion[22]. When the MMR system develops a functional error or defect, this results in a specific phenotype

Table 1 Clinical studies about pembrolizumab

Indication	Study								
	Reference & clinical trial	*n*	Objective response rate (ORR) % (95%CI)	Treatment-related (TR) all grades adverse events (%)	TR grade 3–4 adverse events (%)	Survival *vs.* control therapy survival	Control therapy & ORR % (95% CI)	Control therapy TR all grades adverse events (%)	Control therapy TR grade 3–4 adverse events (%)
Unresectable or metastatic melanoma	Schachter et al.[44] (KEYNOTE-006)	279 (10 mg/kg every 2 weeks)	37 (31–43)	82 (*n*=278)	17 (*n*=278)	55% *vs.* 43% (24-month overall survival rate)	Ipilimumab 13 (10–18) (*n*=278)	74 (*n*=256)	20 (*n*=256)
Metastatic non-small cell lung cancer with PD-L1 expression	Reck et al.[45] (KEYNOTE-024)	154	44.8 (36.8–53.0)	73.4	26.6	80.2% *vs.* 72.4% (6-month overall survival rate)	Chemotherapy 27.8 (20.8–35.7) (*n*=151)	90 (*n*=150)	53.3 (*n*=150)
Recurrent or metastatic head and neck squamous cell carcinoma	Mehra et al.[46] (KEYNOTE-012)	192	17.7 (12.6–23.9)	64	12	8.5 months (median overall survival)			
Refractory classical Hodgkin's lymphoma	Chen et al.[47] (KEYNOTE-087)	210	69 (62.3–75.2)	28.6					
Locally advanced or metastatic urothelial carcinoma	Balar et al.[48] (KEYNOTE-52)	370	24 (20–29)	61	15 (one case has grade 5 myositis)	2 months (median progression -free survival)			
MSI-H or dMMR solid tumors	Le et al.[28] Diaz et al.[29] Seiwert et al.[30]	149	39.6 (31.7–47.9)						
Gastric cancer with PD-L1 expression	Fuchs et al.[49] (KEYNOTE-059)	259	11.2 (7.6–15.7)						

called microsatellite instability (MSI), which is characterized by the insertion or deletion of short, repetitive sequences of DNA and results in mutations in cancer-related genes[23]. MSI-H/dMMR causes an increase of mutation-associated neoantigens, which cause more immune cells to infiltrate into tumors, trigger a greater anti-tumor immune response, and provide important targets for checkpoint blockade therapies[24-27]. Furthermore, the clinical trials validated the efficiency of MSI-H/dMMR as markers of PD-1/PD-L1 blocking immunotherapy, and the FDA approval is based on five such clinical trials: KEYNOTE-016 (NCT01876511, 58 patients)[28], KEYNOTE-164 (NCT02460198, 61 patients)[29], KEYNOTE-012 (NCT01848834, 6 patients)[30], KEYNOTE-028 (NCT02054806, 5 patients), and KEYNOTE-158 (NCT02628067, 19 patients)[29]. A total of 15 cancer types with MSI-H or dMMR were identified in the 149 patients who were enrolled across the above five clinical trials. For these 149 patients who were treated with pembrolizumab, the objective response rate (ORR) was 39.6%, and the response lasted at least six months in 78% of these patients. Accordingly, the FDA granted accelerated approval to pembrolizumab for MSI-H or dMMR solid tumors[31].

The studies that allowed nivolumab to achieve FDA approval are listed in **Table 2**, and the studies that allowed avelumab, atezolizumab and durvalumab to acquire FDA approval are listed in **Table 3**. The respective indications, references, clinical trials, ORR, adverse events, survivals, and control treatments are listed in each table. As shown in **Table 1** and **Table 2**, pembrolizumab and nivolumab had better performances and less treatment-related (TR) adverse events than the respective control treatments.

Universality and sustainability

As listed in **Tables 1–3**, PD-1/PD-L1 blocking drugs have been approved by the FDA for the treatment of many cancers. Additional clinical trials of PD-1/PD-L1 blocking drugs are in progress. PD-1/PD-L1 blocking therapies target the repressed immune system to re-wake the anti-tumor immune response rather than target particular molecule of cancer cells in which case cancer cells can escape the therapy by the mutation of the targeted molecule. Thus, PD-1/PD-L1 blocking therapies have a wide range of applications to many different types of cancer and consistent therapeutic effects, even after that cancer has progressed in the previous PD-1/PD-L1 blocking treatments. A large, international, phase 3 study (NCT01668784), in consistent with the results from the phase 2 study (NCT01354431), demonstrated that nivolumab for patients treated beyond RECIST progression (TBP) with nivolumab before resulted in additional clinical benefits again[32,33]. Tumor burden reduction was observed in patients who initially responded with nivolumab treatment and then progressed, and in patients with stable disease or progressive disease as their best overall response brfore[32,33].

Can higher cut-off standards promote the ability of PD-L1 to function as an indicative marker?

While the FDA has approved the MSI-H/dMMR of solid tumors as an indication for pembrolizumab after successful clinical trials, PD-L1 still has not been approved as an indicative marker of PD-1/PD-L1 blocking therapy for pan-cancer treatment. This situation can be attributed to some studies indicating that PD-L1 expression levels in tumor cells or tumor infiltrating immune cells don't correlate with the efficiency of PD-1/PD-L1 blocking therapy[34,35]. However, the cut-off standards of defining PD-L1 positive was relatively low in these studies (e.g. PD-L1 positive defined as > 1% of either tumor cells or immune cells staining for PD-L1). With higher PD-L1 positive thresholds, better outcomes have been seen in patients who were treated with PD-1/P-L1 blocking therapies. In the clinical trial NCT02108652, the ORR was 26% in the IC2/3 group (PD-L1≥5%), 18% in the IC1/2/3 group PD-L1≥1%), and 15% in all patients. The median overall survival was 11.4 months in the IC2/3 group, 8.8 months in the IC1/2/3, and 7.9 months across all patients[36]. In the clinical trial NCT02008227, the median overall survival was 12.6 months in the PD-L1 low or undetectable subgroup (≤1% of either tumor cells or immune cells staining for PD-L1), 13.2 months in the PD-L1>1% subgroup, and 20.5 months in the PD-L1 high expression subgroup (PD-L1≥50%)[36]. In the clinical trial NCT01693562, the ORR was 27.6% in the PD-L1 high expression subgroup (≥25% of either tumor cells or immune cells staining for PD-L1) and 5.1% in the PD-L1 low expression subgroup (<25% of either tumor cells or immune cells staining for PD-L1)[37]. Furthermore, the studies that are listed in **Tables 1–3** have indicated that PD-L1 negative patients may also benefit from PD-1/PD-L1 blocking therapies. Altogether, with more clinical studies, higher cut-off standards of the rates of PD-L1 expressing tumor cells may promote PD-L1 working as an indicative marker of pan-cancer PD-1/PD-L1 blocking treatments. Moreover, different tumors may require different PD-L1 cut-off thresholds.

Safety

As shown in **Tables 1–3** and many other studies, PD-1/PD-L1 blocking therapies produced a significantly lower rate of

Table 2 Clinical studies about nivolumab

Indication	Study								
	Reference & clinical trial	*n*.	Objective response rate (ORR) % (95%CI)	Treatment-related (TR)all grades adverse events (%)	TR grade 3–4 adverse events (%)	Survival *vs*. control therapy survival	Control therapy & ORR % (95% CI)	Control therapy TR all grades adverse events (%)	Control therapy TR grade 3–4 adverse events (%)
Unresectable or metastatic melanoma	Weber et al.[50] (CHECKMATE-037)	120	31.7 (23.5–40.8)	68 (*n*=268)	9 (*n*=268)	48% *vs*. 34% (6-month progression-free survival rate)	Chemotherapy 10.6 (3.5–23.1) (*n*=47)	80 (*n*=102)	32 (*n*=102)
Adjuvant treatment of melanoma	Weber et al.[51] (CHECKMATE-238)	452		96.9	25.4	70.5% *vs*. 60.8% (12-month recurrence-free survival rate)	Ipilimumab	98.5	55.2
Metastatic non-small cell lung cancer	Brahmer et al.[34] (CHECKMATE-017)	135	20 (14–28)	58 (*n*=131)	7 (*n*=131)	9.2 months *vs*. 6.0 months (median overall survival)	Docetaxel 9 (5–15) (*n*=137)	86 (*n*=129)	55 (*n*=129)
Renal cell carcinoma	Motzer et al.[52] (CHECKMATE-025)	410	25	79 (*n*=406)	19 (*n*=406)	25.0 months *vs*. 19.6 months (median overall survival)	Everolimus 5 (*n*=411)	88 (*n*=397)	37 (*n*=397)
Classical Hodgkin's lymphoma	Younes et al.[53] (CHECKMATE-205)	80	66.3 (54.8–76.4)	89	25	76·9% (6-month progression-free survival rate)			
Recurrent or metastatic squamous cell carcinoma of the head and neck	Ferris et al.[54] (CHECKMATE-141)	240	13.3	58.9 (*n*=236)	13.1 (*n*=236)	7.5 months *vs*. 5.1 months (median overall survival)	Standard therapy 5.8 (*n*=121)	77.5 (*n*=111)	35.1 (*n*=111)
Locally advanced or metastatic urothelial carcinoma	Sharma et al.[55] (NCT02387996)	270	19.6 (15.0–24.9) (*n*=265)	64	18	8.74 months (median overall survival)			
Hepatocellular carcinoma	El-Khoueiry et al.[56] (CHECKMATE-040)	214	20 (15–26)		19	83% (6-month overall survival rate)			
MSI-H/dMMR metastatic colorectal cancer	Overman et al.[57] (CHECKMATE-142)	74	31.1 (20.8–42.9)	70	21	14.3 months (median progression-free survival)			

Table 3 Clinical studies about avelumab, atezolizumab and durvalumab

Indication	Study								
	Reference & clinical trial	*n*.	Objective response rate (ORR) % (95%CI)	Treatment-related (TR)all grades adverse events (%)	TR grade 3–4 adverse events (%)	Survival *vs*. control therapy survival	Control therapy & ORR % (95% CI)	Control therapy TR all grades adverse events (%)	Control therapy TR grade 3–4 adverse events (%)
Avelumab									
Metastatic merkel cell carcinoma	Kaufman et al.[58] (NCT02155647)	88	31.8 (21.9–43.1)	70	5	40% (6-month progression-free survival rate)			
Locally advanced or metastatic urothelial carcinoma	Patel et al.[59] (NCT01772004)	161	17 (11–24)	58	8 (one case has grade 5 pneumonitis)	6.5 months (median overall survival)			
Atezolizumab									
Locally advanced or metastatic urothelial carcinoma	Rosenberg et al.[60] (NCT02108652)	310	15 (11–19)	69	16	7.9 months (median overall survival)			
Locally advanced or metastatic urothelial carcinoma	Rittmeyer et al.[36] (NCT02008227)	425	14	64	15	13.8 months *vs*. 9.6 months (overall survival)	Docetaxel 16 (*n*=425)	86	42
Durvalumab									
Locally advanced or metastatic urothelial carcinoma	Powles et al.[37] (NCT01693562)	191	17.8 (12.7–24.0)	60.7	6.8	1.5 months (median progression-free survival)			

high-grade TR adverse events than other immunotherapies, chemotherapies, and standard therapies[38,39]. This mainly be attributed to the mechanisms of the PD-1/PD-L1 pathway functioning. The PD-1/PD-L1 pathway negatively regulates the immune response mainly in peripheral tissues including the tumor microenvironments[40]. Moreover, as PD-1/PD-L1 blocking therapy mainly activates the inactivated, mature T cells and B cells, and prevents the inactivation of mature T cells and B cells, it mainly affects the late phase of the immune response. Thus, PD-1/PD-L1 blocking therapies produced significantly lower rate of high-grade TR adverse events. According to the studies listed in **Tables 1–3**, fatigue was the most common TR adverse events. Decreased appetite, asthenia, diarrhea, pneumonitis, rash, and pruritus were also common TR adverse events.

Combination therapies

Besides working as monotherapy, PD-1/PD-L1 blocking therapies can also be used in combination with other anti-tumor therapies, and some of these combination therapies have had successful and inspiring effects. In the clinical trial NCT02039674, pembrolizumab was combined with chemotherapy for the treatment of non-small cell lung cancer (NSCLC). The ORR was 55% in the combination group and 29% in the chemotherapy alone group[41]. The incidences of grade 3 or worse TR adverse events were similar between the two groups (39% in the pembrolizumab plus chemotherapy group and 26% in the chemotherapy alone group)[41]. Based on these clinical trial results, the FDA approved pembrolizumab in combination with pemetrexed and

carboplatin as the first-line treatment of patients with metastatic non-squamous NSCLC. In the clinical trial (NCT01024231), nivolumab in combination with ipilimumab resulted in an objective response in that 53% of patients, and all with tumor reductions of 80% or more; however grade 3 or 4 TR adverse events occurred in 53% of the patients[42]. In the clinical trial (NCT01927419), the ORR and median progression free survival (PFS) in the nivolumab and ipilimumab combined group were 61% and 8.9 months respectively, while the ORR and median PFS were 11% and 4.7 months respectively in the ipilimumab monotherapy group[43]. In this trial, the median tumor volume was a 68.1% decrease in the combination group and a 5.5% increase in the ipilimumab monotherapy group[43]. However, the TR grade 3-4 adverse events was 54% in the combination group, versus 24% in the ipilimumab monotherapy group[43]. Based on these results, the FDA approved nivolumab and ipilimumab combination therapy for unresectable or metastatic melanomas. By now, the FDA only approved the above two PD-1/PD-L1 blocking therapies related combination therapies. Due to the great potential of combination therapies, more and more combination therapy clinical trials are currently in process. With better efficiency, the FDA may approve more combination therapies in the future.

Future prospective

Over the past several years, cancer immunotherapy has advanced greatly and some have achieved the FDA approval for cancer treatment. Moreover, the combination therapies that include PD-1/PD-L1 blocking therapies have shown great potencies and efficacies. In the future, combination therapies may become mainstream therapy for cancer treatments. Meanwhile, TR adverse events, including immune-related adverse events, have emerged with the development of cancer immunotherapies, and require more attention and solution. Furthermore, with more clinical studies and higher PD-L1 expression cut-off rates, PD-L1 may also be an indicative marker for pan-cancer treatment with PD-1/PD-L1 blocking therapies.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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