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REVIEW

Multi-target combinatory strategy to overcome tumor immune escape

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Abstract **Immune therapy has become the fourth approach after surgery, chemotherapy, and radiotherapy in cancer treatment. Many immune checkpoints were identified in the last decade since ipilimumab, which is the first immune checkpoint inhibitor to cytotoxic T-lymphocyte associated protein 4, had been approved by the US Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma in 2011. The use of several antibody drugs that target PD1/PD-L1 for various cancer treatments has been approved by the FDA. However, fewer people are benefitting from immune checkpoint inhibitor treatment in solid cancers. Approximately 80% of patients do not respond appropriately because of primary or acquired therapeutic resistance. Along with the characterization of more immune checkpoints, the combinatory treatment of multi-immune checkpoint inhibitors becomes a new option when monotherapy could not receive a good response. In this work, the author focuses on the combination therapy of multiple immune checkpoints (does not include targeted therapy of oncogenes or chemotherapy), introduces the current progression of multiple immune checkpoints and their related inhibitors, and discusses the advantages of combination therapy, as well as the risk of immune-related adverse events.**

Keywords immune checkpoints; multi-target; immune escape; immune-related adverse events; combination therapy

Introduction

Immune therapy has become the fourth approach after surgery, chemotherapy, and radiotherapy in cancer treatment. Immune checkpoint is an important scientific discovery in the 1990s. Cytotoxic T-lymphocyte associated protein 4 (CTLA4) is the first immune checkpoint. Ipilimumab is the targeted drug approved by the US Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma in 2011. Since then, multiple immune checkpoints were identified in the last decade. Several antibody drugs that target PD1/PD-L1 for various cancer treatments have been approved by the FDA. In 2017, the FDA approved the use of pembrolizumab as a therapeutic drug based on a tumor's biomarker of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) rather than the specified tumor locations in the body [1]. In 2018, James Allison and Tasuku Honjo received the Nobel Prize in Physiology or Medicine for discovering CTLA4 and PD1 co-inhibitory receptor on T cells. Their important discovery drives the development of immune checkpoint inhibitors. Generally, immune checkpoints are present in a receptor–ligand paradigm. The receptor is expressed on lymphocyte, whereas the ligand is expressed on immune cells or non-hematopoietic cells, such as antigen-presenting cells (APC) and cancer cells. Co-stimulatory and co-inhibitory receptors are present on T cells. Co-stimulatory signals drive T cell activation, and co-inhibitory signals regulate T cell functions negatively. The homeostasis is maintained by co-stimulatory and co-inhibitory receptors (Fig. 1). Co-inhibitory signals could weaken T cell functions and play critical roles in tumor immune escape [2]. These co-inhibitory signals hinder the cytotoxic effect, thereby allowing tumors to escape from T cell attack. Immune checkpoint inhibitors block the conduction of inhibitory signals by interfering the binding of immune checkpoints to their ligands, hence enhancing the cytotoxic effect.

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Complex immunosuppressive microenvironment in solid cancers

The immune checkpoint inhibitor targeted to PD1 for

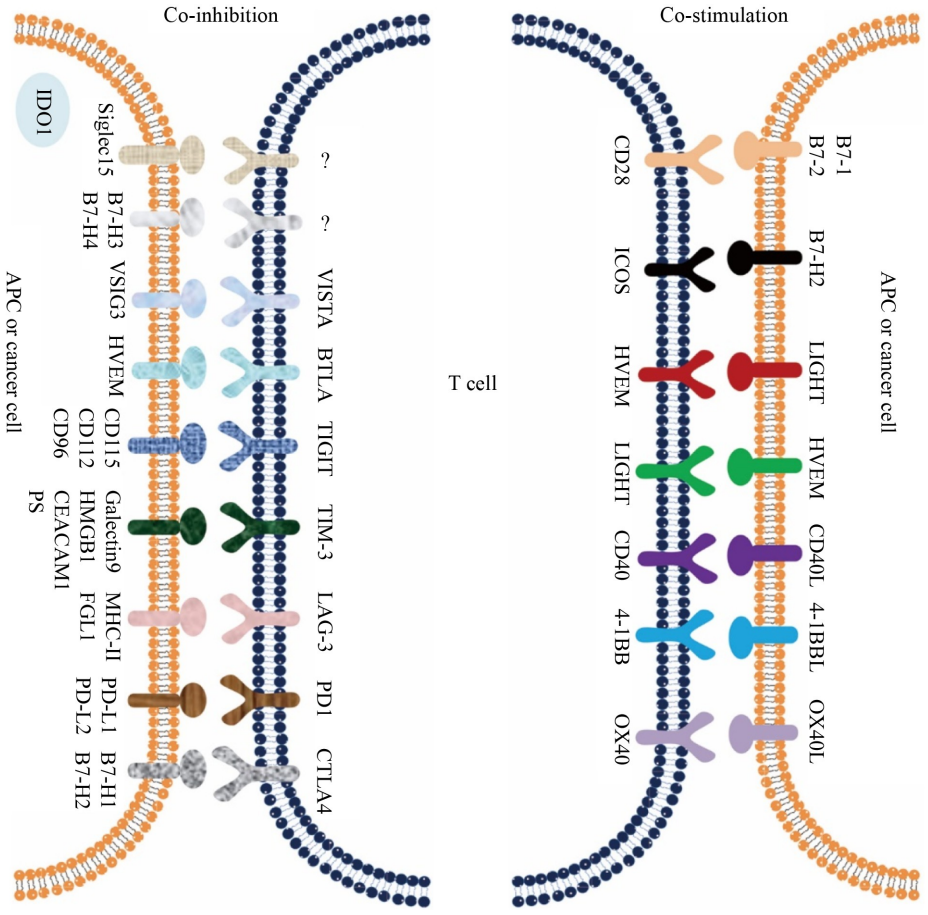

Fig. 1 Schematic of well characterized receptors and corresponding ligands on T cells, antigen presenting cells (APCs), and cancer cells. Left: Co-inhibitory molecules of T cells and their ligands on APC or cancer cells. Right: Co-stimulatory molecules of T cells and their ligands on APCs or cancer cells.

treating hematopoietic malignancy was approved by the FDA in 2014. However, fewer people are benefitting from anti-PD1 in solid cancers. Approximately 80% of patients do not respond appropriately because of primary or acquired therapeutic resistance. The poor responsive rate is associated with complex immune microenvironments. In fact, beyond the PD1/PD-L1 pathway, tumors can escape from the host immune attack by relying on multiple immune checkpoint pathways, such as TIM-3 path [3], LAG-3 path [4], VISTA path, TIGIT path [5], B7-H3 path [6], IDO1 path, and SIGLEC-15 path [7–9]. Along with more characterized immune checkpoints, the combinatory treatment of multi-immune checkpoint inhibitors becomes a new option when monotherapy could not receive a good response. Recently, the combination of anti-CTLA4 and anti-PD1 in metastatic melanoma revealed increased overall survival and progression-free survival compared with monotherapy. The overall survival rate at 3 years was 58%, which is significantly higher than any other monotherapy (34%–52%). However, combination regimens are related to higher toxicity. The incidence of immune-related adverse events (irAE) of grade 3 or 4 caused by drug is about 21% for anti-PD1 and 28% for anti-CTLA4 but increases to 59% in the combination regimen of both drugs [10]. Therefore, drug safety is a problem that cannot be ignored.

TIM-3, LAG-3, TIGIT and so on comprise the next generation of immune checkpoints. These T cell receptors also regulate immune responses together with CTLA4 or PD1. This finding suggests that the rational design of combinatorial clinical trials, particularly in combination with existing immune checkpoint inhibitors, will improve the therapeutic response. Parra *et al.* examined the expression of multiple immune checkpoints on non-small cell lung cancer and found that the infiltrating monocytes in tumor not only included lymphocytes that expressed PD-L1, B7-H3, B7-H4, IDO1, VISTA, LAG-3, ICOS, TIM-3, and OX40 but also included myeloid-derived suppressor cells that expressed CD68, CD66b, CD14, CD33, Arg-1, and CD11b [11].

Immune checkpoint inhibitors

To date, the FDA has approved seven immune checkpoint inhibitors for cancer treatment. One is anti-CTLA4 (e.g.,

Table 1 Information of immune checkpoints and related inhibitors[a]

Immune checkpoint	Inhibitor	Trade name	Half-life	Description
CTLA4 (CD152)	Ipilimumab	Yervoy®	8–15 d	Unresectable malignant pleural mesothelioma, metastatic non-small cell lung cancer, hepatocellular carcinoma, advanced renal cell carcinoma, and unresectable or metastatic melanoma
	Nivolumab	Opdivo®	15–25 d	Urothelial carcinoma, esophageal or GEJ cancer, metastatic gastric cancer and esophageal adenocarcinoma, advanced renal cell carcinoma, unresectable malignant pleural mesothelioma, esophageal squamous cell carcinoma, metastatic non-small cell lung cancer, hepatocellular carcinoma, and advanced melanoma
	Pembrolizumab	Keytruda®	15–27 d	Renal cell carcinoma, triple-negative breast cancer, endometrial carcinoma, gastric cancer, esophageal or GEJ cancer, locally recurrent unresectable or metastatic triple-negative breast cancer, classical Hodgkin lymphoma, BCG-unresponsive bladder cancer, metastatic head and neck squamous cell carcinoma, metastatic urothelial carcinoma, advanced or metastatic gastric cancer or GEJ cancer, advanced melanoma, and solid tumors with specific genetic feature
PD1 (CD279)	Cemiplimab	Libtayo®	12–19 d	Advanced non-small cell lung cancer, advanced and metastatic basal cell carcinoma, and advanced skin squamous cell carcinoma
PD-L1 (CD274)	Atezolizumab	Tecentriq®	21–27 d	Unresectable hepatocellular carcinoma, metastatic non-small cell lung cancer, urothelial carcinoma, advanced bladder cancer, metastatic triple-negative breast cancer, and advanced melanoma
PD-L1	Durvalumab	Imfinzi®	17–21 d	Extensive-stage small cell lung cancer and advanced bladder cancer
PD-L1	Avelumab	Bavencio®	4–6 d	Metastatic Merkel cell carcinoma, advanced renal cell carcinoma, and advanced urothelial carcinoma
TIM-3	TSR-022	/	/	/
TIGIT	MK-7684 BMS-986207 OMP-313M32 (Etigilimab)	/	/	/
LAG-3 (CD223)	BMS-986016 (Relatlimab) MK-4280 LAG525 EOS8844488 TJT6 AB154 TSR-033 IMP321	/	/	/
BTLA	HVEM (14-39) peptide	/	/	/
VISTA	CA-170 JNJ-61610588 (Onvatilimab)	/	/	/
SIGLEC-15	α-S15 NC318 (NCT03665285)	/	/	/
IDO1	Epacadostat (INCB024360)	/	2.4–7.3 h	/

[a]Resource: FDA oncology (cancer) /hematologic malignancies approval notifications website.

ipilimumab), three are anti-PD1 (e.g., nivolumab, pembrolizumab, and cemiplimab), and others for anti-PD-L1 (e.g., atezolizumab, avelumab, and durvalumab). The indications already covered 20 types of cancers. More than 6000 clinical trials are ongoing [12,13]. Anti-PD1/PD-L1 treatment is currently the best known and most clinically effective method for normalization cancer immunotherapy. However, it is only effective in 20% to 30% of solid cancers. These drugs showed objective response rates in some patients clinically, but the efficacy of single-drug treatment was inconsistent. The low efficiency indicates the presence of other potential immunosuppressive pathways, such as the newly discovered SIGLEC-15 pathway, as well as the LAG-3-fibrinogen-like protein 1 (FGL1) pathway. They are the possibility of tumor immune escape and are potential targets for cancer immunotherapy [14]. Therefore, the inhibitors that target other immune checkpoints have been actively developed. Multiple immune checkpoints, their inhibitors, commercial names, half-life of drugs *in vivo*, as well as the

Table 2 The main progression of multi-target combinatory therapy in real world

Authors	Reports	Targets	Drugs	Case number	Response	Reference
Hollebecque A, *et al.*	Phase I	PD-L1, TIM-3	LY3300054, LY3321367	*n* = 42 MSI-H/dMMR tumors of colorectal and endometrial cancers	Manageable safety profiles with objective responses occurred in 32.5% of monotherapy, and 45.0% in combination cohort	[24]
Atkinson V, *et al.*	Phase I	PD1, LAG-3	Pembrolizumab, eftilagimod alpha	*n* = 24 Metastatic melanoma	Well tolerated with overall response rate of 33% (in patients with pembrolizumab-refractory) to 50% (in patients with PD1 naïve)	[25]
McGregor BA, *et al.*	Phase II	PD1, CTLA4	Nivolumab and ipilimumab	*n* = 55 Genitourinary cancers	The objective response rate was 6% to 37% in different cohorts, but 22 patients (40%) developed treatment-related grade 3 or higher toxicities	[26]
Powles T, *et al.*	Phase III	PD-L1, CTLA4	Durvalumab and tremelimumab	*n* = 346 (durvalumab) *n* = 342 (durvalumab plus tremelimumab) *n* = 344 (chemotherapy) Unresectable, locally advanced or metastatic urothelial carcinoma	Median overall survival was 14.4 months in the durvalumab monotherapy group, 15.1 months in the durvalumab plus tremelimumab group, while 12.1 months in the chemotherapy group. The study did not meet its coprimary endpoints	[27]
Takahashi A, *et al.*	Phase II	PD1, CTLA4	Nivolumab and ipilimumab	*n* = 57 Unresectable advanced melanoma	The overall response rate 26.3% (with complete response 3.5% and partial response 22.8%), stable disease 21.1%, and progressive disease 52.6%. The adverse events of grade 3 or worse occurred in 56.1%	[28]
Gaudreau PO, *et al.*	Phase I/II	PD-L1, CTLA4	Durvalumab and tremelimumab	*n* = 40 Non-small cell lung cancer	The trial is actively screening and enrolling patients	[29]
Ebata T, *et al.*	Phase I	PD-L1, IDO1	Atezolizumab and navoximod	*n* = 20 Thymic cancer, pancreatic cancer, small-cell lung cancer, etc.	The treatment related adverse events of grade 3 were 10% to 30%. In stage 1, stable disease 50%, progressive disease 50%. In stage 2, stable disease 80%, progressive disease 20%	[30]
Hammers HJ, *et al.*	Phase I	PD1, CTLA4	Nivolumab and ipilimumab	*n* = 47 Metastatic renal cell cancer	Manageable safety with objective response rate of 40.4%. The 2-year over survival was 67.3% and 69.6%	[31]
Jung KH, *et al.*	Phase I	PD-L1, IDO1	Atezolizumab, navoximod	*n* = 157 Melanoma, pancreatic, prostate, etc.	The partial response or complete response was 9% to 11% with acceptable safety and tolerability	[32]
Wu RY, *et al.*	Pre-clinical	PD-L1, IDO1	Pembrolizumab or nivolumab, regorafenib	Animal experiments Melanoma	Regorafenib alone caused a 45% tumor reduction. Anti-PD1 caused a slight tumor repression without statistical significance. The combined treatment significantly reduced for xenograft tumor volume and tumor weight	[33]

indication approved by the FDA, are listed in Table 1. This information should be referenced when considering the combination therapy for multiple checkpoints, especially noticing the half-life *in vivo* [15–19]. Immune checkpoint inhibitor, as a new therapeutic drug, shows obvious advantages compared with traditional chemotherapy. Considering that immune checkpoint inhibitor could induce the memory T cells to anti-tumor immune, it could improve the durability of the response and achieve a long-term survival. However, immune checkpoint inhibitor also shows some disadvantages, such as low responsive rate, higher adverse effects, drug resistance, and higher price.

Progression of multi-target combinatory therapy

The combinatory therapy of multi-target inhibitors has been recommended as a new strategy to improve the responsive rate of immunotherapy. The combination of CTLA4/PD1 inhibitors (ipilimumab/nivolumab) has been approved for treating 13 types of advanced cancers with positive biomarkers of DNA mismatch repair-deficient/microsatellite instability-high (MSI-H), such as advanced non-small cell lung cancer, metastatic colon cancer, and localized urothelial cancer [20, 21]. As Table 1 shows, the seven FDA-approved immune checkpoint inhibitors are mainly targeted to CTLA4, PD1, and PD-L1. One is anti-CTLA4 (e.g., ipilimumab), three are anti-PD1 (e.g., cemiplimab, nivolumab, and pembrolizumab), and another three anti-PD-L1 (e.g., atezolizumab, avelumab, and durvalumab). The indications of these monoclonal antibody drugs covered over 20 kinds of cancers. The combinatory regimens for CTLA4 and PD1/PD-L1 dual-target have been approved by the FDA for cancer therapy. The alternative combination regimens of anti-PD1/PD-L1 with new generation of immune checkpoint inhibitors are ongoing clinical trials [22]. In China, a total of 17 types of cancer are proper for using immune checkpoint inhibitors in accordance to the guidelines provided by the Chinese Society of Clinical Oncology (CSCO). A total of 11 immune checkpoint inhibitors, including four Chinese domestic immune checkpoint inhibitors (e.g., camrelizumab, toripalimab, sintilimab, and tislelizumab), are recommended. From the published data, the overall response rate of monotherapy is not more than 20% [23]. Combination therapy for multiple immune checkpoint inhibitors is a promising strategy, which is in the exploration stage in China or abroad. The main progression of multi-target combinatory therapy is presented in Table 2.

Although different immune checkpoints attenuate T cell activation, they may rely on different mechanisms. Anti-CTLA4 primarily affects the priming stage of T cells, and anti-PD1 enhances the T cell activity in the effective phase [34]. Researchers conducted different experimental therapies to improve the effectiveness of immune checkpoint inhibitors. Recently, our group explored the drugs that could target dual-target of PD-L1/IDO1 and published our finding of "Dexamethasone suppresses immune evasion by inducing GR/STAT3 mediated downregulation of PD-L1 and IDO1 pathways" in *Oncogene*, a leading international journal in oncology. By drug repurposing strategy, we identified a group of compounds that may inhibit PD-L1 and IDO1 dual-target [35]. Dexamethasone revealed its anti-tumor effect on several models *in vitro* and *in vivo*. Dexamethasone could mediate the transcriptional suppression of PD-L1 and IDO1 by the nuclear translocation of glucocorticoid receptor. Our study suggests that the dual-target of PD-L1 and IDO1 might be potential targets for combination therapy, and dexamethasone could be used as a sensitization reagent of immune checkpoint inhibitors [2]. Recently, Bronte and coworkers reported three cases of non-small cell lung cancer patients who received three immune checkpoint inhibitor therapies. The regimen is the combination of anti-CTLA4 (ipilimumab) plus anti-PD1 (nivolumab) plus anti-LAG-3 (relatlimab). They observed the clinical and radiological course during treatment. Two cases discontinued the immunotherapy because of confirmed radiological progression, and the platinum-based chemotherapy began. The treatment with immunological triplet in one case lasted for 5 cycles and then underwent left upper lobectomy after the finding of a reduction of pulmonary tumor mass [34]. In real world, the combination of immune checkpoint inhibitor with targeted drug for oncogene or chemotherapy is actively ongoing. Recently, a phase III (KEYNOTE-811) study revealed that the anti-PD1 (pembrolizumab) plus anti-HER2 (trastuzumab) and chemotherapy for unresectable or metastatic HER2-positive gastric or gastro-esophageal junction adenocarcinoma obviously reduced tumor size and induced complete responses in some participants [36].

In addition, the beneficiary of the combination therapy of multiple immune checkpoints inhibitors is not clear yet. In general, increased tumor mutation burden (TMB) is taken as an indication for immune therapy. Recently, Hsiehchen *et al.* reported that according to FDA recommendation of 10 mut/Mb as cut-off for immune checkpoints inhibitors, patients from the black and Asian racial groups are not proper, because they have lower TMB [37]. Zhou and coworkers analyzed the TMB of five types of cancers in Chinese population and found that the median TMBs are lower than 10 mut/Mb, such as cholangiocarcinoma (2.71 mut/Mb), nervous system tumor (2.97 mut/Mb), gastric cancer (3.69 mut/Mb), hepatocellular carcinoma (4.31 mut/Mb), and colorectal cancer (4.64 mut/Mb) [38]. Thus, TMB threshold criterion may vary for different cancers. Moreover, TMB does not indicate response for what types of immune checkpoint inhibitors. Upregulation of PD-L1 expression on cancer cells usually predicts the well response to inhibitors of PD1-PD-L1 pathway. Currently, no specific

biomarkers are available for predicting therapeutic response to multi-target combination therapy. Based on our pre-clinical study, the high simultaneous expression of PD-L1 and IDO1 on cancer cells could predict the well response to the combination of low-dose dexamethasone plus pembrolizumab combing therapy [2].

Immune-related adverse events

With the increasing use of immune checkpoint inhibitors across tumor types, many clinicians are faced with their adverse effects. The immune checkpoint inhibitor-activated T cells can attack normal tissues and organs in the body, thereby leading to a variety of adverse effects [39]. The incidence of irAEs during the treatment of immune checkpoint inhibitors is as high as 90% of patients undergoing CTLA4 inhibitor therapy and 70% of those undergoing PD1 and/or PD-L1 inhibitor therapy [40]. However, most of them are mild to moderate, only affecting the skin, gastrointestinal tract, liver, endocrine organ, and muscles. Cunningham *et al.* retrospectively analyzed the liver enzyme elevations and hepatotoxicity in patients treated with anti-PD1, PD-L1, or CTLA4 therapy in phase I/II clinical trials. The liver enzyme elevation occurred in 21.6% of patients. Immunotoxicity was associated with higher peak ALT than other causes of enzyme elevation [41].

According to clinical trials, the odds ratios for treatment-related death for CTLA4 inhibitors (ipilimumab and tremelimumab) and for PD1/PD-L1 inhibitors (nivolumab, pembrolizumab, and atezolizumab) were 1.80 (95% confidence interval 1.25–2.59) and 0.63 (95% confidence interval 0.31–1.30), respectively [42]. Ji *et al.* performed data mining and found that the common adverse effects of CTLA4 and PD1 antibodies were rash, diarrhea, colitis, and thyroid dysfunction. Thyroid dysfunction, type 1 diabetes mellitus, and pneumonitis often occurred in patients who received anti-PD1 treatment; whereas colitis, diarrhea, hypophysitis, and adrenal insufficiency were more closely associated with anti-CTLA4. Skin rash and hepatitis occurred similarly in both instances [43]. Immune-related pneumonitis is another subset of irAEs, which is an important and potentially fatal complication during immune checkpoint inhibitor therapy [44]. The incidence of immune-related pneumonitis is higher in patients who receive an anti-PD1/PD-L1 antibody than in those receiving an anti-CTLA4 antibody (3%−5% vs. < 1%, respectively). The incidence of grade ⩾ 3 immune related pneumonitis could reach 1% for receiving anti-PD1 or anti-PD-L1 antibodies [39].

The severe toxicities, including cardiovascular and neurologic systems, are rare but deadly. Some complications can cause life-threatening cytokine storms [45]. Death occurred in about 0.3%–1.3% of patients for immune checkpoint inhibitor treatments [46,47]. The immune checkpoint inhibitor-associated myocarditis occurred in 1.06% for anti-PD1 treatment [48]. Immune checkpoint inhibitor-associated myocarditis is a severe irAE with a high mortality of 39.7%–66.7%. The median onset time was 18–56 days after the first dose [49]. Neurological irAEs accounted for 7.7%–11.9% of all reported irAEs. Neurological irAEs generally occurred within the first 3 months after the initiation of immune checkpoint inhibitors [47]. Duong and colleagues retrospectively analyzed the data of immune checkpoint inhibitor-associated neurotoxicities in 18 patients. The neurotoxicities comprised central demyelinating disorder, autoimmune encephalitis predominantly affecting the gray matter, and aseptic meningitis [50]. The grade 3–4 neurotoxicity developed in 14 out of 18 (78%) patients, of whom 6 patients died (33.33%) [51].

Conclusions

Immune checkpoint inhibitors mark the beginning of a new era in cancer treatment. The ultimate goal is to drive the host immune system to normalize. This strategy is likely to be one of the potential cures for cancers. At present, new targets are constantly being discovered, and clinical trials of various combinations of multi-target targeting are actively on going. Given the risk of the super activation of T lymphocytes in combinatory therapy, such as cytokine storms, examining the drug dose in combination therapy actively is necessary. Furthermore, in-depth research on the molecular mechanisms of different immune checkpoints must be conducted to minimize toxicity and maximize the benefits.

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Compliance with ethics guidelines

Yingyan Yu declares no conflicts of interest. This article does not involve a research protocol that requires the approval of a relevant institutional review board or ethics committee.

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