Guidelines for Integrated Surgical Pharmaceutical Service of Immune Checkpoint Inhibitors (ICIs)

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Major treatment options for malignancy include surgery, radiotherapy, and pharmacotherapy. In terms of drug treatment, traditional chemotherapy kills tumour cells and simultaneously damages normal cells, leading to severe adverse reactions including neutropenia, anaemia, alopecia, nausea, vomiting and oral mucositis. Therefore, novel anticancer drugs with strong targeting and less side effect have become the mainstream focus of research and development. In comparison to a variety of small-molecule tyrosine kinase inhibitors and large-molecule monoclonal antibodies, the tumor immunotherapy represented by immune checkpoint inhibitors (ICIs) is the most striking one among many new anti-tumor drugs approved in recent years.

Tumor immunotherapy typically targets cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), programmed cell deathreceptor 1 (PD-1), and programmed cell death ligand1 (PD-L1). ICIs targeting CTLA-4, PD-1 and PD-L1 can regulate the body's own immune response to play an anti-tumor role. Therefore, ICIs can be referred to as "broad-spectrum anti-tumor drugs" or "pan-tumor anticancer drugs", which have demonstrated clinical efficacy in many types of cancer. Various types of ICIs have been endorsed by the US Food and Drug Administration (FDA) and the China National Medical Products Administration (NMPA) for the treatment of advanced non-small cell lung cancer, melanoma, Hodgkin's lymphoma, and other tumors.

From July 2018 to October 2022, four imported and nine domestic PD-1/PD-L1 inhibitors, one CTLA-4 inhibitor and one bispecific PD-1/CTLA-4 inhibitor have been marketed in China and widely used clinically. The mechanism of ICIs is distinct from that of traditional cytotoxic and targeted drugs, and the characteristics of adverse reactions are also markedly different. Full emphasis should be placed on the efficacy and safety of ICIs and effective management of drug-related adverse events in clinical translation.

ICIs have been progressively approved for neoadjuvant/adjuvant therapy in surgery in recent years to enhance the survival benefit of patients compared with neoadjuvant/adjuvant chemotherapy. As a discipline to study the medication for patients during operation, surgical pharmacy plays a significant role in the treatment of patients with cancer. The cancer therapy is a complex and enormous project. Surgical and medical treatment are often combined with each other without obvious boundaries. Neoadjuvant treatment offers the possibility for surgical operation, while postoperative adjuvant treatment is to prolong the life of patients.

PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors and bispecific PD-1/CTLA-4 antibodies are relatively new to the market, and there is still a lack of systematic and comprehensive pharmaceutical guidelines for the safe use and medication monitoring of these drugs. Guangdong Pharmaceutical Association organized clinical pharmacists and medical professionals to elaborate and complie a full-process pharmaceutical service guideline from two aspects: rational clinical use of drugs and comprehensive management of adverse reactions, so as to provide a basis for the safe and rational use of these drugs and provide reference for pharmacists to review prescriptions and medical order of these drugs. Since the concept of a surgical pharmacy was proposed, the focus on ICIs has transitioned from general medical treatment to neoadjuvant/adjuvant administration before and after surgery. Such a change in medication reflects not only the update of drug indications, but also prompts pharmacists to pay new attention to drugs in the field of surgery.

1. Pharmacologic features of PD-1/PD-L1/CTLA-4 inhibitors

PD-1, fully known as programmed cell death receptor 1, exists on the surface of T cell membrane with immune function in human body, and is a very important immune checkpoint.

PD-L1, fully known as programmed cell death ligand 1, is highly expressed on the surface of various tumour cells and surrounding tissues, such as melanoma, lung cancer, urothelial carcinoma, squamous cell carcinoma of head and neck.

CTLA-4, fully known as cytotoxic T-Lymphocyte associated protein 4, is an important regulator of T-cell activity, and its negative regulation reduces the proportion of effector T-cells.

Checkpoints are molecules that play a protective role in the human immune system, similar to the "brakes" of T-cell, which can prevent T-cell from overactivating and causing damage to normal tissues[1, 2]. Tumour cells take advantage of this property to over-express immune checkpoint molecules to achieve immune suppression and escape.

The body's immune system has the capacity to monitor and eliminate the mutant cells, and the collapse of antitumour immunity has been proved to be the fundamental reason for the proliferation and metastasis of tumour cells. Cancer cells escape immune surveillance by altering their phenotype during the early stages of tumorigenesis. During disease progression and metastasis, more mechanisms are required to ensure that they are not cleared by the body. Tumor cells, tumor-associated antigen presenting cells or stromal cells can up-regulate the PD-L1 level via IFN-γ in the process of sustained immune response. The PD-L1 expression in tumor cells allows the tumor to evade the host immune response and immune therapy. For example, immunotherapy, represented by ICIs such as monoclonal antibodies to PD-1/PD-L1, utilizes the body's own immune system to resist and fight cancer and induce apoptosis of cancer cells by blocking PD-1/PD-L1 signaling pathway, while blocking CTLA-4/B7.1/B7.2 signaling pathway can further increase the activity of effector T-cells, which has the potential to treat various types of tumors and substantially enhance the overall survival of cancer patients.

Currently, PD-1 inhibitors marketed in China consist of humanized or fully humanized human immunoglobulin G4 (IgG4) or monoclonal human immunoglobulin G1 (IgG1) antibodies (HuMAbs), and have been used in the development of clinical trials, which have roughly the same pharmacokinetic (PK) features as other monoclonal therapeutic antibodies (mAbs). They are rarely or almost unaffected by renal/hepatic impairment, and have limited diffusion from the blood into tissues with a long half-life (about 5.5~25 days for PD-1 inhibitors currently marketed in China), the clearance of which is primarily receptor mediated. Therefore, the individual/intra-individual PK differences of PD-1 inhibitors are primarily affected by the synthesis of anti-drug antibodies, the effect of tumor burden, the changes of proteolytic function, and the genetic polymorphism of human neonatal Fc receptor (FcRn) [3].

Continued exploration of ICIs has led to the introduction of bispecific antibody (BsAb) drugs. Currently, drugs targeting both PD-1 and CTLA-4 signaling pathways have been brought to the market, which suppress antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) effects, enhancing the binding efficiency, effectively blocking the immunosuppressive response, and promoting immune activation of tumor-specific T-cells by modifying the Fc segment of the antibody and introducing two binding targets.

2. Guidelines for integrated surgical pharmaceutical services for PD-1/PD-L1/CTLA-4 inhibitors

Nine PD-1 inhibitors are included with two varieties imported: nivolumab (trade name: Opdivo) and pembrolizumab (trade name: Keytruda), and seven domestic varieties: toripalimab (trade name: Tuoyi), sintilimab (trade name: Daboshu), camrelizumab (trade name: Airuika), tislelizumab (trade name: Baizean), penpulimab (trade name: Annike), zimberelimab (trade name: Yutuo) and serplulimab (trade name: Hansizhuang). Four PD-L1 inhibitors are included, containing two varieties imported: durvalumab (trade name: Imfinzi) and atezolizumab (trade name: Tecentriq), and two domestic varieties: envafolimab (trade name: Enweida) and sugemalimab (trade name: Zejiemei). One imported CTLA-4 inhibitor is included: ipilimumab (trade name: Yervoy), and one domestic bispecific PD-1 / CTLA-4 inhibitor is included: cadonilimab (trade name: Cadoni).

PD-1/PD-L1/CTLA-4 inhibitors are drugs based on macromolecular proteins that utilize human DNA fragments and rely on bacterial or animal cell lines for their biosynthesis. Monoclonal antibody production is a complex, heterogeneous, and highly variable process with a complex spatial structure consisting of four steps. Each monoclonal immunoglobulin molecule, composed of four peptides, contains about 25,000 atoms, of which about 1,300 are amino acids, and has a molecular weight of about 150,000 Daltons. Compared to chemostructured small molecule drugs, the stability of PD-1/PD-L1/CTLA-4 inhibitors is more sensitive to various external factors such as room temperature, light, and vibration. Therefore, medical institutions should pay attention to indications, dosage,

administration of infusions, adverse reaction monitoring, adverse reaction management and patient education to ensure the safe, reasonable, economical and appropriate use of PD-1/PD-L1 inhibitors. At the same time, this objective is also the goal of the *Guidelines for Integrated Pharmaceutical Service*.

2.1 Clinical use of PD-1/PD-L1/CTLA-4 inhibitors[4-22]

2.1.1 Clinical indications for PD-1/PD-L1/CTLA-4 inhibitors

(1) Nivolumab

Nivolumab was developed by Bristol-Myers Squibb Company (BMS) and was approved for marketing by the FDA in December 2014. It has been approved for use as a second-line therapy for advanced non-small cell lung cancer in mainland China. Nivolumab is widely used internationally and has been approved for 15 indications in 11 tumour types including lung, melanoma, bowel, liver, urinary tract, squamous cell carcinoma of the head and neck, lymphoma, malignant pleural mesothelioma, and esophagus and stomach cancers. The indications of nivolumab **approved by NMPA and FDA** are listed in Table 1.

Table 1 Indications approved by NMPA and FDA for nivolumab

Tumor	Indications	NMPA	FDA
Non-small cell lung cancer (NSCLC)	Adult patients with EGFR-negative and ALK-negative locally advanced or metastatic non-small cell lung cancer who have progressed on or are intolerable to prior platinum-based chemotherapy.	√	√
	First-line combination with ipilimumab in adult patients with metastatic non-small cell lung cancer who are EGFR-negative and ALK-negative and have positive PD-L1 expression (≥1%).		√
	Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.		√
	Adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.		√
Melanoma	Patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.		√
	Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.		√
Malignant pleural mesothelioma	Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.	√	√
Colorectal cancer	As a single agent or in combination with ipilimumab in adult and pediatric patients (≥12 years of age) with metastatic colorectal cancer with high microsatellite instability (MSI-H) or mismatch gene repair deficiency (dMMR) who have previously been treated with fluorouracil, oxaliplatin, and irinotecan and have progressed.		√
Hepatocellular carcinoma (HCC)	Patients with hepatocellular carcinoma who have been previously treated with sorafenib in combination with ipilimumab.		√
Urothelial carcinoma (UC)	Primary or metastatic urothelial carcinoma where the patient has progressed on a prior platinum-based regimen or has progressed within 12 months on platinum-based neoadjuvant/adjuvant chemotherapy.		√
	Adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing radical resection of UC.		√
Renal cell carcinoma (RCC)	Patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab.		√
	Patients with advanced renal cell carcinoma who have received prior anti angiogenic therapy.		√
	Patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib.		√
Squamous cell carcinoma of the head and neck (SCCHN)	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.		√
	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck expressing PD-L1 (≥1%) with disease progression on or after a platinum-based therapy.	√	

Classical hodgkin lymphoma (cHL)	Adult patients with classical Hodgkin lymphoma who have relapsed or progressed following: autologous hematopoietic stem cell transplantation (HSCT) plus brentuximab vedotin or more than 3 systemic chemotherapies including HSCT.		√
Esophageal squamous cell carcinoma (ESCC)	Patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.		√
	Patients with unresectable advanced or metastatic ESCC as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.	√	√
	Patients with unresectable advanced or metastatic ESCC as first-line treatment in combination with ipilimumab.		√
Gastroesophageal junction adenocarcinoma	Patients with advanced or metastatic gastroesophageal junction adenocarcinoma who have been previously treated with two or more of systemic therapy.	√	
Esophageal cancer (EC) or gastroesophageal junction cancer (GEJC)	Patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).	√	√
Gastric cancer (GC), GEJC, and esophageal adenocarcinoma (EAC)	Patients with advanced or metastatic GC, GEJC, and EAC as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.	√	
	Patients with advanced or metastatic GC, GEJC, and EAC in combination with fluoropyrimidine- and platinum-containing chemotherapy.		√

(2) Pembrolizumab

Pembrolizumab is produced by Merck Sharp & Dohme Company and was approved for marketing by FDA in September 2014. It was approved in mainland China for second-line treatment of advanced malignant melanoma and first-line single drug/combination chemotherapy treatment of advanced non-small cell lung cancer. As of November 2020, pembrolizumab has been approved abroad for the treatment of 31 indications, including malignant melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, bladder cancer, cervical cancer, gastric cancer, B-lymphocytoma, colorectal cancer, triple-negative breast cancer, and cutaneous squamous cell carcinoma. The indications of pembrolizumab approved by NMPA and FDA are listed in Table 2.

Table 2 Indications approved by NMPA and FDA for pembrolizumab

Tumor	Indications	NMPA	FDA
Non-small cell lung cancer (NSCLC)	First-line combination pemetrexed and platinum-based chemotherapy for metastatic non-squamous NSCLC that is EGFR mutation-negative or ALK negative.	√	√
	First-line combination carboplatin and paclitaxel/nab-paclitaxel (FDA only) for metastatic squamous NSCLC.	√	√
	First-line monotherapy in locally advanced or metastatic NSCLC with positive PD-L1 expression (TPS ≥1%), EGFR mutation-negative or ALK-negative.	√	√
	As a single agent for treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥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.		√
Melanoma	For the treatment of patients with unresectable or metastatic melanoma.		√
	For the treatment of patients with unresectable or metastatic melanoma who have been previously treated with first-line treatment.	√	
	Adjuvant therapy for patients with stage IIB, IIC, or III melanoma who have undergone complete surgical resection.		√
Squamous cell carcinoma of the head and neck (SCCHN)	In combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.		√
	As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a FDA-approved test.	√	√
	For second-line treatment of recurrent or metastatic HNSCC that has progressed on or after platinum-based chemotherapy.		√
Classical hodgkin lymphoma (cHL)	For the treatment of refractory cHL in adults and children, or relapse after second-line and above treatment.		√

Primary mediastinal large B-cell lymphoma (PMBCL)	For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. Not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.		√
Urothelial carcinoma	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy.		√
	For the treatment of 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.		√
	For the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.		√
Microsatellite instability-high or mismatch repair deficient cancer	For the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. The safety and effectiveness of pembrozulimab in pediatric patients with MSI-H central nervous system cancers have not been established.		√
Colorectal cancer (CRC)	For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC, without KRAS, NRAS and BRAF genomic tumor aberrations.	√	
	For the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test.		√
Gastric cancer	In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma.		√
Esophageal cancer	For the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either in combination with platinum- and fluoropyrimidine-based chemotherapy, or as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA approved test.		√
	For the treatment of patients with locally advanced or metastatic esophageal squamous cell carcinoma after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an approved test.	√	
	In combination with platinum- based chemotherapy for the first-line treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation.	√	
Cervical cancer	As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.		√
	In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.		√
Hepatocellular carcinoma (HCC)	For the treatment of patients with HCC who have been previously treated with sorafenib.		√
Merkel cell carcinoma (MCC)	For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.		√
Renal cell carcinoma (RCC)	In combination with axitinib, for the first-line treatment of adult patients with advanced RCC.		√
	In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.		√
	For the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.		√
Endometrial carcinoma	In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.		√
	As a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.		√

High tumor mutational burden (TMB-H) cancer	For the treatment of adult and pediatric patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. The safety and effectiveness of pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established.		√
Cutaneous squamous cell carcinoma (cSCC)	For the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.		√
Triple-negative breast cancer (TNBC)	For the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.		√
	In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.		√

*: Including first-line and above treatment.

(3) Toripalimab

In December 2018, NMPA conditionally approved the marketing and registration of toripalimab on the basis of efficacy data from the completed Phase II study and the safety data of seven clinical studies in advanced melanoma in China conducted by Shanghai Junshi Biosciences. The indications of toripalimab approved by NMPA are listed in Table 3.

Table 3 Indications approved by NMPA for toripalimab

Tumor	Indications	NMPA
Melanoma	For the treatment of patients with unresectable or metastatic melanoma who have been previously treated with systemic therapy.	√
Nasopharyngeal carcinoma	For the treatment of patients with relapsed/metastatic nasopharyngeal carcinoma after 2 or more lines of systemic therapy.	√
	In combination with cisplatin and gemcitabine for the first-line treatment of patients with locally advanced or metastatic nasopharyngeal carcinoma.	√
Urothelial carcinoma	Patients with locally advanced or metastatic urothelial carcinoma who have been previously treated.	√
Esophageal cancer	In combination with platinum-based chemotherapy for the first-line treatment of patients with locally advanced or metastatic esophageal squamous cell carcinoma.	√

(4) Sintilimab

In December 2018, sintilimab was officially approved for commercial release by NMPA on the basis of the results of the ORIENT-1 study conducted by Cinda/Lilly Company. The indications of sintilimab approved by NMPA are listed in Table 4.

Table 4 Indications approved by NMPA for sintilimab

Tumor	Indications	NMPA
Hodgkin lymphoma	For the treatment of patients with relapsed or refractory classical Hodgkin lymphoma that has relapsed after 2 or more lines of systemic therapy.	√
Non-small cell lung cancer	In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with advanced non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	√
	In combination with gemcitabine and platinum chemotherapy, as first-line treatment of patients with unresectable, locally advanced or metastatic squamous NSCLC.	√
Hepatocellular carcinoma	In combination with bevacizumab for the first-line treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.	√
Esophageal cancer	In combination with chemotherapy (cisplatin + paclitaxel/cisplatin + 5- fluoropyrimidine) for the first-line treatment of patients with esophageal squamous cell carcinoma.	√

Gastric cancer	In combination with chemotherapy (oxaliplatin + capecitabine), for the first-line treatment of patients with unresectable, locally advanced, relapsed or metastatic gastric or gastroesophageal junction adenocarcinoma.	√

(5) Camrelizumab

In May 2019, camrelizumab was officially approved for marketing by NMPA on the basis of the results of SHR-1210-II-204 study conducted by Jiangsu Hengrui Pharmaceuticals Company. The indications of camrelizumab approved by NMPA are listed in Table 5.

Table 5 Indications approved by NMPA for camrelizumab

Tumor	Indications	NMPA
Hodgkin lymphoma	For the treatment of patients with relapsed or refractory classical Hodgkin lymphoma that has relapsed after 2 or more lines of systemic therapy.	√
Hepatocellular carcinoma	For the treatment of patients with advanced hepatocellular carcinoma who have been previously systemic treatment with sorafenib and/or oxaliplatin.	√
Non-small cell lung cancer	In combination with pemetrexed and carboplatin chemotherapy, as first-line treatment of patients with unresectable, locally advanced or metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	√
	In combination with paclitaxel and carboplatin, as first-line treatment of patients with metastatic squamous NSCLC.	√
Esophageal cancer	For the treatment of patients after one or more prior lines of therapy with locally advanced or metastatic esophageal squamous cell carcinoma.	√
	In combination with paclitaxel and cisplatin as first-line treatment of patients with advanced esophageal squamous cell carcinoma.	√
Nasopharyngeal carcinoma	For the treatment of patients after two or more prior lines of therapy with advanced nasopharyngeal carcinoma.	√
	In combination with cisplatin and gemcitabine as first-line treatment of patients with locally advanced or metastatic nasopharyngeal carcinoma.	√

(6) Tislelizumab

In December 2019, tislelizumab was officially approved for marketing by NMPA based on the results of the BGB-A317-314 study by BeiGene Company. The indications of tislelizumab approved by NMPA are listed in Table 6.

Table 6 Indications approved by NMPA for tislelizumab

Tumor	Indications	NMPA
Hodgkin lymphoma	For the treatment of patients with relapsed or refractory classical Hodgkin lymphoma that has relapsed after 2 or more lines of systemic therapy.	√
Urothelial carcinoma	Patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy and have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	√
Non-small cell lung cancer	In combination with paclitaxel and carboplatin, as first-line treatment of patients with unresectable, locally advanced or metastatic squamous NSCLC.	√
	In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with unresectable, locally advanced or metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	√
	For the treatment of patients after two or more prior lines of therapy with locally advanced or metastatic NSCLC.	√
Hepatocellular carcinoma	As a single agent for the treatment of HCC patients after one or more prior lines of systemic therapy.	√
MSI-H/dMMR solid tumors	For the treatment of adult patients with advanced, unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.	√
Esophageal cancer	For the treatment of patients after one or more prior lines of therapy with locally advanced or metastatic esophageal squamous cell carcinoma.	√
Nasopharyngeal carcinoma	For the first-line treatment of patients with relapsed or metastatic nasopharyngeal carcinoma.	√

(7) Durvalumab

Durvalumab was developed by AstraZeneca Co., Ltd., and was approved for marketing in the US in May 2017 for the treatment of NSCLC and small cell lung cancer. It was marketed in China in December 2019 and is the first PD-L1 inhibitor marketed in China for the treatment of patients with non-resectable and stage III non-small cell lung cancer who have not progressed after platinum-based chemotherapy with concomitant radiotherapy. In February 2021, AstraZeneca applied to FDA to

voluntarily withdraw the indication for second-line treatment of advanced bladder cancer. The indications of durvalumab approved by NMPA and FDA are listed in Table 7.

Table 7 Indications approved approved by NMPA and FDA for durvalumab

Tumor	Indications	NMPA	FDA
Non-small cell lung cancer (NSCLC)	For the treatment of adult patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.	√	√
Small cell lung cancer (SCLC)	In combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).		√
Biliary tract cancer (BTC)	In combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic BTC.		√

(8) Atezolizumab

Atezolizumab was developed by Roche and approved for marketing by FDA in May 2016 for nine indications in five tumor types, including lung, liver, and urologic tumors, and melanoma. It was approved in mainland China for the first-line treatment of extensive-stage small cell lung cancer and in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma who have not received previous systemic therapy. The indications of atezolizumab approved by NMPA and FDA are listed in Table 8. In July 2021, the indication for atezolizumab in combination with paclitaxel and an anthracycline chemotherapeutic agent for triple-negative breast cancer was withdrawn by FDA.

Table 8 Indications approved by NMPA and FDA for atezolizumab

Tumor	Indications	NMPA	FDA
Non-small cell lung cancer (NSCLC)	For the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥50% of tumor cells [TC ≥50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥10% of the tumor area [IC ≥10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.	√	√
	In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.		√
	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.		√
	For the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving atezolizumab.		√
	In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	√	
	As adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.	√	√
Small cell lung cancer (SCLC)	In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).	√	√
Hepatocellular carcinoma (HCC)	In combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.	√	√
Urothelial carcinoma	For the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥5% of the tumor area), as determined by an FDA-approved test, or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.		√

Melanoma	In combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.		√

(9) Ipilimumab

Ipilimumab was developed by Bristol-Myers Squibb Company (BMS), and was approved for marketing by FDA in March 2011 for nine indications in six tumor types, including melanoma, renal cell tumor, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer and malignant pleural mesothelioma. It was approved in mainland China for the first-line treatment of malignant pleural mesothelioma. The indications of ipilimumab approved by NMPA and FDA are listed in Table 9.

Table 9 Indications approved by NMPA and FDA for ipilimumab

Tumor	Indications	NMPA	FDA
Malignant pleural mesothelioma	Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.	√	√
Melanoma	Treatment of unresectable or metastatic melanoma in adults and pediatric patients (≥12 years of age).		√
	Treatment of adult patients with unresectable or metastatic melanoma, in combination with nivolumab.		√
	Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.		√
Renal cell carcinoma (RCC)	Treatment of patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab.		√
Colorectal cancer	Treatment of adult and pediatric patients (≥12 years of age) with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab.		√
Hepatocellular carcinoma	Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab.		√
Non-small cell lung cancer (NSCLC)	Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab.		√
	Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.		√
Esophageal cancer	Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first line treatment in combination with nivolumab.		√

(10) Penpulimab

In August 2021, penpulimab was officially approved for marketing by NMPA based on the results of AK105-201 study by Akeso biopharmaceutical. Indications of penpulimab: It is used for adult patients with relapsed or refractory classic Hodgkin’s lymphoma who have undergone at least second-line systemic chemotherapy.

(11) Zimberelimab

In August 2021, zimberelimab was officially approved for marketing by NMPA based on the results of GLS-010 study by Gloria Biosciences. Indications of zimberelimab: It is used for adult patients with relapsed or refractory classic Hodgkin's lymphoma who have undergone at least second-line systemic chemotherapy.

(12) Envafolimab

In November 2021, envafolimab was officially approved for marketing by NMPA based on the results of CN006 study by Alphamab Oncology company. The indications of envafolimab approved by NMPA are as listed in Table 10.

Table 10 Indications approved by NMPA for envafolimab

Tumor	Indications	NMPA
Colorectal cancer	For the treatment of patients with advanced colorectal cancer who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan.	√
Solid tumors	For the treatment of patients with other solid tumors who have been previously treated but no satisfactory treatment.	√

(13) Sugemalimab

In December 2021, sugemalimab was officially approved for marketing by NMPA based on the results of CS1001-302 study by CStone pharmaceuticals. The indications of sugemalimab approved by NMPA are listed in Table 11.

Table 11 Indications approved by NMPA for sugemalimab

Tumor	Indications	NMPA
Non-small cell lung cancer	In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	√
	In combination with paclitaxel and carboplatin, as first-line treatment of patients with metastatic squamous NSCLC.	√
	For the treatment of patients with unresectable, Stage III non-small cell lung cancer whose disease has not progressed following concurrent platinum-based chemotherapy and chemoradiotherapy.	√

(14) Serplulimab

In March 2022, serplulimab was officially approved for marketing by NMPA based on the results of HLX10-010-MSI201 study by Henlius. The indications of serplulimab approved by NMPA are listed in Table 12.

Table 12 Indications approved by NMPA for serplulimab

Tumor	Indications	NMPA
Colorectal cancer	For the treatment of patients with advanced colorectal cancer who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan.	√
Gastric cancer	Patients with advanced gastric cancer who have been previously treated with two or more of therapy but progressed and no satisfactory treatment.	√
Solid tumors	For the patients with solid tumors after first-line therapy and has progressed or no satisfactory treatment.	√

(15) Cadonilimab

In June 2022, based on the results of AK104 study, cadonilimab was officially approved by NMPA for marketing by Guangdong Kangfang Biological Company for the treatment of patients with recurrent or metastatic cervical cancer who have failed prior platinum-based chemotherapy.

2.1.2 Usage and dosage for PD-1/PD-L1 inhibitors

There are currently two modes of dosage design for PD-1 inhibitors: body weight-based or fixed dosage. The dosage of PD-1 inhibitors differs between domestic and foreign package inserts. See Table 13 for details.

Table 13 Usage and dosage for PD-1/PD-L1 inhibitors

Drugs	NMPA-approved usage and dosage	FDA-approved usage and dosage
Nivolumab	Non-small cell lung cancer, squamous cell carcinoma of the head and neck, adenocarcinoma of stomach/esophagogastric junction: 3 mg/kg or 240 mg q2w, intravenous infusion	240 mg q2w, or 480 mg q4w, or 360 mg q3w, intravenous infusion
	Esophageal squamous cancer or adenocarcinoma of esophagogastric junction: 240 mg q2w or 480 mg q4w for 16 weeks, followed by 480 mg q4w, intravenous infusion	In combination with ipilimumab before administration of ipilimumab: 3 mg/kg q2w/q3w (1 mg/kg for metastatic melanoma and hepatocellular carcinoma) or 360 mg q3w, intravenous infusion

	Malignant pleural mesothelioma: 360 mg q3w or 3mg/kg q2w, intravenous infusion	
	Gastric carcinoma, adenocarcinoma of esophagogastric junction or esophageal squamous cancer: 360 mg q3w or 240 mg q2w, intravenous infusion	< 40 kg pediatric usage: 3 mg/kg q2w/q3w, intravenous infusion
	Esophageal squamous cancer: 240 mg q2w or 480 mg q4w, intravenous infusion	
Pembrolizumab	200 mg q3w or 400 mg q6w, intravenous infusion	200 mg q3w or 400 mg q6w, intravenous infusion
		Pediatric patients: 2 mg/kg (less than 200 mg) q3w, intravenous infusion
Toripalimab	3 mg/kg q2w, intravenous infusion	/
Sintilimab	200 mg q3w, intravenous infusion	/
Camrelizumab	Classical Hodgkin lymphoma, esophageal squamous cancer, nasopharyngeal carcinoma: 200 mg q2w, intravenous infusion	/
	Advanced hepatocellular carcinoma: 3 mg/kg q3w, intravenous infusion	
	Advanced or metastatic non-squamous non-small cell lung cancer, local recurrence, or metastatic nasopharyngeal carcinoma: 200 mg q3w, intravenous infusion	
Tislelizumab	200 mg q3w, intravenous infusion	/
Durvalumab	10 mg/kg q2w, intravenous infusion	NSCLC: body weight ≥30 kg, 10 mg/kg q2w or 1500 mg q4w; body weight <30 kg, 10 mg/kg q2w, intravenous infusion
		ES-SCLC/BTC: body weight ≥30 kg, 1500 mg q3w (combined chemotherapy), 1500 mg q4w (monotherapy); body weight <30 kg, 20 mg/kg q3w (combined chemotherapy), monotherapy of ES-SCLC: 10 mg/kg q2w, monotherapy of BTC: 20 mg/kg q4w, intravenous infusion
Atezolizumab	1200 mg q3w, intravenous infusion	840 mg q2w or 1200 mg q3w or 1680 mg q4w, intravenous infusion
Ipilimumab	1mg/kg q6w, intravenous infusion	3 mg/kg q3w or 10 mg/kg q3w or 1 mg/kg q3w or 1 mg/kg q6w, intravenous infusion
Penpulimab	200 mg q2w, intravenous infusion	/
Zimberelimab	240 mg q2w, intravenous infusion	/
Envafolimab	150 mg qw, subcutaneous injection	
Sugemalimab	1200 mg q3w, intravenous infusion	/
Serplulimab	3 mg/kg q2w, intravenous infusion	/
Cadonilimab	6 mg/kg q2w, intravenous infusion	/

The combination of PD-1/PD-L1 inhibitors with chemotherapy or other agents is described in detail below:

(1) Pembrolizumab should be administered first when given in combination with chemotherapy.

(2) Camrelizumab should be administered first by intravenous infusion, followed by chemotherapy at least 30 minutes later when it is combined with chemotherapy.

(3) In the case of atezolizumab in the treatment of small cell lung cancer: in the induction phase, atezolizumab is administered intravenously on day 1 at a recommended dose of 1200mg, followed by carboplatin and then by etoposide. Intravenous etoposide is administered on day 2 and day 3. Such drugs should be administered every three weeks for four cycles of treatment.

(4) Atezolizumab for hepatocellular carcinoma (HCC) treatment: Atezolizumab is first administered intravenously at a recommended dose of 1200mg followed by bevacizumab at 15mg/kg. Such drugs should be administered every three weeks.

(5) Atezolizumab in combination with pemetrexed and platinum in treatment of NSCLC: During induction, pemetrexel is administered first, followed by intravenous pemetrexel followed by either carboplatin or cisplatin, and the regimen is administered every three weeks for four or six treatment cycles. Atezolizumab and pemetrexel are administered intravenously every three weeks during maintenance.

(6) When tislelizumab is administered in combination with chemotherapy, if given on the same day, tislelizumab is administered first.

(7) When ipilimumab is used in combination with nivolumab, nivolumab should be administered first, followed by ipilimumab on the same day.

(8) Sintilimab in combination with bevacizumab should be given to the patient at least five minutes apart, and bevacizumab is recommended for the same day.

(9) In combination with fluorouracil and platinum-based chemotherapy, nivolumab should be administered first, followed by fluorouracil and platinum-based chemotherapy.

2.1.3 Configuration and infusion of PD-1/PD-L1 inhibitors[4-22]

All types of PD-1 inhibitors marketed domestically and internationally do not contain a preservative and should, in principle, be prepared immediately before use. The specific steps in the configuration of PD-1/PD-L1/CTLA-4 inhibitors are as follows:

(1) Precautions before PD-1/PD-L1 inhibitors' configuration

Table 14 Precautions before PD-1/PD-L1 inhibitors' configuration

Generic name	Trade name	Specification	Rewarming before configuration	Time to keep after removing from refrigerator	Appearance	Visual inspection
Nivolumab	Opdivo	100 mg:10 mL 40 mg:4 mL	Not mentioned in the instruction	Not mentioned in the instruction. Complete the configuration as soon as possible	Colorless to pale-yellow liquid	May contain light (few) particles
Pembrolizumab	Keytruda	100 mg:4 mL	Return the vial to room temperature (25℃ or below)	(25℃ or below) no more than 24 hours	Clear to slightly opalescent, colorless to slightly yellow solution	Discard the vial if visible particles are observed
Toripalimab	Tuoyi	240 mg:6 mL	Not mentioned in the instruction	Diluent configuration should be completed within 24 hours	Colorless or yellowish clear liquid with slight opalescence	Discard the vial if visible particles or abnormal color are observed
Sintilimab	Daboshu	100 mg:10 mL	Return the vial to room temperature (25℃ or below)	(25℃ or below) no more than 24 hours	Clear to light emulsion, colorless to light yellow liquid	Discard the vial if visible particles are observed
Camrelizumab	Airuika	200 mg (powder)	Redissolve and dilute immediately	Redissolve and dilute immediately after	Colorless or slightly yellow liquid after	Not mentioned in the instruction

			after refrigerator removal	refrigerator removal	resolution	
Tislelizumab	Baizean	100 mg:10 mL	Not mentioned in the instruction	(25℃ or below) no more than 2 hours before diluted	Clear to light emulsion, colorless to light yellow liquid	Discard the vial if visible particles or abnormal color are observed
Durvalumab	Imfinzi	500 mg:10 mL 120 mg:2.4 mL	Not mentioned in the instruction	(Room temperature 25℃) no more than 4 hours	Clear to milky, colorless to slightly yellow liquid	Discard the vial if solution in the bottle is observed to be cloudy, discolored or contain visible foreign matter.
Atezolizumab	Tecentriq	1200 mg/20 ml (60 mg/ml)	Not mentioned in the instruction	Not mentioned in the instruction. Complete the configuration as soon as possible	Colorless to pale-yellow clear liquid	Not mentioned in the instruction
Ipilimumab	Yervoy	50 mg:10 mL 200 mg:40 mL	Not mentioned in the instruction	Room temperature (20℃-25℃) no more than 24 hours	Clear to slightly opaline, colorless to pale yellow liquid	May contain light (few) particles
Penpulimab	Annike	100 mg:10 mL	Return to room temperature before use	Room temperature (25℃ or below) no more than 24 hours	Colorless to pale-yellow clear liquid, no foreign matter	Discard the vial if visible particles are observed
Zimberelimab	Yutuo	120 mg:4 mL	Return the vial to room temperature (25 ℃ or below)	Room temperature (25℃ or below) no more than 24 hours	Colorless to slightly yellow, clear to a micro emulsion liquid	Discard the vial if visible precipitation, flocculation, or particles are observed
Envafolimab	Enweida	200 mg:1 mL	Not mentioned in the instruction	Not mentioned in the instruction. Complete the configuration as soon as possible	Clear liquid	Isolate and store the vial, and replace the normal injection if impurities or precipitates are seen by naked eye.
Sugemalimab	Pfizer	600 mg:20 mL	Not mentioned in the instruction	Not mentioned in the instruction. Complete the configuration as soon as possible	Clear, transparent, no visible particles	Not mentioned in the instruction
Serplulimab	Henlius	100 mg:10 mL	Not mentioned in the instruction	Not mentioned in the instruction. Complete the configuration as soon as possible	Clear to opaline, colorless or pale brownish-yellow liquid	Not mentioned in the instruction
Cadonilimab	Cadoni	125mg:10mL	Return to room temperature before use	Not mentioned in the instruction. Complete the configuration as soon as possible	Colorless to pale-yellow clear liquid, no foreign matter	Discard the vial if visible particles are observed

Note: rewarming refers to taking the drug out of the refrigerator before it is prepared, and placing it at room temperature (20~25℃) for 15~30 min.

(2) Key points of PD-1/PD-L1 inhibitors' configuration

Table 15 Key points of PD-1/PD-L1 inhibitors' configuration

Generic name		Nivolumab	Pembrolizumab	Toripalimab	Sintilimab	Camrelizumab	Tislelizumab	Durvalumab	Atezolizumab	Ipilimumab	Penpulimab	Zimberelimab	Envafolimab	Sugemalimab	Serplulimab	Cadonilimab
Trade name		Opdivo	Keytruda	Tuoyi	Daboshu	Airuika	Baizean	Imfinzi	Tecentriq	Yervoy	Annike	Yutuo	Enweida	Pfizer	Henlius	Cadoni
Specification		100 mg:10 mL 40 mg:4 mL	100 mg:4 mL	240 mg:6 mL	100 mg:10 mL	200 mg (powder)	100 mg:10 mL	500 mg:10 mL 120 mg:2.4 mL	1200 mg/20 ml (60 mg/ml)	50 mg:10 mL 200 mg:40 mL	100 mg:10 mL	120 mg:4 mL	200 mg:1 mL	600 mg:20 mL	100 mg:10 mL	125mg:10 mL
Usage and dosage		3 mg/kg q2w	2 mg/kg q3w	3 mg/kg q2w	200 mg q3w	200 mg q2w	200 mg q3w	10 mg/kg q2w	1200 mg q3w	1 mg/kg q6w	200 mg q2w	240 mg q2w	150 mg qw	1200 mg q3w	3 mg/kg q2w	6mg/kg q2w
Solvent		0.9%NS 5%GS	0.9% NS 5% GS	0.9% NS	0.9% NS	0.9% NS 5% GS	0.9% NS	0.9% NS 5% GS	0.9% NS	0.9% NS 5% GS	0.9% NS	0.9% NS 5% GS	Use the stock solution directly	0.9% NS	0.9% NS	0.9%NS
Packaging material of infusion line		No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction	-	No special requirements in the instruction	No special requirements in the instruction	No special requirements in the instruction
Final concentration		1~10 mg/mL	1~10 mg/mL	1~3 mg/mL	1.5~5.0 mg/mL	Redissolve and transfer to 100mL solvent	1~5 mg/mL	1~15 mg/mL	-	1~4 mg/mL	1.0~5.0 mg/mL	2.4 mg/mL	-	Add 250 mL normal saline	Make the total volume 100 mL	0.2~5.0mg /mL
Storage after configuration	2~8℃	≤24 h	≤24 h (25℃ or below) no more than 6 hours	≤24 h	Keep in dark place: ≤24 h (25℃ or below) no more than 6 hours	≤24 h	≤24 h	≤24 h	≤24 h	≤24 h	≤24 h	≤24 h	No need for configuration	≤24 h	≤24 h	≤4h（包括给药时间）
	Room temperature	20~25℃, room light: ≤8 h	≤6 h	≤8 h	20~25℃, room light: ≤6 h	≤6 h	≤4 h	≤4 h	20~25℃, room light: ≤8 h	≤24 h	20~25℃, room light: ≤6 h	≤4 h		≤6 h (Including infusion time)	≤6 h (Including administration time)	≤4h (Including administration time))

Note: (1) The stock solution and diluent of the medicine should not be frozen. (2) Storage time of the solution at room temperature after configuration under aseptic operation: including storage in the infusion bag and duration of the drug infusion process.

(3) Illustration for PD-1/PD-L1/CTLA-4 inhibitors' configuration procedure

Table 16 Illustration for PD-1/PD-L1/CTLA-4 inhibitors configuration procedure

Generic name	Nivolumab	Pembrolizumab	Toripalimab	Sintilimab	Camrelizumab	Tislelizumab	Durvalumab	Atezolizumab	Ipilimumab	Penpulimab	Zimberelimab	Envafolimab	Sugemalimab	Serpluli mab	Cadonilimab
Trade name	Opdivo	Keytruda	Tuoyi	Daboshu	Airuika	Baizean	Imfinzi	Tecentriq	Yervoy	Annike	Yutuo	Enweida	Pfizer	Henlius	Cadoni
Specification	100 mg:10 mL 40 mg:4 mL	100 mg:4 mL	240 mg:6 mL	100 mg:10 mL	200 mg (powder)	100 mg:10 mL	500 mg:10 mL 120 mg:2.4 mL	1200 mg/20 ml (60 mg/ml)	50 mg:10 mL 200 mg:40 mL	100 mg:10 mL	120 mg: 4 mL	200 mg:1 mL	600 mg:20 mL	100 mg:10 mL	125mg:10 mL
Usage and dosage	3 mg/kg q2w	2 mg/kg q3w	3 mg/kg q2w	200 mg q3w	200 mg q2w	200 mg q3w	10 mg/kg q2w	1200 mg q3w	1 mg/kg q6w	200 mg q2w	240 mg q2w	150 mg qw	1200 mg q3w	3 mg/kg q2w	6mg/kg q2w
Aperture of infusion line filter (μm)	0.2~1.2	0.2~5	0.2 or 0.22	0.2~5	0.2	0.2 or 0.22	0.2 or 0.22	-	-	0.2 or 0.22	0.2	-	-	0.2~5	0.2 or 0.22
0.2 μm	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√
0.22 μm	√	√	√	√	×	√	√	√	√	√	×	×	√	√	√
5 μm	×	√	×	√	×	×	×	√	√	×	×	×	√	√	×
Infusion way	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Subcutaneous injection	Intravenous infusion	Intravenous infusion	Intravenous infusion
Infusion time	30 or 60 min	>30 min	30~60 min	30~60 min	30~60 min	30~60 min	>60 min	30~60 min	30 min	60 min-120 min	>45 min	0.06 ml/s	>60 min	30~60 min	60±10min
Whether need to avoid light during infusion	20~25℃ room light: no more than 6 hours (including the time of administration)	25℃ or below: no more than 6 hours (light is not mentioned in the instruction)	Room temperature: no more than 8 hours (including the time of administration. Light is not mentioned in the instruction)	20~25℃ room light: no more than 6 hours (including the time of administration)	Room temperature: no more than 6 hours after diluted (including the time of infusion)	Return to room temperature (25℃ and below) and complete infusion within 4 hours (light is not mentioned	Room temperature 25℃ or below: no more than 4 hours (light is not mentioned in the instruction)	20~25℃ room light: no more than 8 hours (including the time of administration)	25℃ or below: no more than 24 hours (light is not mentioned in the instruction)	20~25℃ room light: no more than 6 hours (including the time of administration)	25℃ room temperature: no more than 8 hours (light is not mentioned in the instruction)	-	Room temperature: no more than 6 hours (including the time of administration. Light is not mentioned in the instruction)	Room temperature: no more than 6 hours (Including the time of administration. Light is not	Room temperature: no more than 4 hours (Including the time of administration. Light is not mentioned in the instruction

						in the instruction)								mentioned in the instruction)	)

Note: (1) There was no mention of vial washing after extraction of various PD-1 inhibitors. (2) The remaining liquid medicine should be treated as medical waste together with the original packaging vial; (3) Avoid the release of drugs in the environment. Prohibit drugs from being discarded in waste water or domestic garbage. (4) Any unused medicines, liquid wastes or other wastes should be disposed of in accordance with the relevant regulations of the medical institutions.

(4) Safe infusion of PD-1/PD-L1 inhibitors

- Key points should be noticed during the infusion of PD-1/PD-L1 inhibitors are listed as follows:

①Family members should accompany the patients for the first administration.

②Effective intravenous access should be established with 0.9% NS injection before administration.

③Choose an appropriate infusion set, adjust the infusion speed according to the infusion time, and instruct the patient and family members not to adjust the infusion speed by themselves.

④Nurses make regular rounds throughout the course to check infusion lines and patients' conditions.

⑤In case of infusion reaction, the process below should be followed: Continue the treatment under close monitoring in patients with mild or moderate infusion reactions; Analgesic/anti-inflammatory medications and antihistamines can be considered for prophylaxis; Stop the infusion and permanently discontinue for severe and life-threatening infusion reactions.

⑥Flush the tubes with 0.9% NS after the infusion.

⑦There is no need for ECG monitoring during the whole course of administration.

Table 17 Key points during the infusion of PD-1/PD-L1 inhibitors

Generic name	Nivolumab	Pembrolizumab	Toripalimab	Sintilimab	Camrelizumab	Tislelizumab	Durvalumab	Atezolizumab	Ipilimumab	Penpulimab	Zimberelimab	Envafolimab	Sugemalimab	Serplulimab	Cadonilimab
Trade name	Opdivo	Keytruda	Tuoyi	Daboshu	Airuika	Baizean	Imfinzi	Tecentriq	Yervoy	Annike	Yutuo	Enweida	Pfizer	Henlius	Cadoni
Specification	100 mg:10 mL 40 mg:4 mL	100 mg:4 mL	240 mg:6 mL	100 mg:10 mL	200 mg (powder)	100 mg:10 mL	500 mg:10 mL 120 mg:2.4 mL	1200 mg/20 mL	50 mg:10 mL 200 mg:40 mL	100 mg:10 mL	120 mg：4 mL	200 mg:1 mL	600 mg:20 mL	100 mg:10 mL	125mg:10mL
Usage and dosage	3 mg/kg q2w	2 mg/kg q3w	3 mg/kg q2w	200 mg q3w	200 mg q2w	200 mg q3w	10 mg/kg q2w	1200 mg q3w	1 mg/kg q6w	200 mg q2w	240 mg q2w	150 mg qw	1200 mg q3w	3 mg/kg q2w	6mg/kg q2w
Aperture of infusion line filter (μm)	0.2~1.2	0.2~5	0.2 or 0.22	0.2~5	0.2	0.2 or 0.22	0.2 or 0.22	-	-	0.2 or 0.22	0.2	-	-	0.2~5	0.2or 0.22
0.2 μm	√	√	√	√	√	√	√	√	√	√	√	×	√	√	√
0.22 μm	√	√	√	√	×	√	√	√	√	√	×	×	√	√	√
5 μm	×	√	×	√	×	×	×	√	√	×	×	×	√	√	×
Infusion way	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Subcutaneous injection	Intravenous infusion	Intravenous infusion	Intravenous infusion
Infusion time	30 or 60 min	>30 min	30~60 min	30~60 min	30~60 min	30~60 min	>60 min	30~60 min	30 min	60 min-120 min	>45 min	0.06 ml/s	>60 min	30~60 min	60±10min
Whether need to avoid light during infusion	20~25℃ room light: no more than 6 hours (including the time of administration)	25℃ or below: no more than 6 hours (light is not mentioned in the instruction)	Room temperature: no more than 8 hours (including the time of administration, Light is not mentioned in the instruction)	20~25℃ room light: no more than 6 hours (including the time of administration)	Room temperature: no more than 6 hours after diluted (including the time of infusion)	Return to room temperature (25℃ and below) and complete infusion within 4 hours (light is not mentioned in the instruction)	Room temperature 25℃ or below: no more than 4 hours (light is not mentioned in the instruction)	20~25℃ room light: no more than 8 hours (including the time of administration)	25℃ or below: no more than 24 hours (light is not mentioned in the instruction)	20~25℃ room light: no more than 6 hours (including the time of administration)	25℃ room temperature: no more than 8 hours (light is not mentioned in the instruction)	-	Room temperature: no more than 6 hours (including the time of administration. Light is not mentioned in the instruction)	Room temperature: no more than 6 hours (including the time of administration. Light is not mentioned in the instruction)	Room temperature: no more than 4 hours (include the time of administration. Light is not mentioned in the instruction)

Note: (1) intravenous push or single rapid intravenous administration should not be used. (2) Do not use the same infusion tube with other medications. (3) Requirements of infusion set: sterile, without pyrogen, low protein binding, meet the pore size requirements. (4) All kinds of infusion sets should be stored by classification, counted regularly, and used in sequence. (5) Various

PD-1/PD-L1 inhibitors are intended for one-time use only, and any remaining drugs after a single use must be discarded. (6) Avoid systemic corticosteroids or immunosuppressants before using PD-1/PD-L1 inhibitors.

2.1.4 Use of PD-1/PD-L1/CTLA-4 inhibitors in specific population

PD-1/PD-L1 inhibitors exert anti-tumor effects by activating the body's immune system, with unique pharmacological effects. Adverse effects include immune-related and infusion-related adverse events and potential off-target effects. Compared with traditional antitumor drugs, PD-1/PD-L1/CTLA-4 inhibitors may involve special population with autoimmune diseases, patients with hepatitis, patients undergoing transplantation, etc. Specific patients carry the risk of potential immune-related adverse effects or other unexpected adverse effects. Advantages and disadvantages should be weighed and carefully chosen prior to the medication administration. See Table 18 for the recommended use of PD-1/PD-L1/CTLA-4 inhibitors in special population.

Table 18 Recommended use of PD-1/PD-L1/CTLA-4 inhibitors in special population

Special population	Recommendations
Pediatric patients	All PD-1/PD-L1/CTLA-4 inhibitors previously marketed in China are indicated in the instructions: The safety and effectiveness have not been established in pediatric patients age under 18 years of age. Atezolizumab did not show clinical benefit in pediatric patients in a clinical trial.
	Foreign instruction manual of nivolumab, pembrolizumab and ipilimumab: There are pediatric indications and usage (see the section on clinical indications, usage and dosage of PD-1 inhibitors for details).
Elderly patients	Patients over 65 years old: Use with caution with no need to adjust dosage.
Patients with poor general condition (ECOG ≥2)	Use PD-1/PD-L1 inhibitors with caution.
Patients with renal insufficiency	Pembrolizumab, nivolumab, tislelizumab, durvalumab, ipilimumab, penpulimab, and sugemalimab：No dose adjustment is recommended in patients with mild or moderate renal impairment. Medication data for patients with severe renal impairment are limited.
	Toripalimab, sintilimab, camrelizumab, zimberelimab, envafolimab, and serplulimab: Use with caution in patients with mild renal impairment without dose adjustment. It is not recommended in patients with moderate to severe renal insufficiency. Atezolizumab: No dose adjustment is recommended in patients with renal impairment. Tislelizuma and durvalumab: It is not recommended for patients with severe renal impairment.
Patients with hepatic dysfunction	Pembrolizumab: No dose adjustment is recommended in patients with mild hepatic impairment. Medication data for patients with moderate to severe hepatic impairment are limited.
	Nivolumab: No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Medication data for patients with severe hepatic impairment are limited. Patients with severe (total bilirubin >3 ULN and any AST) liver injury should use this product with caution.
	Toripalimab, sintilimab, camrelizumab, tislelizumab, durvalumab, atezolizumab, zimberelimab, penpulimab, envafolimab, serplulimab, and sugemalimab: Use with caution in patients with mild hepatic impairment without dose adjustment. It is not recommended for patients with moderate to severe hepatic impairment.
	Ipilimumab: No dose adjustment is recommended in patients with mild hepatic impairment. Use with caution in patients with baseline aminotransferase ≥5 ULN or bilirubin >3 ULN。
Pregnant patients	PD-1/PD-L1/CTLA-4 inhibitors are not recommended.
Lactating patients	Pembrolizumab, nivolumab, and ipilimumab: Risk to the infant/newborn cannot be ruled out so that stop breastfeeding or discontinue treatment is advised.
	Toripalimab and camrelizumab: Lactating women should stop breastfeeding during treatment for at least 2 months after the last dose.
	Sintilimab, atezolizumab, zimberelimab, penpulimab, and envafolimab: Lactating women should stop breastfeeding during treatment for at least 5 months after the last dose.
	Durvalumab: Lactating women should stop breastfeeding during treatment for at least 3 months after the last dose.

	Serplulimab and sugemalimab: Lactating women should stop breastfeeding during treatment for at least 6 months after the last dose.
Patients with autoimmune diseases [16]	Consider to use in some cases (the dose of prednisone should be minimized to less than 10 mg/day before initiating PD-1 inhibitor therapy). Not recommended for patients with autoimmune neurological diseases or life-threatening autoimmune diseases, especially those who cannot be controlled by immunosuppressive drugs or need high-dose immunosuppressive drugs to control the disease. ● Atezolizumab: Data on patients with autoimmune disease are not available, and atezolizumab should be used with caution in such patients, and the potential risk-benefit should be evaluated before use. ● Durvalumab: No relevant data is available.
Carriers of hepatitis B virus (HBV) or hepatitis C virus (HCV)	PD-1/PD-L1 inhibitors can be used with efficacy comparable to uninfected patients. ● Patients with HBV infection: PD-1 inhibitor therapy should be initiated only after HBV-DNA is below 2000 IU/mL. Even if HBV-DNA quantification is not high, antiviral therapy prior to the first PD-1/PD-L1 inhibitor administration and regular monitoring are recommended when HBsAg (+) and/or HBcAb (+). ● Patients with HCV infection: Antiviral therapy with a PD-1/PD-L1 inhibitor is unnecessary, but regular monitoring of viral RNA levels is required.
Patients receiving hematopoietic stem cells or organ transplant [16]	Consider to use with caution in some cases (for example, no evidence for graft rejection and in the maintenance period of immunotherapy, weak evidence, expert recommendation).
Carriers of the AIDS virus (HIV)	Consider to use in some cases.
Immunized patients	PD-1/PD-L1 inhibitors can be used. ● Vaccines with inactivated or inactivated preparations are permitted. ● Live vaccines are not recommended.
NSCLC patients with positive driver gene mutations [16]	Consider to use in some cases (weak evidence, expert recommendation).
Patients receiving other immune checkpoint inhibitors [16]	Consider to use in some cases (weak evidence, expert recommendation).

2.2 Comprehensive management of adverse events of immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs), like other anti-tumor drugs, show definite efficacy with various adverse events related to their mechanism, which are known as immunotherapy-related adverse effects (irAEs). The anticancer mechanism of ICIs mainly acts on the body's immune system. Theoretically, such adverse events can occur in any tissue and organ, among which adverse events in the skin, endocrine system, liver, gastrointestinal tract, lung, rheumatoid/skeletal muscle, and perfusion reactions are the most common, while the adverse events in nerves, blood, kidney, heart, and eye are less frequent[23-26]. IrAEs can happen at any time, but most of them are mild, reversible or only temporary, with the exception of adverse effects on endocrine organs that may last for a long period of time. The incidence of cardiac and nervous system toxicity from ICIs is low, but the consequences are severe, among which myocarditis, pulmonary, and nervous system adverse effects are particularly to be noted. Pharmacists should pay attention to the comprehensive management of ICIs-related adverse events, including irAEs adverse reaction spectrum, risk factors, identification of special population, medication and integrated monitoring, including the following:

(1) Understand the adverse reaction spectrum of irAEs. The most common ones include colitis and diarrhea, and adverse reactions in the skin and mucous membrane, liver, and endocrine. IrAEs can also occur in rarely affected organs, including heart, kidney, eyes, nerves, blood and other organs and systems. Generally speaking, PD-1 and PD- L1 inhibitors are more tolerant than CTLA-4 inhibitors. Studies have shown that grade 3 or 4 irAEs accounts for 31% of all irAEs of CTLA-4 inhibitors, but only 10% of PD-1 inhibitors. Grade 3 or 4 irAEs of the bispecific PD-1 and CTLA-4

antibody candonilimab accounts for 28% of the cases. Patients treated with CTLA-4 inhibitors are more likely to have colitis, hypophysitis and rash, while patients treated with PD-1 inhibitors are more likely to have pneumonia and thyroiditis[27-30]. Different ICIs' toxicity spectra vary. Nivolumab is likely to cause endocrine toxicity, and pembrolizumab can lead to arthritis, pneumonia, and liver toxicity; Camrelizumab is likely to cause reactive hyperplasia of the skin capillaries; Atezolizumab is likely to cause hypothyroidism, nausea, and vomiting; Cadonilimab is likely to cause anemia, hypothyroidism and impaired liver function; Ipilimumab is likely to cause rash, colitis, and nephrotoxicity [23].

(2) Identify risk factors of immune-related adverse events, including personal and family history of autoimmune diseases, tumor infiltration, opportunistic pathogens, combined medication and occupational exposures.

(3) Beware of special patients, including elderly patients (≥65 years old), pregnant and lactating women, patients with autoimmune diseases, viral carriers, patients with organ transplantation or hematopoietic stem cell transplantation.

(4) Master the treatment of irAEs, including systemic corticosteroids or other immunosuppressants, intravenous immunoglobulin and plasmapheresis.

(5) Evaluate and closely monitor irAEs in the whole process, including three steps: before, during and after treatment.

Before treatment: Patients should be assessed for their susceptibility to irAEs, including disease history and family history, general medical conditions, autoimmune disease, baseline laboratory and imaging examination (chest, abdomen, pelvic CT and head MRI in most cases), as well as adverse events of previous treatments.

During treatment: Closely monitor and timely assess new symptoms in time; Three possibilities should be considered for adverse events during treatment: disease progression, accidental events or irAEs. It is important to differentiate adverse events during treatment from side effects caused by combined treatment with other drugs or from the symptoms of the disease itself.

After treatment: IrAEs should be considered when the disease is stable. The assessment should be made every three months in the first year and every six months thereafter.

(6) Patient education: Patients and/or their family members/caregivers should be informed of the types and manifestations of potential adverse events of immunotherapy before ICIs treatment begins. Patients need to be accompanied by their family members/caregivers when taking medicine for the first time. In case of adverse events, patients and/or their family members/caregivers should report symptoms directly to the treatment team (doctors, nurses, and pharmacists). A clear understanding of ICIs-related adverse reactions by patients and/or their family members/caregivers is important for early identification, timely reporting and effective treatment of adverse events.

2.2.1 Spectrum of irAEs

(1) Adverse skin events[23]

Adverse skin events are the most common irAEs associated with PD-1 inhibitors, which can affect up to 50% of patients, most of whom are mild reactions. The most common adverse skin events are erythema, rash (maculopapule and pustules), pruritus, reactive cutaneous capillary endothelial hyperplasia (RCCEP is more common in patients treated with karelizumab, of which 66.8% were treated with karelizumab alone) and vitiligo (vitiligo is most common in melanoma patients). Rare adverse events include alopecia areata, stomatitis, xerosis cutis and photosensitivity; There are also reports of psoriasis exacerbation, and psoriasis or lichenoid skin reactions in patients with

no previous cutaneous history[31]. Rare are toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS) and acute febrile neutrophilic dermatosis (Sweet syndrome). Adverse skin reactions occur early, usually within two to four weeks after PD-1 inhibitor treatment.

(2) Adverse endocrine events[23]

ICIs-related adverse endocrine events mainly include thyroid dysfunction (hypothyroidism, thyroid function hyperfunction and thyroiditis) and acute pituitary gland inflammation (central hypothyroidism, adrenal insufficiency at central and lower gonadotropin gonad hypofunction disease), with the incidence of 5~10% and 0.4% respectively. The incidence of hypothyroidism caused by candonilimab (basically grade 1~2 irAEs) is about 20%. Other immune-related endocrine disorders have also been reported, but rarely occur, including primary adrenal hypofunction, Type I diabetes, hypercalcemia and hypoparathyroidism. Adverse endocrine events related to PD-1 inhibitors occur over a large time span, but usually appear slowly, usually in week 10~24 during treatment, while endocrine toxicity related to ipilimumab treatment, such as hypophysitis, may occur in the earliest week 7~8.

During ICIs treatment, the possibility of hypothyroidism should be considered in patients with unexplained weakness, weight gain, hair loss, chills, constipation, depression, and other symptoms; If the patient has unexplained palpitations, sweating, increased eating and defecation and weight loss, the possibility of hyperthyroidism should be considered; If the patient has unexplained persistent headache and/or visual disturbance, immediate evaluation of hypophysitis is needed., but pay attention to distinguish brain metastasis cancer, pia mater disease and cerebrovascular disease.

(3) Adverse hepatic events[23]

ICIs-related hepatic adverse events mainly include immune-related hepatitis, which is characterized by elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) with or without elevated bilirubin. Generally, there are no characteristic clinical manifestations, and some patients may be accompanied by non-specific manifestations such as fatigue, fever, loss of appetite, early satiety. When bilirubin rises, yellow skin, sclera staining and brown urine may appear. The incidence of hepatitis is about 5% when PD-1 inhibitors are used alone, and increased to 25~30% when combined with CTLA-4 inhibitors. The incidence of hepatitis caused by candonilimab is 2%. ICIs-related adverse hepatic events can occur at any time, most often in week 8~12 after the first use. The incidence of adverse hepatic events varies greatly, ranging from 0.7% to 16%, depending on the type and dosage of ICIs, and the combination therapy is used or not. The incidence of adverse hepatic events of any grade is the lowest among PD-1 inhibitors (0.7%~2.1%) and about 0.9%~12% among PD-L1 inhibitors and CTLA-4 inhibitors.

The hepatic function should be comprehensively assessed before the first ICIs treatment. For patients with HBV infection, immunotherapy should be started only after the HBV-DNA is lower than 2000IU/ml. Infliximab is not considered for the treatment of patients with ICIs-related adversehepatic events because of its potential hepatotoxicity.

(4) Adverse gastrointestinal events[23,25]

ICIs-related adverse gastrointestinal events are one of the most common adverse reactions, mainly manifested as diarrhea and colitis. Diarrhea is the most common adverse gastrointestinal reaction, with an incidence of <19%. It usually occurs after an average of three ICIs treatment, or it may occur immediately after the first treatment. When diarrhea complicated with abdominal pain, bloody stool, mucous stool and/or fever occur, we should be alert to the occurrence of colitis. In addition, diarrhea and/or colitis can also appear several months after discontinuation of immunotherapy, with clinical manifestations similar to those of chronic inflammatory bowel disease. The risk of gastrointestinal toxicity of CTLA-4 inhibitors is much higher than that of PD-1/PD-L1 inhibitors, and it can occur

at any time during treatment, which needs special attention. The median time of gastrointestinal toxicity of PD-1/PD-L1 inhibitors is 6~8 weeks after medication, and that of occurrence of immune-related diarrhea and colitis with candonilimab is 4 weeks.

(5) Adverse pulmonary events[23]

Immune-associated pneumonia is a rare but fatal serious adverse events, accounting for 35% of deaths related to PD-1/PD-L1 inhibitors. Clinical symptoms mainly include dyspnea (53%), cough (35%), fever (12%) or chest pain (7%), Occasionally, hypoxia will occur and worsen rapidly, leading to respiratory failure. However, about 1/3 patients have no symptoms except for imaging abnormalities (ground-glass nodules or patchy nodules infiltrating). Clinical studies have shown that the incidence of pneumonia in patients receiving PD-1/PD-L1 inhibitor monotherapy is less than 5%, and the incidence of pneumonia above grade 3 is 0~1.5%. Patients who received PD-1 inhibitor monotherapy have a higher incidence of immune-associated pneumonia than those who received PD-L1 inhibitors, which resulted in 3.6% and 1.3% of all grades of pneumonia respectively, and 1.1% and 0.4% of severe pneumonia. Immune-associated pneumonia can occur at any stage of treatment, with a median occurrence time of about 2.8 months.

(6) Adverse osteoarticular and muscular events[23,25,26]

ICIs-related adverse osteoarticular and muscle events mainly include swelling and pain of joint, inability to move/stiffness in the morning for 30~60 minutes; NSAIDS or glucocorticoids can improve related symptoms. The incidence of arthralgia is about 15% in patients treated with ICIs, and that of arthritis has not been systematically reported. Myositis caused by ICIs is rare, but can be life-threatening in severe cases. It may lead to fulminant necrosis, including rhabdomyolysis involving myocardium, which is life-threatening and requires emergency treatment.

(7) Infusion events[23,24]

ICIs-related infusion events show fixed symptoms such as fever, stiffness, pruritus, hypotension, dyspnea, chest discomfort, rash, urticaria, angioedema, wheezing or tachycardia, and anaphylactic reactions requiring emergency management. The incidence of most ICIs-related infusion reactions is less than 10%, and most of them are mild and occur during the first infusion

(8) Adverse neurological events[23,32]

ICIs-related adverse neurological events are rare, with the incidence of 3.8% in patients treated with CTLA-4 inhibitors and about 6.1% in patients treated with PD-1 inhibitors. The incidence of grade 3~4 and above immune-related nervous system toxicity is less than 1%. The adverse neurological reactions include myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathy, aseptic meningitis, and encephalitis. The median occurrence time is week 6 after taking the medicine.

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(9) Adverse hematologic events[23,25,26]

ICIs-related adverse hematologic events are rare, but they do occur, including hemolytic anemia, aplastic anemia, thrombocytopenia and hemophilia. The active adverse reactions of blood system should be distinguished from the abnormal results of temporary tests at the initial stage of immunotherapy. Currently, the best treatment for immune-related adverse reactions in hematology system remains uncertain. It is suggested to consult haematology department in time to assist in diagnosis and treatment.

(10) Adverse renal events[23]

The incidence of ICIs-related adverse renal events is less than 5%, which can be manifested as oliguria, hematuria, edema, anorexia and abnormal laboratory examination. It generally occurs 3~10 months after the start of PD-1 inhibitor treatment, and CTLA-4 inhibitor-related renal injury occurs earlier, usually 2~3 months after ICIs treatment.

(11) Adverse cardiovascular events[23,32,33]

ICIs-related adverse cardiovascular events are rare, with a potential risk of death, accounting for about 6.3% of all irAEs, but the mortality rate has been reported to be as high as 35%. Common adverse cardiovascular events include coronary artery disease, heart failure, myocarditis, atrial fibrillation, and pericardial disease. The median time of occurrence of adverse cardiovascular events is 6 weeks. Among them, the mortality of myocarditis is as high as 39.7%~50%. In a survey of 12 tertiary hospitals in China, the incidence of myocarditis is 1.05%, but the true incidence may be underestimated. The incidence of myocarditis with PD-1 and PD-L1 inhibitors are 0.5% and 2.4% respectively. The median occurrence time of myocarditis in China is 38 days after taking medicine with a median occurrence age of 65 years, and 81.2% occurred in the first or second time of ICIs.

Myocarditis can be clinically manifested as asymptomatic, mild, overt or fulminant. The initial symptoms are mostly nonspecific, such as fatigue, palpitation and shortness of breath. Typical clinical syndromes of myocarditis include palpitations, chest pain, acute or chronic heart failure, pericarditis, and pericardial effusion.

(12) Adverse ocular events[23,25]

The most common immune-related adverse ocular events include uveitis, but the incidence is < 1%. Patients should be alert to the first appearance of blurred vision, floaters, flashes, color vision changes, pink eyes, photophobia and sensitivity to fire, visual field changes, eyelid edema or protrusion or diplopia.

2.2.2. Treatment principles of ICIs-related adverse events[23,24]

Treatment of ICIs-related adverse events should be carried out according to the principle of grading. The related adverse events can be divided into five grades: Grade 1, mild adverse events; Grade 2, moderate adverse events; Grade 3, severe adverse events; Grade 4, life-threatening adverse events; Grade 5, death related to adverse events. The classification corresponds to the *Common Terminology Criteria for Adverse Events (CTCAE_5.0)* issued by the Cancer Institute of the National Institutes of Health (NIH) of the US.

The treatment of ICIs-related adverse events largely depends on the use of glucocorticoid, which are commonly used immunosuppressants. According to the grade of adverse events, it is necessary to determine whether to use glucocorticoids, and the dosage form and dose of glucocorticoids. Oral glucocorticoids are generally used for Grade 1~2 adverse events. However, due to the dangerous adverse reactions of certain organs, such as heart, lung, liver and nervous system, high-dose intravenous infusion of glucocorticoid is preferred. Since delayed use (>5 days) may affect the final treatment effect of some ICIs-related adverse reactions, such as diarrhea and colitis, glucocorticoids should be used in time. To prevent recurrence of toxicity, glucocorticoid should be reduced gradually (more than 4 weeks, sometimes 6~8 weeks or longer). Glucocorticoids are not recommended for the prevention of infusion reaction, so as not to compromise the therapeutic effect of ICIs. See Table 19 for the general treatment principles of different graded adverse events.

Table 19 General treatment principles of adverse events in different grades of ICIs

Grade	Hospitalization	Glucocorticoid*	Other immunosuppressant&	Immunotherapy and further application
1	No hospitalization required	Not recommended	Not recommended	Keep using
2	No hospitalization required	Topical hormones** or systemic hormone therapy, oral prednisone 0.5~1 mg/kg/d	Not recommended	Temporary discontinuation***
3	Hospitalization	Systemic hormone therapy, oral prednisone or intravenous methylprednisolone 1-2	Patients whose symptoms do not relieve after 3 to 5 days of hormone therapy may be considered for use	Discontinuation, discuss whether to resume ICIs based on the patient's risk/benefit ratio

		mg/kg/ d	under the guidance of a specialist	
4	Hospitalization; consider the referral to ICU	Systemic hormone therapy, intravenous methylprednisolone 1-2 mg/kg/d for 3 days. If the symptoms are relieved, the dose is gradually reduced to 1 mg/kg/d for maintenance, then gradually reduced the dose to drug withdrawal in about 6 weeks	Patients whose symptoms do not relieve after 3 to 5 days of hormone therapy may be considered for use under specialist guidance.	Permanent discontinuation

*: Hypothyroidism and other endocrine adverse reactions (e.g., diabetes) do not require glucocorticoid therapy, and alternative hormone therapy is recommended.

&: Other immunosuppressants, including TNF-α inhibitors (infliximab), mycophenolate mofetil, tacrolimus, and biological immune inhibitors such as anti-human thymocyte globulin (ATG) can be used if glucocorticoid is ineffective.

**: In case of rash, local short-term use of strong corticosteroids is recommended, rather than long-term use of weak corticosteroid.

***: ICIs treatment can be continued only with skin or endocrine symptoms.

2.2.3. Management of some common adverse events of ICIs[23,34]

(1) Management of adverse cutaneous events

Table 20 Management of cutaneous adverse effects

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
Maculopapular rash/rash			
1	Maculopapular rash/rash area is less than 10% of total body surface area (BSA), with or without symptoms (e.g., itching, burning, or tightness)	● Continue immunotherapy ● Use emollient locally ● Take an oral antihistamine ● Use moderate potency glucocorticoids (local application)	● Perform blood routine, liver and kidney function tests if necessary
2	Maculopapular rash/rash area is about 10~30% of total BSA, with or without symptoms (e.g., itching, burning, or tightness); daily tools usage** is limited.	● Consider suspending immunotherapy ● Use emollient locally ● Take an oral antihistamine ● Use potent glucocorticoids (local application)* and/or prednisone 0.5~1 mg/kg/d	● Blood routine and liver and kidney function tests should be performed if necessary, and referral to dermatology for skin biopsy should be considered
3	Maculopapular rash/rash area is greater than 30% of total BSA, with or without symptoms (e.g., erythema, purpura or epidermal shedding); self-care ability is limited&	● Suspend immunotherapy ● Use potent glucocorticoids (local application)* and/ or prednisone 0.5~1 mg/kg/d (the dose can be increased to 2 mg/kg/d if without improvement)	● Consider hospitalization, seek an urgent consultation in dermatology, and obtain a skin biopsy ● Blood routine and liver and kidney function tests should be performed if necessary
Pruritus			

1	Slight or local	● Continue immunotherapy ● Take an oral antihistamine ● Use moderate glucocorticoid for external use	● Blood routine and liver and kidney function tests should be performed if necessary
2	Intense or extensive; Intermittently; skin damage caused by scratching (e.g., edema, papules, desquamation, mossy, exudation, crusting); daily tools usage is limited	● Continue immunotherapy with enhanced itch relief ● Use potent glucocorticoids (local application) ● Take an oral antihistamine ● Consider discontinuation of immunotherapy in some severe patients	● Consult the dermatology department and refer to the dermatology department if necessary ● Blood routine and liver and kidney function tests should be performed if necessary
3	Intense or extensive; persistently; self-care ability is limited obviously or sleep is affected	● Suspend immunotherapy ● Prednisone/methylprednisolone 0.5~1 mg/kg/d (the dose can be increased to 2 mg/kg/d if without improvement) ● Take an oral antihistamine ● γ-aminobutyric acid (GABA) agonist (gabapentin, pregabalin), aprepitant or omalizumab may be used for refractory pruritus (if the blood IgE level is increased)	● Consider hospitalization, seek urgent consultation in dermatology, and check serum IGE and histamine ● Blood routine and liver and kidney function tests should be performed, and biopsies should be taken if necessary
Dermatitis bullosa/Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)			
1	Asymptomatic, blister area is less than 10% of total BSA	● Suspend immunotherapy ● Use potent glucocorticoid for external use	● Urgent dermatological consultation, blood routine, liver and kidney function, electrolytes, C-reactive protein (CRP) tests
2	Blister area is about 10~30% of total BSA, accompanied with pain; self-care ability is limited obviously	● Suspend immunotherapy until toxicity < grade 1 ● Prednisone/methylprednisolone 0.5~1 mg/kg/d	● Urgent dermatological consultation, blood routine, liver and kidney function, electrolytes, CRP tests
3	Blister area >30% of total BSA; self-care ability is limited obviously; SJS or TEN		● Hospitalization is required, and admission to intensive care unit or burn unit when there is indicated
4	Blister area >30% of total BSA, accompanied with fluid and electrolyte imbalance; fatal SJS or TEN	● Terminate immunotherapy permanently ● Prednisone/methylprednisolone 1~2 mg/kg/d	● Consult the department of dermatology, ophthalmology, or urology for an urgent consultation ● Blood routine, liver and kidney function, electrolytes, CRP, complement and other related inflammatory factors should be examined ● Skin biopsy if necessary
Reactive cutaneous capillary endothelial proliferation（RCCEP）			
1	Single or multiple nodules, maximum diameter <10 mm, with or without rupture hemorrhage	● Continue immunotherapy ● Gauze can be used to protected skins easy to rub from bleeding; Patients with ulceration and bleeding can be treated with local compression hemostasis	
2	Single or multiple nodules, maximum diameter >10 mm, with or without rupture hemorrhage	● Continue immunotherapy ● Gauze can be used to protected skins easy to rub from bleeding; Patients with ulceration and bleeding can be treated with	

		local compression hemostasis ● Consider local treatments, such as lasers or surgical resection, depending on the condition ● Patients with bleeding are treated locally to prevent infection	
3	Generalized, can be complicated with infection, and may require hospitalization	● Suspend immunotherapy until toxicity ≤ grade 1 ● Gauze can be used to protected skins easy to rub from bleeding. Patients with ulceration and bleeding can be treated with local compression hemostasis ● Consider local treatments, such as lasers or surgical resection, depending on the condition ● Patients with local infection were treated with anti-infective therapy	
Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)			
	Dermatology urgent consultation; if not, consider skin biopsy	● Terminate immunotherapy permanently ● Prednisone/methylprednisolone 1-2 mg/kg/d ● Consider intravenous immunoglobulin (IVIG) (1 g/kg/day for 3-4 days, each package used separately)	● Requiring hospitalization ● Urgent consultation of dermatology, ophthalmology, and urology

*: Short-term use of potent glucocorticoids is recommended (weakly potent: 0.1% mometasone furoate cream; Moderately potent: 0.05% betamethasone dipropionate cream; Highly potent: 0.05% fluocinonide cream/ointment and 0.1% mometasone furoate ointment), instead of long-term use of weak glucocorticoids.

**: Tools for daily use refer to cooking, shopping, using the phone and wealth management.

&: Self-care in daily life refers to bathing, dressing, eating, washing, and taking medicine without being bedridden.

Management of adverse endocrine events

Table 21 Management of adverse endocrine events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
Hypothyroidism*			
1	Asymptomatic: only clinical or diagnostic tests are required, treatments are not required	● Continue immunotherapy	● TSH and free T4 should be monitored every 4 to 6 weeks ● If central hypothyroidism is confirmed, refer to hypophysitis for treatment
2	Symptomatic: thyroid hormone replacement therapy is required; daily tools usage is limited**	● Continue immunotherapy ● Elevated TSH (>10 μIU/mL), supplement with thyroid hormone (0.5~1.5 μg/kg/d) or levothyroxine (1.6 μg/kg/d or 75~100 μg/d)	● TSH and free T4 should be monitored every 4 to 6 weeks ● Consultation with endocrinology department ● If central hypothyroidism is confirmed, refer to hypophysitis for treatment
3	Severe symptoms: self-care ability is limited&; requiring hospitalization	● Continue immunotherapy ● Elevated TSH (>10 μIU/mL), supplement with thyroid hormone	
4	Life-threatening and requires urgent	● Continue immunotherapy ● Elevated TSH (>10 μIU/mL),	

	intervention	supplement with thyroid hormone	
Hyperthyroidism			
1	Asymptomatic: only clinical or diagnostic tests are required, treatments are not required	● Continue immunotherapy ● If there are symptoms in patients, propranolol, metoprolol, or atenolol should be taken orally to relieve symptoms	● Reexamine thyroid function (TFTs) 4-6 weeks later, no further treatment is required if patients get relief. If TSH remains below normal and free T4/ total T3 is elevated, 4-hour or 24-hour iodine uptake rates are recommended to determine whether hyperthyroidism or diffuse goiter disease (Graves' disease) is present ● Hyperthyroidism often progresses to hypothyroidism, monitoring TSH levels, and thyroxine supplementation is initiated if TSH levels are elevated (>10 μIU/mL)
2	Symptomatic: thyroid hormone suppression therapy is required; daily tools usage is limited**		
3	Severe symptoms: self-care ability is limited&; requiring hospitalization		
4	Life-threatening and requires urgent intervention		

*: Central hypothyroidism is treated as hypophysitis and requires the use of hormones.

**: Tools for daily use refer to cooking, shopping, using the phone and wealth management.

&: Self-care in daily life refers to bathing, dressing, eating, washing, and taking medicine without being bedridden.

(3) Management of adverse hepatic events

Table 22 Management of adverse hepatic events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1	AST or ALT <3 ULN; total bilirubin <1.5 ULN	● Continue immunotherapy	● Test liver function every week ● Reduce monitoring frequency appropriately if liver function is stable
2	AST or ALT: 3~5 ULN; total bilirubin: 1.5~3 ULN	● Suspend immunotherapy ● Oral prednisone, 0.5~1 mg/kg/d ● Slowly reduce the dose if liver function improves, and the total course of treatment is at least 4 weeks ● The dose of prednisone is reduced to less than or equal to 10mg/d, and if the liver toxicity is less than or equal to grade 1, immunotherapy can be restarted	● Monitor liver function every 3 days ● Liver biopsy if necessary
3	AST or ALT: 5~20 ULN; total bilirubin: 3~10 ULN	● Terminate immunotherapy permanently ● Intravenously prednisone 1~2 mg/kg/d ● After hepatotoxicity reduces to grade 2, prednisone can be replaced by equivalent oral doses and slowly reduced for a total course of at least 4 weeks ● Reintroduction of immunotherapy should be used with caution only after consultation, which will increase the incidence of severe hepatic toxicity (dose of prednison reduce to ≤10 mg/	● Monitor liver function every 1 or 2 days ● Consult hepatic specialists ● Perform CT or ultrasound examination of the liver ● Liver biopsy if necessary

		day, and hepatotoxicity ≤ grade 1) ● Mycophenolate mofetil (0.5-1 g, q12h) should be added on the basis of hormone therapy if the hormone therapy does not improve or worsens after 3 days. If still not effective, tacrolimus should be added ● Infliximab is not recommended	
4	AST or ALT> 20 ULN; total bilirubin> 10 ULN	● Terminate immunotherapy permanently ● Intravenously prednisone 2 mg/kg/d ● After hepatotoxicity reduces to grade 2, prednisone can be replaced by equivalent oral doses and slowly reduced for a total course of at least 4 weeks ● Mycophenolate mofetil (0.5-1 g, q12h) should be added on the basis of hormone therapy if the hormone therapy does not improve or worsens after 3 days. If still not effective, tacrolimus should be added ● Infliximab is not recommended	

(4) Management of adverse gastrointestinal events

Table 23 Management of adverse gastrointestinal events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1	Asymptomatic: only clinical or diagnostic observations are required (grade 1 diarrhea: less than 4 times/day)	● Continue immunotherapy ● Oral rehydration if necessary, and symptomatic treatment with antidiarrheal medications ● Avoid high fiber/lactose diets	● Baseline examinations: blood routine, liver and kidney function, electrolytes, and thyroid function ● Stool examinations: white blood cells, eggs, parasites, viruses, clostridium difficile, and cultural-resistant pathogens ● Observe closely whether there are changes and progression occurring within 24 to 48 hours
2	Stomachache: stool mucous or bloody (grade 1 diarrhea: 4~6 times/d)	● Suspend immunotherapy ● Hormone therapy can initiate without colonoscopy: oral prednisone, 1-2 mg/kg/d ● Once the symptoms improve to less than grade 1 toxicity, hormone maintenance therapy started for 4~6 weeks ● If there is no improvement or exacerbation of hormone therapy within 48 to 72 hours, increase the dose to 2 mg/kg/d and consider adding infliximab 5 mg/kg	● Baseline examinations: blood routine, liver and kidney function, electrolytes, and thyroid function ● Stool examinations: white blood cells, eggs, parasites, viruses, clostridium difficile, and cultural-resistant pathogens ● Gastrointestinal X-rays are performed if there are signs of colitis ● Schedule colonoscopy and biopsy
3	Severe stomachache; changed stool habits; medical intervention is required; peritoneal irritation sign (grade 3 diarrhea: ≥7 times/day)	● Suspend immunotherapy ● Diet guidance (fasting, liquid food, total parenteral nutrition) ● Hormone therapy can initiate without colonoscopy: intravenously methylprednisolone 2 mg/kg/d ● Once the symptoms improve to	● Baseline examinations: blood routine, liver and kidney function, electrolytes, and thyroid function ● Stool examinations: white blood cells, eggs, parasites, viruses, clostridium difficile, and cultural-resistant pathogens

		less than grade 1 toxicity, hormone maintenance therapy started for 4~6 weeks ● If there is no improvement or exacerbation of hormone therapy within 48 hours, infliximab 5 mg/kg should be considered in addition to hormonal therapy (vedolizumab 300 mg should be considered in contraindicated or resistant patients or enrolled in clinical studies)	● Gastrointestinal X-rays are performed if there are signs of colitis ● Schedule colonoscopy and biopsy ● Blood routine, liver and kidney function, and electrolytes daily
4	Symptoms are life-threatening; urgent intervention is required	● Terminate immunotherapy permanently ● Diet guidance (fasting, liquid food, total parenteral nutrition) ● Hormone therapy can initiate without colonoscopy: intravenously methylprednisolone 2 mg/kg/d ● Once symptoms improve to less than grade 1 toxicity, hormone maintenance therapy started for 4~6 weeks ● If there is no improvement or exacerbation of hormone therapy within 48 hours, Infliximab 5 mg/kg should be considered in addition to hormonal therapy (vedolizumab 300 mg should be considered in contraindicated or resistant patients or enrolled in clinical studies)	

(5) Management of adverse pulmonary events (pneumonia)

Table 24 Management of adverse pulmonary events (pneumonia)

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1	Asymptomatic; confined to a single lobe or less than 25% of the lung parenchyma	● Delay immunotherapy whenever appropriate ● Close follow-up and treatment resumption if there are improvements in imageology ● Continue treatment and follow up closely until new symptoms appear if there are no changes in imageology ● Upgrade the therapeutic schedule and suspend immunotherapy if there are no progress in imageology	● Baseline examination: chest CT, oxygen saturation, routine blood test, liver and kidney function, electrolytes, thyroid function (TFTs), erythrocyte sedimentation rate (ESR), lung function ● Sputum examination to rule out pathogen infection ● Monitor symptoms and review oxygen saturation every 2 to 3 days ● Subsequent visit of the chest physical examination, repeated oxygen saturation and chest CT to follow-up changes in symptom every week.
2	New symptoms or worsen symptoms, including shortness of breath, cough, chest pain, fever and lack of oxygen,	● Suspend immunotherapy until adverse effects are reduced to less than or equal to grade 1, which could to be used after assessment	● Perform chest high-resolution CT, blood routine, liver and kidney function, electrolytes, and lung function analysis ● Perform examination of nasal

	involving multiple lobes and reaching 25 to 50% of the lung parenchyma, affecting daily tools usage** and pharmacological intervention is required	● Intravenously methylprednisolone 1~2 mg/kg/d ● If symptoms improve after 48 to 72 hours of treatment, the hormone dose should be gradually reduced by 5 to 10 mg per week for 4 to 6 weeks ● If symptoms do not improve, escalate the treatment according to grade 3 to 4 adverse effects ● If infection cannot be ruled out, empiric anti-infective therapy should be considered	swab, sputum culture and drug sensitivity, blood culture and drug sensitivity, urine culture and drug sensitivity to exclude pathogen infection ● Monitor every 3 to 7 days: disease history and physical examination, oxygen saturation (resting and active) ● Perform examination of chest CT, blood and lung function every week ● Bronchoscopy or bronchoalveolar lavage was performed as appropriate, and biopsy should be considered for atypical lesions
3	Severe new symptoms involving all lobes or more than 50% of the lung parenchyma and limited self-care ability&, oxygen and hospitalization is required	● Terminate immunotherapy permanently, hospitalization is required ● Intravenously methylprednisolone 2 mg/kg/d ● Use lung ventilation as appropriate ● If symptoms improve after 48 hours of treatment, continue treatment until the adverse effect is reduced to less than or equal to grade 1, and then gradually reduce the hormone dose over 4-6 weeks ● If 48 hours of hormone therapy does not improve or worsens, consider adding infliximab 5 mg/kg or mycophenolate mofetil (1-1.5 g, q12h) or intravenous immunoglobulin (IVIG) to hormonal therapy.	● Perform chest high-resolution CT, blood routine, liver and kidney function, electrolytes, and lung function analysis ● Perform examination of nasal swab, sputum culture and drug sensitivity, blood culture and drug sensitivity, urine culture and drug sensitivity to exclude pathogen infection ● Bronchoscopy or bronchoalveolar lavage was performed as appropriate, and biopsy should be considered for atypical lesions
4	Life-threatening breathing difficulties, acute respiratory distress syndrome (ARDS), emergency interventions such as intubation are required		

**: Tools for daily use refer to cooking, shopping, using the phone and wealth management.

&: Self-care in daily life refers to bathing, dressing, eating, washing, and taking medicine without being bedridden.

(6) Infusion events**

Table 25 Infusion events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1	Mild transient reaction	● Interrupt the infusion is unnecessary, or downregulate the rate of infusion by 50% ● Suspend until symptoms disappear, and then resume infusion according to tolerance ● Consider pretreatment with NSAIDS and antihistamines before the next infusion	
2	More severe reactions	● Consider suspend immunotherapy or downregulate the rate of infusion by 50% ● Consider pretreatment with NSAIDS and antihistamines before the next infusion ● Glucocorticoids should be used if necessary	
3	Symptoms recurred	● Consider pretreatment with	

	after initial treatment	NSAIDS and antihistamines before the next infusion ● Glucocorticoids should be used if necessary	
4	Life-threatening consequences	● Terminate ICIs permanently ● Emergency treatment	

**: Mild or moderate infusion events require symptomatic treatment, slowing down the infusion rate, or suspending the infusion. Rapid management of severe, life-threatening infusion events is recommended by referring to various infusion response guidelines. Permanent termination of the drug is recommended for patients with Grade 3~4 infusion events, and permanent termination should also be considered for patients with recurrent infusion events.

(7) Management of adverse cardiovascular events

Table 26 Management of adverse cardiovascular events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1（Subclinical myocardial injury）	There are cardiac injury biomarkers exists without changes in cardiovascular symptoms, electrocardiogram, ultrasound electrocardiogram	● Continue immunotherapy if the heart injury biomarker is mildly abnormal and remains stable ● Immunotherapy should be suspended if progressive elevation occurs, and glucocorticoids given if necessary ● When diagnosed as asymptomatic myocarditis, methylprednisolone (initial dose of 1-4 mg/kg/d) should be given immediately for 3-5 days, followed by tapering, and hormone therapy can be continued for 2-4 weeks after the cardiac injury biomarkers returning to baseline ● Immunotherapy can be continued after baseline levels of cardiac injury biomarkers have been restored, but enhanced monitoring is required	● Cardiovascular consultation ● Examinate cardiac injury markers, natriuretic peptide, D-dimer, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, white blood cell count), viral titer, ECG, etc. Cardiac magnetic resonance examination should be performed if possible
2	Mild cardiovascular symptoms with cardiac injury biomarkers and/or ECG abnormalities	● Suspend immunotherapy ● Methylprednisolone (initial dose of 1-4 mg/kg/d) should be given immediately for 3-5 days, followed by tapering, and hormone therapy can be continued for 2-4 weeks after the cardiac injury biomarkers returning to baseline	● Cardiovascular consultation ● Electrocardiogram monitoring ● Examinate cardiac injury biomarkers, natriuretic peptide, ECG, etc. Cardiac magnetic resonance examination should be performed when possible ● Endocardial and myocardial biopsies should be performed when necessary

3-4	Significant cardiovascular symptoms or life threatening. Hospitalization for emergency treatment is required	● Terminate immunotherapy permanently ● Methylprednisolone shock therapy should be administered immediately, 500-1000 mg/d, for 3-5 days, followed by tapering, and hormone therapy can be continued for 4 weeks after the cardiac injury biomarkers returning to baseline ● Other immunosuppressive agents with or without plasma exchange and other measures with or without life support should be added if hormone treatment does not improve in 24 hours ● Patients with arrhythmia are fitted with pacemakers when necessary, and critically ill patients are given circulatory and respiratory support in time	● Rest in bed ● Multidisciplinary team (cardiovascular, critical care medicine, etc.) consultation ● ICU-level care ● Examinate cardiac injury biomarkers, natriuretic peptide, ECG, UCG, CMR. Endocardial and myocardial biopsies should be performed when necessary

(8) Management of adverse pancreatic events

Table 27 Management of adverse pancreatic events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1	Nausea, bloating, belching, abdominal pain, or back pain	● Continue immunotherapy ● Intravenous hydration	● Consider gastroenterology referral
2	Two of the following features: elevation in amylase/lipase >3 ULN and/or CT imaging results and/or clinical symptoms	● Consider holding immunotherapy ● Prednisone/methylprednisolone 0.5-1 mg/kg/d ● Intravenous hydration	● Evaluate for symptoms of pancreatitis ● Abdominal CT with contrast
3-4	Elevation in amylase/lipase and/or CT imaging results and/or intense abdominal pain or vomiting and hemodynamic instability	● Permanently discontinue immunotherapy ● Prednisone/methylprednisolone 1-2 mg/kg/d. Treat until symptoms improve to grade ≤1, then taper over 4-6 weeks ● Intravenous hydration	● Evaluate for symptoms of pancreatitis ● Abdominal CT with contrast

(9) Management of adverse renal events

Table 28 Management of adverse renal events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; creatinine level increase of > 0.3 mg/dL; creatinine 1.5–2.0 ULN	● Consider temporarily holding ICPi, pending consideration of potential alternative etiologies ● Check and stop nephrotoxicity related drugs (PPI or NSAIDs)	● Follow urine protein/creatinine ration every 3-7 days

2	Moderate symptoms; creatinine 2–3 ULN	● Consider holding immunotherapy ● Limit/discontinue nephrotoxic medication and creatinine clearance ● Start prednisone 0.5-1 mg/kg/d and maximum dose <60 to 80 mg/d if other causes are ruled out. If improved to grade 1, Continue immunotherapy	● Follow urine protein/creatinine ration every 3-7 days ● Nephrology consultation and consider renal biopsy
3	Severe or medically significant but not immediately life-threatening, disabling, limiting selfcare ADL; creatinine >3 ULN or >4.0 mg/dL	● Permanently discontinue immunotherapy ● Hospitalization or prolongation of hospitalization ● Prednisone/methylprednisolone 1-2 mg/kg/d. Consider adding the following if kidney injury remains > grade 2 after 1 weeks of steroids: azathioprine/cyclophosphamide/cyclosporine/infliximab / mycophenolate mofetil	● Follow urine protein/creatinine ration every day ● Nephrology consultation and consider renal biopsy
4	Life-threatening consequences	● Permanently discontinue immunotherapy ● Need for urgent intervention ● Prednisone/methylprednisolone 1-2 mg/kg/d. Consider adding the following if kidney injury remains > grade 2 after 1 weeks of steroids: azathioprine/cyclophosphamide/cyclosporine/infliximab / mycophenolate mofetil	● Follow urine protein/creatinine ration every day ● Nephrology consultation and consider renal biopsy ● Dialysis is recommended

(10) Management of adverse muscular and skeletal events

Table 29 Management of adverse muscular and skeletal events

Grade	Clinical symptoms	Treatment recommendations	Assessment and examination
Inflammatory arthritis			
1	Mild pain with inflammation (ameliorated by exercise or warming), erythema, joint swelling	● Continue immunotherapy ● NSAIDs ● If inadequately controlled, initiate prednisone 10-20 mg/d for 4 weeks ● If no improvement, treat as grade 2	● Monitor with rheumatologic examinations every 4-6 weeks after treatment
2	Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	● Consider holding immunotherapy ● Prednisone 0.5 mg/kg/d or prednisolone 10-20 mg/d for 4-6 weeks ● If no improvement, treat as grade 3	● Consider intra-articular steroids in affected joint(s), depending on joint location and number involved ● If no improvement by 4 weeks, rheumatology consultation is recommended
3-4	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	● Temporarily or permanently discontinue immunotherapy ● Prednisone 1 mg/kg/d or prednisolone 10-20 mg/d for 4-6 weeks ● Consider additional disease-modifying anti-rheumatic drugs: infliximab, tocilizumab, methotrexate, sulfasalazine, leflunomide	● If no improvement by 2 weeks, rheumatology consultation is recommended
Myalgias			

1	Mild stiffness and pain	● Continue immunotherapy ● Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications	
2	Moderate stiffness and pain, limiting age-appropriate instrumental ADL	● Consider holding immunotherapy and resuming upon symptom control, prednisolone <10 mg ● if worsens, treat as grade 3 ● Initiate prednisone 20 mg/d or equivalent; if symptoms improve, start to taper dose ● If no improvement after 4 weeks, escalate to grade 3	● Rheumatology consultation is recommended
3-4	Severe stiffness and pain, limiting self-care ADL	● Hold immunotherapy until recovery to grade 1 or less ● Initiate prednisone 20 mg/d or prednisolone 1-2 mg/kg or equivalent. If no improvement or need for higher dosages for prolonged time, offer a corticosteroid-sparing agent (methotrexate or tocilizumab) ● Pain treatment as indicated	● Rheumatology consultation is recommended ● Intravenous immunoglobulin therapy ● Plasma exchange

2.2.4 Management of ICIs-related adverse events[23]

Adverse events monitoring is as important as efficacy evaluation during ICIs treatment, including in-treatment monitoring and follow-up after treatment. During ICIs treatment, middle-level monitoring means that some test indexes and organ functions are detected regularly or irregularly, so that adverse events can be found early and timely. Post-treatment follow-up refers to the early and timely discovery of some delayed adverse events by regularly or irregularly testing some test indexes and organ functions within a period of time after ICIs treatment. Patients should be monitored for at least one year after ICIs treatment. See Table 30 for ICIs adverse reaction monitoring items.

Table 30 ICIs adverse reaction monitoring items

Monitoring items	Contents
General conditions	● It should be assessed at each follow-up, including physical examination including neurological examination, bowel habits, etc.
Imaging examination	● Chest, abdomen and pelvic CT is recommended every 4-6 weeks during ICIs treatment ● Irregular CT examination of specific site is recommended according to specific symptoms ● Brain MR and whole-body scan is recommended every half a year to 1 year (weak evidence, expert recommendation)
General hematological examination	● Routine blood tests and blood biochemistry (complete set) is recommended every 2-3 weeks or as indicated during ICIs treatment ● Detect irregularly Hb1Ac, HBsAg, HBsAb, HBcAb, HCVAb, CMV antibody, HIV antigen (p24) if indicated ● Detect irregularly HBV-DNA, HCV-RNA if indicated (weak evidence, expert recommendation)
Skin, mucosa	● Skin and mucous membrane examinations is recommended during each pharmaceutical ward round, especially for patients with a history of autoimmune skin diseases ● Monitor affected body surface area and lesion type, and take photographic records ● Skin biopsies is recommended if indicated (weak evidence, expert recommendation)
Pancreas	● If asymptomatic, no routine monitoring is required ● Check timely serum, urine amylase and pancreatic imaging if indicated

Thyroid	● Monitor thyroid function (TFTs) every 4-6 weeks during ICIs therapy, and monitor it every 12 weeks according to symptoms ● If TSH is high, irregularly check TPOAb ● If TSH is low, irregularly check TRAb
Adrenal gland, pituitary gland	● Check plasma cortisol, ACTH, and TFTs collected at 8 AM every 2 to 3 weeks during treatment with ICIs, and perform follow-up every 6 to 12 weeks ● Check LH, FSH, and testosterone irregularly if necessary
Lung	● Check oxygen saturation at rest or during activity and routine lung imaging every 4-6 weeks during ICIs therapy ● Patients with history of lung disease (e.g., COPD, NSIP, sarcoidosis, or pulmonary fibrosis) perform irregular lung function and 6-minute walk tests (6 MWT) ● Lung biopsy if necessary (weak evidence, expert recommendation)
Cardiovascular	● Check ECG, myocardial enzymes, etc. every 2-4 weeks during ICIs treatment ● Check irregularly myocardial infarction markers (such as troponin I or T), BNP or pro-BNP ● Check 24-hour ambulatory ECG if necessary (weak evidence, expert recommendation)
Inflammation/skeletal muscle	● If asymptomatic, routine monitoring is not required ● Perform joint examination/functional assessment irregularly if preexisting disease

2.2.5 Patient education for ICIs[35-37]

ICIs-related adverse events have a lower incidence compared with traditional tumor chemotherapy and are mostly mild/moderate and reversible, but a few severe adverse events can lead to life-threatening consequences. Early identification, reporting and treatment are important for the management of ICIs-related adverse events. Clinical pharmacists should focus on publicizing and educating patients and/or their family members/ caregivers about ICIs-related adverse events before and during treatment, including the following:

(1) The name, dosage and treatment period of ICIs currently used by patients;

(2) The types and manifestations of ICIs-related adverse events, and their occurrence time and whether they can be reversed;

ICIs-related adverse events can occur at any time after the treatment starts, even after the discontinuation of treatment, but most of them occur within a few weeks to six months (see Table 31 for details). The majority of adverse events are mild and reversible if they can be identified early and treated in a timely manner.

Table 31 Median time of onset of ICIs-related adverse events

Organ	Median time (week)
Skin	4-7
Gastrointestinal tract	3-6
Liver	5-18
Lung	15-31
Endocrine	8-12
Kidney	7-11
Nervous system	11-13

(3) Self-management in case of ICIs-related adverse events:

①Patients need to be accompanied by family members/caregivers when receiving the first medication;

②Regular monitoring of relevant adverse reactions according to the doctor's advice (see Section 4 "Management of ICIs-related adverse events" for details);

③If case of the following symptoms during or after medication, patients should promptly receive emergency treatment and/or inform the doctor in charge:
a. Symptoms of allergic reaction during or after infusion, such as dizziness, palpitation, facial swelling and dyspnea;
b. Suspected infection symptoms, such as fever (≥38℃) with chills, severe sore throat with productive cough (purulent or greenish sputum), turbid or smelly urine, skin redness/pain/tenderness/sores;
c. Diarrhea/change in bowel habits: black tarry stool, blood/mucous stool, severe abdominal pain;
d. Pulmonary symptoms, such as new or worsening cough, chest pain, hemoptysis, shortness of breath, and dyspnea;
e. Renal symptoms, such as backache, hematuria, foot/calf swelling , urine volume/color change;
f. Hyperglycaemia symptoms, such as thirst and/or frequent urination.

④Patients should inform the doctor in charge of the following symptoms in time during or after medication:
a. Anemia symptoms, such as abnormal fatigue or weakness
b. Liver-related symptoms, such as yellow sclera/skin, white or clay-colored stool;
c. Thyroid-related symptoms, such as abnormal weight gain or loss, fear of cold/heat, and hoarseness;
d. Visual changes, eye pain or redness;
e. Skin rash, blisters or itching.

Table 32 Self-care for common adverse events

Type of adverse reactions	Symptoms	Self-care
Cutaneous adverse reactions	Rash, pruritus	● Skin protection ■ When cleaning the skin, use non-irritating soap and bath solution, and the water temperature should not be too high ■ Apply alcohol-free, non-irritating moisturizing creams daily in the direction of hair growth until completely absorbed ■ Avoid sunlight exposure when going out and take sunscreen measures, such as wearing sunscreen hats, playing umbrellas, and applying sunscreen supplies ● Skin care ■ Keep skin clean and moist, use moisturizing lotion 2-3 times a day ■ Avoid wiping back and forth when using soft paper towel, use warm water to bathe, and avoid damaging skin with excessive water temperature ■ Wear cotton clothes with soft and loose texture, and do not wear clothes with chemical fiber and with hard texture to prevent skin damage due to rough or friction of clothing materials ■ Cut nails frequently to avoid scratching the skin with long nails, avoid scratching the skin with hands when itching, and tap gently to relieve local discomfort ■ Keep air cool while sleeping ■ In case of pruritus or erythema, topical

		cooling agents (peppermint) or cloth could be applied cold or tapped on the local skin ■ Oral or topical medications should be used correctly according to the physician's prescription in condition of severe skin reactions
Gastrointestinal adverse reactions	Diarrhoea, abdominal pain, visible blood in stool	● Keep the perianal skin clean, clean with soft toilet paper after each defecation, and wash the perianal region with warm water to avoid perianal skin damage ● Keep water intake about 3000 mL/day ● Defecate 4 times or more a day. When the stool is bloody, go to the hospital for treatment ● Reduce the consumption of the following foods: high fiber, high fat, raw and cold food, dairy products, wine, coffee, sugar, etc.
Hepatic adverse reactions	Nausea and vomiting, fatigue, yellow skin and/or sclera (jaundice), yellow urine	● Regularly monitor liver function ● Eat more foods containing vitamins, such as fruits and vegetables ● Avoid high-fat diet intake, such as red meat (pigs, cattle and sheep), butter, etc. ● Contact the hospital timely when the above symptoms or examination results occur
Pulmonary adverse reactions	Cough expectoration, shortness of breath, chest pain	● When the above pulmonary symptoms occur or the original symptoms worsen, it is necessary to visit the hospital timely. ● Special attention should be paid to the following populations: the elderly, patients with asthma, chronic obstructive pneumonia or other symptoms of cardiopulmonary disease
Endocrine adverse reactions	● Hyperthyroidism: impatience, hyperhidrosis, fear of heat, palpitation, hyperphagia ● Hypothyroidism: fear of cold, weight gain, drowsiness, edema ● Hypophysitis: diplopia, thirst, headache, high urine volume	● Check regularly adrenocorticotropic hormone and thyroid hormone, and perform close follow-up ● If the examination results are abnormal or feel uncomfortable, inform the medical staff timely and visit the hospital if necessary
Arthralgia and arthritis	● Joint pain ● Difficulty walking ● Joint swelling ● Erythema	● In mild symptoms cases, appropriate activities can be performed every day for 30 minutes, which can improve physical strength and sleep, and reduce pain ● Moderate intensity exercise can also be performed, such as yoga, tai chi, qigong, swimming, walking and other aerobic exercises ● Warm up before activities, pay attention to joint protection during activities to prevent falls especially when changing body position (such as getting up, sedentary standing up, etc.), and slow movements ● When feeling uncomfortable, inform the medical staff timely and visit the hospital if necessary

Infusion reaction	Skin flushing, itching, fear of cold, fever, sweating, chest tightness, headache, dizziness and other symptoms occurred during or within 1~2 hours after infusion	● Truthfully inform whether there is a history of drug allergy before treatment ● Patients should be accompanied by family members/caregivers at the first infusion ● The infusion rate should not be arbitrarily adjusted during the infusion; rest for 1 to 2 hours is recommended after the end of infusion, and the patient can leave the hospital without discomfort ● When feeling discomfort, inform the medical staff immediately

2.2.6 Other pharmaceutical care for ICIs-related adverse events[23]

Pharmacists should be alert to the fact that immunosuppressants pose additional risks when used to treat ICI-related adverse reactions. The use of immunosuppressants such as glucocorticoids can result in adverse reactions such as hyperglycemia, water and sodium retention and anxiety. It should also be noted that while long-term use of corticosteroids is less likely, it may result in some complications such as Cushing syndrome, osteoporosis and muscular atrophy. Rapid corticosteroid withdrawal may also cause iatrogenic adrenal insufficiency.

(1) Concerns about glucocorticoids

Long-term use of glucocorticoids increases the risk of opportunistic infections. It is suggested that patients who use glucocorticoids for a long time (prednisone >20 mg/d for more than 4 weeks) should take targeted measures to prevent pneumocystis carinii pneumonia. For patients who use glucocorticoid for a longer time (prednisone >20 mg/d for more than 6 weeks), antifungals (e.g., fluconazole) should also be considered to prevent fungal pneumonia.

For patients with long-term use of glucocorticoids (particularly high-dose glucocorticoids: hydrocortisone >250 mg/d; Equivalent dose of hydrocortisone and dexamethasone: 20mg:0.75mg=266.6mg:10mg; Hydrocortisone: dexamethasone; prednisone: methylprednisolone=20mg:0.75mg:5mg:4mg), if they are using nonsteroidal anti-inflammatory drug (NSAIDs) or anticoagulants (increased risk of bleeding), it is recommended to consider proton pump inhibitors or H2 receptor blockers. For patients who use glucocorticoids for a long time, the risk of osteoporosis is increased. It is recommended to take vitamin D and calcium orally to prevent osteoporosis.

(2) Concerns about other immunosuppressants

Infliximab: Prior to administration, it should be noted that some patients have contraindications: perforations, tuberculosis or other active infections (sepsis, abscess, opportunistic infection), moderate-to-severe heart failure (New York Heart Association Class III/IV). Infliximab should not be used in patients with ICIs-related liver injury due to its own adverse liver reactions; ,Generally,. infliximab takes effect within 1~3 days, but some patients benefit from the second dose 2 weeks later. Prednisone should be taken orally for a long period of time and stopped gradually after using infliximab

Mycophenolate mofetil: Patients with active digestive diseases should use it with caution; Those with severe chronic renal insufficiency (glomerular filtration rate <25 mL/min/1.73m^2) should use it with caution and close monitoring. During medication, patients should pay attention to sun protection, and regularly monitor the complete blood count (once a week in the first month, twice a month in the second and third months, and once a month thereafter).

Tacrolimus: There are case reports of successful treatment with tacrolimus for immune-related adverse reactions that failed hormonal therapy. Tacrolimus is highly variable among individuals, and the dosage should be adjusted according to plasma levels. During medication, routine monitoring includes the monitoring of blood pressure, electrocardiogram, visual acuity, blood cell count, blood glucose concentration, blood

potassium and other electrolytes, renal function, hepatic function, and coagulation function..

Antithymocyte globulin (ATG): ATG is recommended by several guidelines or consensus as an additional treatment for ICIs-related severe myocarditis. The ideal dose and course of treatment of ATG are uncertain. During the treatment, the T lymphocyte subsets should be monitored as much as possible. When using ATG, the principle of individualization should be followed, and the monitoring of adverse reactions should be strengthened to prevent opportunistic infections.

Rituximab: Its standard dose of 375 mg/m^2 is indicated for multiple refractory irAEs, especially for systemic lupus erythematosus, nephritis and encephalitis. The possible infusion-related reactions during the first infusion include fever, chills, cold intolerance, pruritus, angioedema, bronchospasm, urticaria, rash and myalgia. There are also reports of fatal severe infusion reactions. Patients should be treated with antipyretics and analgesics (e.g., acetaminophen) and antihistamines (e.g., diphenhydramine) before rituximab infusion.

Tocilizumab: It can cause extremely rare intestinal perforations, so it should be used with caution or contraindicated for patients with colitis or gastrointestinal metastases.

(3) Concerns about other medicines

Immunoglobulins: Intravenous immunoglobulin is the second-line treatment for ICIs-related cardiovascular and neurological adverse reactions. According to relevant guidelines, 2g/kg intravenous immunoglobulin is used for myocarditis. Immunoglobulin dosage is 20~40 g/d for the first two days, and then changed to 10~20 g/d for 5~7 consecutive days before discontinuation[32]. 0.4g/(kg·d) of gamma globulin is used for neurological adverse reactions for at least five days, and concomitant use with hormones for critically ill patients[37]. It is contraindicated for patients allergic to human immunoglobulin or with a history of other serious allergies.

3 Other ICIs-related issues

3.1 Pharmacokinetic-based drug interactions

ICIs is a humanized or fully humanized monoclonal antibody, and there is no data of pharmacokinetic interaction between ICIs and other commonly used drugs in clinic.

ICIs monoclonal antibodies are catabolized in the same manner as endogenous IgG, cleared from the blood circulation as small peptides and amino acids, and are not metabolized by cytochrome P450 (CYP) enzymes or other drug-metabolizing enzymes. Therefore, the inhibition or induction of these enzymes by concomitant drugs is not expected to affect the pharmacokinetics of ICIs.

3.2 Selection of the dominant population

The discovery and summary of the characteristics of the dominant population helps to advance immunotherapy into a precise era, and better screen out patients who can really benefit from immunotherapy. Currently, there are three kinds of biomarkers in cancer immunotherapy[39]: the first kind of biomarkers reflects the inflammatory state of tumor, such as the expression level of PD-L1; The second kind of to biomarkers reveals the immunogenicity of tumor, that is, the possibility of triggering immune response, such as tumor mutation burden (TMB); The third kind of to biomarkers targets the host environment other than the tumor itself, such as the microbiome, which may also be related to the patient's response to immunotherapy. In the clinical practice of tumor diagnosis and treatment and related detection, the indicators recommended by the current guidelines mainly include:

(1) PD-L1 expression level;
(2) High microsatellite instability (MSI-H) or mismatch repair gene deficiency (dMMR);
(3) TMB.

More research evidence is needed to support the clinical application of other immunotherapy biomarkers, such as POLE/POLD mutations, GEP, and TIL. As scientific research continues to progress, there will be more methods to help clinical screening of patients with treatment advantages.

3.3 The effect of antibiotics on the anticancer efficacy of ICIs

Some human and animal trials have found that the imbalance of intestinal flora could affect the efficacy of ICIs. Regarding the impact of antibiotic on ICIs, there are mostly small sample studies, and several high-level clinical trials attract are highly concerned:.

One is that Derosa, a scholar at Gustave Roussy Cancer Center in France, found that PD-1 CTLA-4 used antibiotics one month before the treatment of metastatic renal cell carcinoma (mRCC), and the progression-free survival (PFS) was shortened from 8.1 months to 2.3 months. The research results were published in 2017 Urogenital Cancer Forum (GUCS)[40].

In a study from the 2018 ESMO meeting, investigators conducted a retrospective analysis of 121 patients with renal cell carcinoma (RCC) and 239 patients with non-small cell lung cancer (NSCLC) who received immunotherapy. Those receiving antibiotics within 30 days of beginning ICI were compared with those who did not. The results showed that, among RCC patients, patients who received antibiotics had shorter median OS (17.3 versus 30.6 months), shorter median PFS (1.9 versus 7.4 months), and increased incidence of primary progressive disease (75% versus 22%); Among NSCLC patients, patients who received antibiotics had shorter median OS (7.9 versus 24.6 months) and shorter median PFS (1.9 versus 3.8 months). In multivariate Cox regression analysis, recent antibiotic use decreased survival benefit and was inversely associated with efficacy. The use of antibiotics for 30 days before immunotherapy adversely affects the efficacy of ICIs. Modulation of antibiotic-related dysbiosis and gut microbiota composition may improve the clinical benefit of ICIs. The findings were published in *Annals of Oncology* in 2018[41].

A clinical study from the UK showed that the overall survival time of patients who received broad-spectrum antibiotics within one month before receiving immunotherapy (PD-1/PD-L1 inhibitor) was 2.5 months vs 26 months in non-small cell lung cancer, 3.9 months vs 14 months in melanoma and 1.1 months vs 11 months in other solid tumors. The overall survival time of patients who used antibiotics within one month before immunization was 2 months on average, while that of patients who did not receive antibiotics was 26 months. The study lasted for 3 years and included 196 patients. It was published in *JAMA Oncology* in 2019[42].

Generally speaking, a number of retrospective analyses suggest that antibiotic use is associated with worse therapeutic effect of PD-1/PD-L1 inhibitors (PFS and OS), which can be used as prognostic indicator. Currently, treatment with ICIs within a month of antibiotic use is not recommended, but more clinical data are needed for further confirmation.

3.4 The influence of proton pump inhibitor (PPI) on the therapeutic effect of PD-1/PD-L1 inhibitors

Regarding the impact of PPI on the therapeutic effect of ICIs drugs, a retrospective analysis from CheckMate069[42] showed that patients receiving PPI derived half the objective response rate, PFS and OS from immunotherapy consisting of nivolumab plus ipilimumab, compared with patients receiving the same combination but not on PPI medication. However, the clinical benefit of patients receiving ipilimumab monotherapy was not affected. The same was true for the multivariate analysis results. The investigators believe that prior to immunotherapy, PPI may establish a unique inflammatory immune state and interfere with the efficacy of immunotherapy. The effects of PPI when applying PD-1-based immunotherapy need to be further confirmed by more clinical data.

In 2020, in *Annals of Oncology*, there was a pooled analysis of POPLAR research and OAK

research with small cell lung cancer, with a total of 1,512 patients. 757 patients received atezolizumab, of which 234 of patients also received PPIs at the same time. The results showed[44] that of patients receiving PPIs had shorter median overall survival (9.6 vs 14.5 months) and mPFS (1.9 versus 2.8 months) compared with patients not receiving PPIs. The reduced efficacy of immunotherapy with PPI drugs may be related to dysbacteriosis of the intestinal flora, decreased bacterial richness, and enhanced T-cell tolerance.

A meta-analysis of the effect of ICIs on cancer patients shows[45] that the use of PPIs is associated with poor clinical outcome of cancer patients treated with ICIs. From the mechanism analysis, PPIs can alter gastrointestinal microbiota and reduce its diversity by increasing gastric pH value and pH-independent pathways, such as inducing hormonal changes and interfering with nutrient absorption, thereby affecting the efficacy and toxicity of ICIs[46]. On the other hand, PPIs can place patients in a pro-inflammatory state by increasing their neutrophil and lymphocyte counts[47], while potentially increasing the risk of Clostridium difficile infection and community-acquired pneumonia infection[48]. These mechanisms have adverse effects on the treatment of ICIs in varying degrees..

3.5 Effect of hormone therapy on the therapeutic effect of immunotherapy

Currently, there is no formal and forward-looking research conclusion to address this issue. Retrospective analysis suggests that the use of steroids (prednisone ≥10 mg/d) at baseline may affect efficacy and reduce the survival benefit of patients[49]; However, short-course hormone therapy for treating PD-1 inhibitor-related adverse reactions has no adverse effect on the prognosis of patients[50]. It is not clear whether the deterioration of efficacy is directly related to the use of hormones, but it is still recommended to use hormones at the beginning of immunotherapy. To answer this question, more details need to be focused on, including the type of immunosuppressants, the timing and duration of use and the treatment outcome of patients.

3.6 Application of ICIs in neoadjuvant/adjuvant therapy

Neoadjuvant therapy refers to medical treatment initiated by reducing the tumor stage in order to achieve a better therapeutic effect prior to surgical intervention. Adjuvant therapy refers to medical therapy performed after surgery in order to reduce the risk of recurrence due to residual disease. Neoadjuvant/adjuvant treatment is usually based on chemotherapy, but its limitations also cause patients to fail to experience survival benefits. As clinical research trials have been updated, it has been found that ICIs have good effects in the neoadjuvant/adjuvant setting. Atezolizumab is currently approved in China as a monotherapy for the adjuvant treatment of PD-L1 positive (TC≥1%) patients with stage II-IIIA non-small cell lung cancer following surgical resection and platinum based chemothrapy[10]. To date, FDA has approved three ICIs for the treatment of neoadjuvant/adjuvant, including nivolumab, pembrolizumab, and ipilimumab, which cover non-small cell lung cancer, melanoma, oesophageal cancer, gastroesophageal junctional cancer, renal cell carcinoma and breast cancer (see Table 33 for details), and more research on other tumor types is still in progress. Therefore, ICIs will hopefully stand out in the neoadjuvant/adjuvant setting and replace traditional chemotherapy for the benefit of cancer patients.

Table 33 Approval of ICIs for neoadjuvant/adjuvant therapy

Tumor	Type	Drugs and approved indications
Non-small cell lung cancer	Adjuvant therapy	Tislelizumab is indicated as monotherapy for the adjuvant treatment of patients with stage II-IIIA non-small cell lung cancer (NSCLC) who have PD-L1-positive (TC ≥1%) and have undergone surgical resection and platinum-based chemotherapy. (NMPA)
	Neoadjuvant therapy	Nivolumab is indicated as neoadjuvant chemotherapy in combination with two cycles of platinum-based doublet chemotherapy for the treatment of adult patients with resectable (tumor diameter ≥4 cm or node-positive) non-small cell lung cancer. (FDA)

Melanoma	Adjuvant therapy	Nivolumab is indicated as adjuvant therapy for patients with lymph node involvement or metastatic melanoma who have undergone complete surgical resection. (FDA)
		Pembrolizumab is used as adjuvant therapy in patients with stage IIB, IIC, or III melanoma who have undergone complete surgical resection. (FDA)
		Adjuvant therapy in patients with lymph node involvement or metastatic melanoma who have undergone complete surgical resection with ipilimumab. (FDA)
Esophageal/gastroesophageal junction cancer	Adjuvant therapy	Nivolumab is indicated for the adjuvant treatment of esophageal cancer or gastroesophageal junction cancer in patients with residual pathology after neoadjuvant chemoradiotherapy and complete surgical resection. (FDA)
Renal cell carcinoma	Adjuvant therapy	Pembrolizumab is used as adjuvant therapy in RCC patients at intermediate or high risk of recurrence following partial or complete nephrectomy. (FDA)
Breast cancer	Neoadjuvant/adjuvant therapy	Pembrolizumab combined with chemotherapy is used as neoadjuvant therapy in patients with early high-risk TNBC and as a single agent after surgery as adjuvant therapy. (FDA)

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