Research progress of sintilimab in the treatment of cancer (Review)

YUAN-YUAN WU and HUA SHAO

Department of Pharmacy, Zhongda Hospital of Southeast University, Nanjing, Jiangsu 210009, P.R. China

Received November 8, 2024; Accepted March 5, 2025

DOI: 10.3892/ol.2025.14986

Abstract. Sintilimab, a fully human immunoglobulin G4 monoclonal antibody targeting the programmed cell death receptor 1 (PD-1) pathway, has emerged as significant in cancer immunotherapy, demonstrating promising antitumor effects in various malignancies. The present review summarizes the current clinical data, highlighting the role of sintilimab in treating various types of cancer, including non-small cell lung cancer, liver cancer, gastric cancer and neuroendocrine tumors. The review also explores the mechanism of action of sintilimab, its structural and pharmacokinetic properties and its safety profile, which includes a comprehensive analysis of immune-related adverse events. Notably, the high binding affinity of sintilimab to PD-1 and its fully humanized nature contribute to its potent immunotherapeutic effects and favorable safety profile. Clinical trials have shown that sintilimab, either used as a monotherapy or in combination with chemotherapeutic agents, can significantly extend progression-free and overall survival in patients with advanced cancers. Furthermore, the economic implications and accessibility of sintilimab, particularly in resource-limited settings, are discussed. The current review reports on the innovative potential of sintilimab in shaping future cancer treatment strategies and emphasizes the need for personalized therapy based on individual patient biomarkers. The study reveals that sintilimab is not only a viable alternative to existing PD-1 inhibitors, but also a promising candidate for further research and development in immuno-oncology.

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Correspondence to: Professor Hua Shao, Department of Pharmacy, Zhongda Hospital of Southeast University, 87 Ding Jia Qiao, Nanjing, Jiangsu 210009, P.R. China
E-mail: 13685650553@163.com

Key words: sintilimab, cancer, curative effect, security, progress

1. Introduction

Cancer, a prevalent malignant neoplasm in clinical settings, can affect various organs, and is characterized by its rapid progression and high fatality rate, posing a threat to human health. The World Health Organization estimates a 60% rise in global cancer incidence within the next 2 decades, underscoring the severity of prevention and control challenges (1). The etiology of cancer is rooted in genetic mutations that trigger uncontrolled cell division, followed by factors that exacerbate this growth, enabling cancer cells to penetrate the basement membrane and metastasize to distant organs; this can result in widespread organ failure and ultimately patient mortality (2,3). The development of cancer is influenced by numerous factors, i.e. external factors, including physical stimuli (such as mechanical stimuli, ultraviolet light, radiation) and biological factors (such as viruses, bacteria); and internal factors, including immune dysfunction, endocrine disorders and genetic factors. All of these factors can increase the risk of cancer by affecting normal cell growth and genetic stability (4,5).

Most types of cancer are initially treated with surgery, which aims to achieve a complete cure. If surgery is not possible, chemotherapy and radiation therapy are used as alternative treatments (6); however, these treatments have poor targeting abilities and can damage normal cells along with cancer cells, leading to serious adverse reactions (7).

Recently, tumor immunotherapy has emerged as a major breakthrough in cancer treatment, which mainly utilizes the human immune system through active or passive methods to enhance the specific anticancer immunity of the patient to kill cancer cells (8). This has achieved notable therapeutic effects in some patients with advanced cancer. Among them, immune checkpoint inhibitors (ICIs), a type of immunotherapy, have markedly prolonged the overall survival (OS) and progression-free survival (PFS) of patients with various advanced cancers, and significantly improved the objective response rate (ORR) (9). Following the success of nivolumab and pembrolizumab in tumor immunotherapy, sintilimab, a programmed cell death receptor 1 (PD-1) inhibitor that was developed in China, stands out for its distinct binding affinity and epitope.

Unlike nivolumab and pembrolizumab, sintilimab targets the FG loop of PD-1, exhibiting a ~10 and 50 times stronger binding affinity, respectively (10). This heightened affinity may endow sintilimab with greater efficacy in blocking the PD-1/programmed death-ligand (PD-L)1 pathway, thus amplifying T cell antitumor activity. As a fully humanized monoclonal antibody, sintilimab also presents lower immunogenicity, potentially minimizing immune-related adverse events. While nivolumab has demonstrated effectiveness across various types of cancer, sintilimab, with its unique pharmacological profile and potential therapeutic advantages, may provide superior outcomes in specific patient cohorts (11).

A single study has revealed that the PFS of sintilimab in combination with platinum-based doublet chemotherapy for non-squamous non-small-cell lung cancer (NSCLC) is comparable to that of pembrolizumab, atezolizumab, tislelizumab, camrelizumab and nivolumab in combination therapies. Additionally, the rates of adverse events at any grade were similar among these PD-L1 inhibitors (12). However, prospective studies and the comparison in animal trials have not yet been reported in the literature, so it is not discussed in this paper. Moreover, considering cost-effectiveness and accessibility, sintilimab is particularly advantageous in resource-limited or price-sensitive settings, offering an affordable alternative that could reshape cancer treatment strategies globally.

2. Introduction to sintilimab

Structure. Sintilimab is a recombinant fully human immunoglobulin G4 (IgG4) monoclonal antibody against PD-1 that was developed using yeast technology. Sintilimab has an IgG4 framework, which is known to have a very low impact on antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) and is an ideal choice for therapeutic antibodies (13). The most important factor affecting the clinical efficacy of anticancer drugs is the ability of the antibody to bind to the target with sufficient strength and duration. Structural analysis has shown that the epitope of the sintilimab/PD-1 complex is located in the FG ring of PD-1, which is different from nivolumab or pembrolizumab. Notably, sintilimab can bind to more PD-1 molecules on $CD3^+$ T cells than nivolumab or pembrolizumab, with superior T cell activation properties. Sintilimab has a good performance in terms of prolonged binding ability, good safety and observed clinical efficacy (14).

Pharmacokinetics. Pharmacokinetics and anti-drug antibody (ADA) analyses of sintilimab have been conducted *in vitro*, in animal models and in human subjects. A single study has indicated that sintilimab does not demonstrate antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity (15). In cynomolgus monkeys, serum concentrations of sintilimab and the area under the curve have been shown to be increased in a dose-dependent manner within the range of 1-30 mg/kg. When administered at a dose of 200 mg/kg for 2 weeks, sintilimab was well tolerated and did not result in any drug-related fatalities (15). Standard pharmacokinetic evaluations following a single intravenous dose of 10 mg/kg in PD-1 knockout mice revealed serum half-lives of 35.6 h for sintilimab, compared with 43.5 h for nivolumab and 42.5 h for pembrolizumab (16). Among 381 patients treated with sintilimab, only 0.52% (2/381) tested positive for ADA, and 0.26% (1/381) developed neutralizing antibodies following sintilimab infusion (17).

Functional role. By binding to PD-1, sintilimab can block its interaction with PD-L1 and PD-L2, thereby inhibiting the PD-1/PD-L1 pathway that leads to tumor immune tolerance, and activating T cell function, enhancing T cell immune surveillance and killing ability against tumors, generating tumor immune responses, thus achieving the goal of treating tumors (18). Notably, the invasion and metastasis of tumors occur through continuous interactions with the surrounding microenvironment. Previous evidence has shown that abnormal tumor blood vessels in the tumor microenvironment promote immune-suppressive cells to evade, thereby promoting tumor angiogenesis. This vicious cycle leads to the ineffectiveness of single immunotherapy or anti-angiogenesis single therapy (19). Therefore, the strategy of combining anti-angiogenesis therapy and immunotherapy seems likely to break the balance of the tumor microenvironment and to improve treatment responses (Fig. 1).

Safety. A previous safety assessment of sintilimab included data from 12 clinical studies involving various tumor types, including NSCLC, esophageal cancer (EC) and liver cancer, with a total of 2,461 patients (20). Of the 568 patients treated with monotherapy, 91.2% experienced an adverse reaction, rising to 98.0% among the 1,893 patients treated with the combination. In addition, common adverse reactions and their incidence in sintilimab treatment have been reported on, including anemia, fever, thyroid dysfunction and more serious grade 3 and above adverse reactions (Table I) (21-24). These detailed safety summaries not only provide a comprehensive view of treatment with sintilimab, but also offer an important reference for future individualized treatment strategies and adverse event management.

3. Specific role of sintilimab in various types of tumors

Sintilimab, as an immunotherapy drug, has shown broad application potential and efficacy in various types of cancer, as shown in Table II.

NSCLC. NSCLC is the second most commonly diagnosed cancer worldwide and a leading cause of cancer-related mortality. NSCLC accounts for >85% of all lung cancer cases, with a 5-year survival rate of 26% after diagnosis and 6% for advanced patients treated with traditional chemotherapy regimens (25). The advent of PD-1/PD-L1 immunotherapy has significantly improved the treatment outlook for patients with inoperable NSCLC, becoming an important option for first-line and subsequent treatments (26).

The ORIENT-11 study, a phase III, randomized, placebo-controlled clinical trial, investigated the efficacy of sintilimab combined with gemcitabine and cisplatin (GemCis) as first-line therapy for patients with advanced non-squamous NSCLC with EGFR or ALK gene mutations. The OS results, published in the journal 'Lung Cancer' in September 2022, demonstrated a median OS time of 24.2 months for the

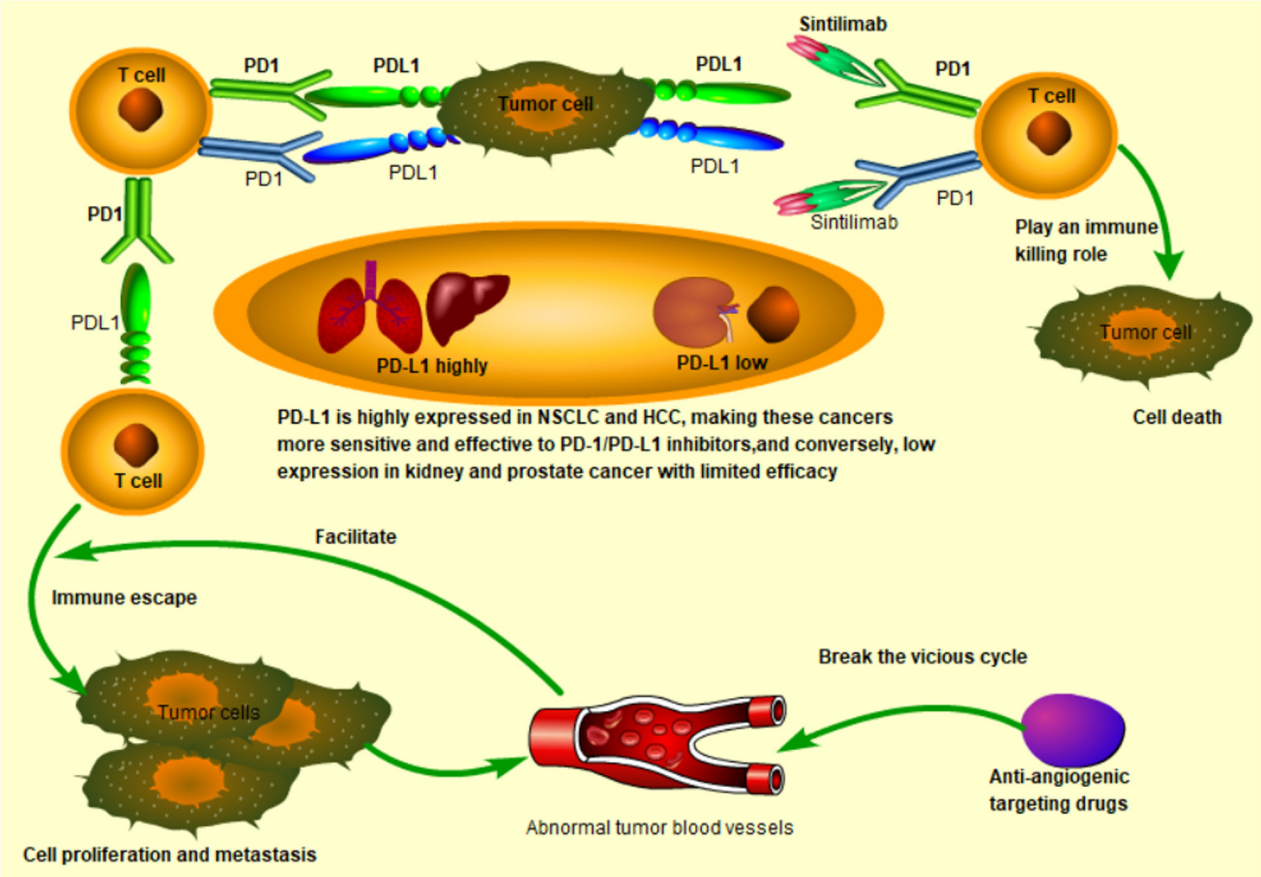

Figure 1. Mechanism of Sintilimab combined with antiangiogenic agents in cancer treatment. The diagram was created using Portable Pathway Builder Tool (version 1.5.2; QIAGEN) to clearly illustrate the molecular pathways and clinical outcomes associated with this combination therapy. Sintilimab blocks PD-1/PD-L1 interaction, enhancing T cell-mediated antitumor immunity. Abnormal tumor blood vessels promote immune evasion, reducing the efficacy of single-agent therapies. Combining anti-angiogenesis with immunotherapy disrupts this cycle, improving treatment outcomes. PD-1, programmed cell death receptor 1; PD-L1, programmed death-ligand 1.

sintilimab plus chemotherapy group, which was significantly increased compared with the 16.8 months of the placebo group, with overall manageable adverse events (27). Furthermore, the combination of sintilimab with other treatments, such as docetaxel, cytokine-induced killer cell immunotherapy, radiotherapy and anlotinib, has shown promising antitumor effects, warranting further exploration (18,28).

In a phase Ib study (ChiCTR-OIC 17013726), the efficacy of sintilimab monotherapy for NSCLC was confirmed. The latest National Comprehensive Cancer Network guidelines recommend platinum-based regimens combined with PD-1 inhibitors (such as pembrolizumab) as the preferred first-line treatment for unresectable or metastatic NSCLC (29); similar combinations with sintilimab are also under investigation (30). In summary, the addition of sintilimab to chemotherapy regimens may significantly prolong the PFS and OS for patients with non-squamous NSCLC, leading to its approval in China as a first-line treatment for non-squamous NSCLC in February 2021.

Liver cancer. The global incidence of primary liver cancer ranks sixth in malignant tumors and its mortality rate ranks third (31). Due to the hidden onset of liver cancer, most patients are in the advanced stage when they are first diagnosed. The effectiveness of surgical resection, radiofrequency ablation and hepatic arterial chemoembolization treatment is limited, and the 5-year survival rate is 18% (32). With the improved understanding of tumor molecular signaling pathways and the tumor microenvironment, targeted therapy has become an area of focus in advanced hepatocellular carcinoma (HCC) clinical research. In addition to targeted therapy, ICIs have made breakthroughs in the treatment of advanced HCC in recent years (33).

In the ORIENT-32 Chinese multicenter phase III study of sintilimab combined with bevacizumab, 571 patients with advanced unresectable liver cancer were randomly assigned to the sintilimab-bevacizumab group (n=380) or sorafenib group (n=191) with a median follow-up time of 10 months. The results showed that the PFS time was 4.6 vs. 2.8 months in the sintilimab-bevacizumab group compared with in the sorafenib group ($P<0.0001$), and the OS time was significantly improved. The ORR of the sintilimab-bevacizumab group was 21%, which was significantly higher than the sorafenib group (4%). This previous study showed that sintilimab combined with bevacizumab can prolong the median OS and PFS of advanced HCC associated with chronic hepatitis B and improve ORR, which further confirms that the combination of immunotherapy and targeted therapy for advanced HCC is highly effective and suits the clinical reality in China (34). In June 2021, the China National Medical Products Administration officially approved

Table I. Sintilimab immune-associated adverse reactions.

	Reaction level, n (%)				
Immune-related adverse reactions	1	2	3	4	5
Immune-associated pneumonia	2 (0.1)	58 (2.4)	33 (1.3)	4 (0.2)	12 (0.5)
Immune-associated diarrhea and colitis	-	4 (0.2)	11 (0.4)	-	-
Immune-associated hepatitis	1 (<0.1)	4 (0.2)	15 (0.6)	8 (0.3)	2 (0.1)
Immune-associated nephritis	1 (<0.1)	3 (0.1)	7 (0.3)	-	-
Immune-associated endocrine diseases	379 (15.4)	200 (8.1)	20 (0.8)	2 (0.1)	-
Thyroid and parathyroid diseases	380 (15.4)	194 (7.9)	3 (0.1)	-	-
Hypothyroidism	265 (10.8)	163 (6.6)	1 (<0.1)	-	-
Hyperthyroidism	182 (7.4)	34 (1.4)	2 (0.1)	-	-
Other thyroid diseases	28 (1.1)	6 (0.2)	-	-	-
Hypophysitis	3 (0.1)	4 (0.2)	5 (0.2)	1 (<0.1)	-
Adrenal insufficiency	2 (0.1)	5 (0.2)	3 (0.1)	-	-
Immune-related skin adverse reactions	57 (2.3)	55 (2.2)	22 (0.9)	1 (<0.1)	-
Immune-associated elevation of amylase and lipase and pancreatitis	44 (1.8)	26 (1.1)	17 (0.7)	6 (0.2)	-
Immune-associated thrombocytopenia	-	1 (<0.1)	3 (0.1)	5 (0.2)	-
Immune-related cardiotoxicity	1 (<0.1)	5 (0.2)	4 (0.2)	-	2 (0.1)
Immune-associated nervous system adverse reactions	-	5 (0.2)	1 (<0.1)	1 (<0.1)	2 (0.1)
Musculoskeletal and connective tissue immune-related adverse reactions	1 (<0.1)	4 (0.2)	2 (0.1)	-	-
Ocular immune-related adverse reactions	2 (0.1)	-	1 (<0.1)	-	-

The table categorizes adverse reactions by severity levels (1 to 5), where higher numbers indicate more severe reactions.

the innovative PD-1 inhibitor sintilimab injection combined with bevacizumab injection for the first-line treatment of unresectable or metastatic HCC that has not previously received systematic therapy (35).

Gastric cancer. Gastric cancer, the fifth most common type of cancer worldwide, is the fourth leading cause of cancer-related mortality (36). While early-stage disease can be effectively treated with surgery and adjuvant chemoradiotherapy, a lack of noticeable symptoms often results in advanced-stage diagnosis (37). Despite advancements in chemotherapy, the survival rate for advanced gastric cancer remains <12 months (38).

The Attract-02 study demonstrated that nivolumab significantly reduced mortality in Asian patients with advanced or metastatic gastric cancer (39), leading to approvals for nivolumab and pembrolizumab as third-line treatments in Japan and the U.S., respectively (40). In China, sintilimab, a domestically developed PD-1 inhibitor, has emerged as a promising second-line treatment, with regulatory approval supported by the ORIENT-16 phase III trial (41). This trial, conducted across 62 Chinese hospitals, involved 650 patients with unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, randomly assigned to sintilimab or placebo in combination with capecitabine and oxaliplatin. Sintilimab improved the OS time to a median of 15.2 months compared with 12.3 months in the placebo group (42). In particular, patients with a PD-L1 combined positive score of ≥5 showed an even more pronounced OS benefit with sintilimab at 18.4 vs. 12.9 months for the placebo. These findings underscore the potential of sintilimab in enhancing survival for specific patient populations, marking a significant advancement in the second-line treatment of advanced gastric cancer (43).

EC. EC is a common, aggressive and poorly prognostic malignant tumor that seriously threatens patient health. Currently, the main treatment methods include surgery, radiation therapy and chemotherapy; however, local recurrence and metastasis after surgery for patients with locally advanced EC are unavoidable (44). Immunotherapy has great potential in the treatment of EC (45). To reduce local and distant recurrence, and to improve survival rates, neoadjuvant chemoradiotherapy (NACT) has been tested. Based on the CROSS study, Western countries such as the UK, Germany, France, the US, Canada, Australia and New Zealand have adopted NACT plus surgery as the standard treatment for patients with locally advanced EC (46). In Asia, particularly in Japan, NACT before surgery has been advocated as the standard treatment based on the results of the JCOG9907 trial (47). ORIENT-15 is the first global phase III study conducted by Chinese researchers targeting patients with EC with immunotherapy and chemotherapy. The study enrolled 659 patients, with 327 receiving sintilimab plus chemotherapy (cisplatin plus paclitaxel or cisplatin plus 5-FU) and 332 receiving a chemotherapy regimen alone (placebo plus cisplatin plus paclitaxel or cisplatin plus 5-FU). The interim

Table II. Research progress of Sintilimab in different cancers.

First author, year	Cancer name	Results		(Refs)
Yang *et al*, 2020; Liu *et al*, 2024; Dehghani *et al*, 2023	NSCLC	Progression-free survival was significantly longer in the sintilimab + IBI305 + chemotherapy group than in the chemotherapy alone group	ORIENT-11 ChiCTR-OIC 17013726	(28-30)
Ren *et al*, 2021	Liver cancer	Sintilimab combined with bevacizumab can prolong the median OS, PFS and increase ORR in advanced HCC associated with chronic hepatitis B	ORIENT32	(34)
Janjigian *et al*, 2021; Xu *et al*, 2023	GC	Compared with placebo, sintilimab significantly improved OS in all patients and in patients with CPS of 5 or more	ORIENT-16	(42,43)
Lu *et al*, 2022	EC	The OS and PFS of sintilimab combined with chemotherapy were better than those of chemotherapy alone, PD-L1 positive patients showed more significant improvement	ORIENT-15	(48)
Zeng *et al*, 2023; Jin *et al*, 2023	BTC	Sintilimab + gemcitabine and cisplatin met pre-specified endpoints and showed an acceptable safety profile	ChiCTR2000036652	(52,53)
Qiu *et al*, 2024	PC	Advantages of S-1 in combination with sintilimab and anlotinib as second-line therapy for patients with pancreatic cancer liver metastases to prolong OS	ChiCTR2000030659	(60)
Xiao *et al*, 2024	CRC	Sintilimab can significantly increase the CR rate of pMMR LARC in NACT	NCT04304209	(64)
Wang *et al*, 2023; Xu *et al*, 2022	Cervical cancer	Treatment with sintilimab in combination with NAB-paclitaxel or anlotinib has shown good antitumor activity and manageable toxicity in patients with advanced cervical cancer	NCT04341883	(69,70)
Jia *et al*,2022	NEN	Sintilimab was well tolerated in patients with NENs and the efficacy was encouraging	NCT02937116	(72)
Liu *et al*, 2024	Nasopharynx cancer	The sintilimab group had a higher event-free survival rate than the standard treatment group	NCT03700476	(73)
Tian *et al*, 2022	STS	Sintilimab combined with doxorubicin is a safe and promising treatment for patients with advanced STS who have failed previous systemic therapy, including anthracycline chemotherapy	ChiCTR1900027009	(74)
Lu *et al*, 2021	ccRCC	TKIs, together with 6-8 cycles of sintilimab followed by the single use of a TKI, are a feasible way to treat metastatic ccRCC patients as second-line treatment	NCT04735861	(75)
Li *et al*, 2021	HNSCC	Addition of sintilimab to IC could provide longer PFS time than traditional chemotherapy regimen	No.201356HN	(76)
Li *et al*, 2022	Ovarian clear cell carcinoma	The combination of sintilimab and bevacizumab has a good effect in the treatment of ovarian clear cell carcinoma	NCT04735861	(77)
Wei *et al*, 2022	Endometrial cancer	Sintilimab plus anlotinib demonstrated robust therapeutic benefits with tolerable toxicity in endometrial can	NCT04157491	(78)

NSCLC, non-small cell lung cancer; OS, overall survival; ORR , objective response rate; HCC, hepatocellular carcinoma; CPS, combined positive score; GC, gastric carcinoma; EC, esophageal cancer; BTC, biliary tract carcinoma; PC, pancreatic cancer; CRC, colorectal cancer; NEN, neuroendocrine tumors; STS, soft tissue sarcoma; ccRCC, cell carcinoma renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma; CR, complete response rate; pMMR, mismatch repair proteins; LARC, locally advanced rectal cancer; NACT, neoadjuvant chemoradiotherapy; NAB-paclitaxel, nanoparticle albumin-bound paclitaxel; TKIs, tyrosine kinase inhibitors.

results as of April 9, 2021 showed that for all populations, the OS and PFS of the sintilimab plus chemotherapy group were greater compared with those of the chemotherapy alone group (OS, 16.7 vs. 12.5 months; PFS, 7.2 vs. 5.7 months), and the improvement was more obvious in PD-L1-positive patients (OS, 17.2 vs. 13.6 months; PFS, 8.3 vs. 6.4 months) (48).

Biliary tract cancer (BTC). BTC is an increasingly prevalent hepatobiliary malignancy with diverse characteristics across regions. Surgery is the only curative option for this type of cancer; however, it is inaccessible to 70% of patients with advanced or metastatic disease due to asymptomatic early stages, resulting in a poor 5-year survival rate of <5% and high recurrence rates post-surgery (49). Monotherapy with anti-PD-1/PD-L1 antibodies, such as pembrolizumab and nivolumab, has shown modest efficacy in BTC, with an ORR of 3-22% (50). The combination of durvalumab with GemCis has demonstrated an improved OS and is now recommended as a first-line regimen by the National Comprehensive Cancer Network guidelines (51). A phase II trial of sintilimab combined with GemCis as a first-line treatment in advanced BTC showed a median OS and PFS time of 15.9 and 5.1 months, respectively, with an ORR of 36.7%, indicating the efficacy and safety of the regimen. Furthermore, sintilimab paired with anlotinib as a second-line therapy for advanced BTC exhibited promising antitumor activity and a manageable safety profile, with a median OS time of 12.3 months, offering a potential second-line treatment option (52,53).

Pancreatic cancer. Pancreatic cancer is a malignant tumor of the pancreas, which can originate from the exocrine glands of the pancreas, endocrine glands or non-epithelial tissues. It has a poor prognosis and a high morbidity and mortality rate compared to most tumors, which is increasing annually (54). A total of 85% of patients are unable to undergo radical surgery at initial diagnosis, and the 5-year survival rate for those who undergo radical resection is <30% (55). In recent years, PD-1 and PD-L1 have become the focus of research and development, and have been shown to have potential as 'cancer killers', with notable results in treating various types of tumors, especially in patients with positive PD-L1, microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) or high tumor mutational burden (TMB) (56,57). Unfortunately, only a small number of patients with pancreatic cancer meet these conditions and limited clinical activity of ICIs has been observed.

In recent years, small-sample clinical trials have yielded positive results for anti-PD-1 antibodies combined with chemotherapy drugs in advanced pancreatic cancer (58,59). A previous study evaluated the efficacy and safety of a combination of S-1, sintilimab and anlotinib as second-line treatment for patients with pancreatic cancer and liver metastases. A total of 23 patients were included in the study, 19 of whom underwent objective efficacy evaluation. In the assessable population, the ORR was 10.5% (95% CI, 0.4-25.7%), PFS was 3.53 months (95% CI, 2.50-7.50) and OS was 8.53 months (95% CI, 4.97-14.20) (60). This study suggests the advantage of S-1 in combination with sintilimab and anlotinib as second-line therapy for prolonging OS in patients with pancreatic cancer and liver metastases.

Colorectal cancer (CRC). CRC, the second most frequent malignant tumor in the digestive system after gastric cancer and EC, is globally on the rise, with some patients presenting with distant metastases that preclude surgical intervention (61). The standard treatment for locally advanced rectal cancer (LARC) involves NACT, followed by total mesorectal excision and adjuvant chemotherapy, which has shown improved local control and high pathological complete response rates (62). The KEYNOTE-177 phase III trial data have led to the recommendation of anti-PD-1 therapy as the first-line treatment for dMMR metastatic CRC, with ICIs also demonstrating benefits in patients with non-metastatic dMMR CRC (63). In a randomized phase II trial (ClinicalTrial.gov no. NCT04304209), the addition of sintilimab, a PD-1 antibody, to NACT in patients with proficient mismatch repair LARC significantly enhanced the complete response rate from 26.9 to 44.8%, with a manageable safety profile. This suggested that PD-L1 positivity can predict which patients may benefit most from combined therapy (64). Other studies have reported that the complete response rate may be related to the duration of exposure to ICIs (65). Therefore, it is suggested that some patients may require a longer neoadjuvant ICI regimen to achieve complete remission.

Cervical cancer. Cervical cancer, a leading gynecological malignancy, often results from the progression of cervical erosion and other diseases, with early detection and treatment being crucial for superior outcomes. Globally, this disease is responsible for >300,000 mortalities annually (66). NACT is now a standard approach to downstage tumors, eliminate micrometastases and mitigate radiation complications before radical surgery (67).

Recently, the KEYNOTE 826 study showed that adding the PD-1 inhibitor pembrolizumab to platinum-based chemotherapy as a first-line treatment, compared with a placebo, in patients with PD-L1-positive tumors significantly improved the PFS and OS (68). A subsequent phase II study (NCT04341883) treated patients with recurrent or metastatic cervical cancer who had progressed after at least one systemic treatment with a combination of sintilimab and nanoparticle albumin-bound paclitaxel (nab-paclitaxel). Among the 27 patients, the ORR was 44.4%, with a disease control rate of 88.9%, a median PFS of 5.2 months and a median OS of 13.1 months, indicating the promising antitumor activity and manageable toxicity of the combination (69). In another phase II study led by Xu *et al* (70), sintilimab combined with anlotinib was evaluated in 42 patients with recurrent or metastatic cervical cancer. The ORR was 54.8%, with 59.0% of the 39 evaluable patients responding to treatment, and a disease control rate of 94.9%. The median PFS was 9.4 months, with a subgroup analysis revealing a median PFS of 11.1 months for squamous cell carcinoma and 5.8 months for adenocarcinoma, suggesting a differential response to sintilimab combined with antiangiogenic therapy based on tumor histology (70).

Neuroendocrine neoplasms (NEN). NENs are tumors that originate from neuroendocrine cells, which are a large group of cells in the body with a neuroendocrine phenotype that can produce a variety of hormones. Neuroendocrine cells are found throughout the body; therefore, NENs can occur anywhere in

the body, but the most common are digestive neuroendocrine tumors (NETs), such as those in the stomach, intestines and pancreas, which account for ~2/3 of all NETs (71). NENs are a group of diseases with high heterogeneity but limited treatment options.

A phase I study evaluated the safety and efficacy of the anti-PD-1 monoclonal antibody sintilimab in the treatment of advanced NENs. This prospective study included patients with pathologically diagnosed NENs after failure of standard treatment, and each patient was treated with sintilimab and assessed for efficacy every 9 weeks. Of the 24 patients included, five had NETs, one had NET G3, 17 had neuroendocrine cancer (NEC), and one had adenocarcinoma and neuroendocrine mixed carcinoma. The most common primary tumor sites were the pancreas and gastrointestinal tract (seven and 10 cases, respectively). In the phase Ia trial, the ORR was 20.8% for all enrolled patients and 27.8% for patients with NEC. The median PFS times for patients with NET and NEC were 2.2 and 2.1 months, respectively. The median OS times for NET and NEC were not applicable (NA) and 10.8 months (95% CI, 4.3, NA), respectively. The duration of response was not achieved and the median follow-up was 20.7 months. Treatment-related adverse events (TRAEs) occurred in 17 patients (70.8%). The most common TRAE was thyroid dysfunction (41.7%). In addition, PD-L1 positivity (tumor proportion score ≥1%) was 18.8% (3 of 16 cases), and PD-L1 expression was not associated with response (72). These results suggested that sintilimab may be well tolerated in patients with NEC and the efficacy is encouraging.

Efficacy in other tumors. In other tumors, sintilimab has also been reported to be effective. In patients with nasopharyngeal carcinoma, a multicenter, randomized controlled phase III trial at nine hospitals in China evaluated the effect of adding sintilimab to standard chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma. A total of 425 patients were included and randomly assigned to sintilimab (n=210) or standard treatment (n=215) groups. At a median follow-up of 41.9 months, the sintilimab group had a higher event-free survival rate (86 vs. 76%) compared with that in the standard treatment group. The OS at 36 months was not significantly different between the two groups (92 vs. 92%) (73).

In patients with soft tissue sarcoma (STS), a retrospective study analyzed the clinical data of 28 patients with advanced STS treated with nab-paclitaxel combined with sintilimab. The ORR, DCR and median PFS were 25%, 50% and 2.25 months, respectively (74). Overall, the therapeutic effect of nab-paclitaxel plus PD-1 inhibitors has been reported to be relatively good.

In a previous study, among patients with clear cell renal cell carcinoma (ccRCC), 17 patients with advanced ccRCC were selected from the Shanghai Cancer Center of Fudan University (Shanghai, China) and were treated with sunitinib as the first line of treatment. After progression of the disease, patients received pazopanib alone after 6-8 cycles of immunotherapy with sintilimab in combination with pazopanib. A total of three patients achieved partial response after second-line treatment, and 12 patients remained stable. Notably, two patients progressed, and one died due to progression. The median PFS time with second-line treatment was 12.2 months (75). This indicates the long-term survival of patients with metastatic disease using this treatment regimen and suggests a potential treatment option for patients with metastatic ccRCC.

In addition, in another study, a total of 163 patients with head and neck squamous cell carcinoma were included; 98 patients received immune checkpoint (IC) therapy alone and 65 patients also received sintilimab. After neoadjuvant therapy, patients underwent surgery (31.9%) or chemotherapy (68.1%). The results showed that the ORR in the IC group was significantly lower compared with that in the IC combined with sintilimab group (68.4 vs 84.6%; P=0.019). The median follow-up time was 28.0 months. In addition, the 2-year PFS was 27% (95% CI, 18-36%) in the IC group and 44% (95% CI, 32-56%) in the IC combined with sintilimab group; the difference was statistically significant (P=0.041) (76). These findings indicated that sintilimab could provide longer PFS duration than conventional chemotherapy.

Sintilimab has also shown good antitumor activity in gynecological tumors, such as ovarian clear cell carcinoma, endometrial carcinoma and breast cancer. The INOVA study was designed to evaluate the effect of sintilimab and bevacizumab combined therapy in patients with recurrent or persistent ovarian clear cell carcinoma. All 38 participants in the study received sintilimab plus bevacizumab. As of July 31, 2022, the ORR was 38.5% and the DCR was 76.9% of the 26 patients included in the evaluation (77). In addition, a phase II trial included 23 patients with endometrial cancer that progressed after platinum chemotherapy. A total of 23 patients received sintilimab intravenously and anlotinib orally. The median follow-up time was 15.4 months, the median PFS was not reached and the 12-month PFS rate was 57.1%. ORR was 73.9% (95% CI, 51.6-89.8%), with four complete responses and 12 partial responses (78).

In a previous study, a 49-year-old woman was diagnosed with triple-negative breast cancer (TNBC) with extensive lung and sternal metastases. After first-line chemotherapy failed, sintilimab in combination with paclitaxel and carboplatin was revealed to be highly effective. After the necessary investigation and clinical trials, this combination therapy may be considered for TNBC (79). In addition, sintilimab is being tested in various other types of cancer and the findings of these analyses could lead to new indications for the drug in the future.

In summary, the present review on sintilimab in cancer treatment provides a comprehensive and detailed analysis of its role across various cancer types, including both common and rare subtypes such as neuroendocrine tumors and biliary tract cancer. While previous studies have often focused on specific cancer types or aspects of sintilimab's mechanism, this study offers a broad overview, detailing its structure, pharmacokinetics and high binding affinity to PD-1. This detailed analysis helps explain why sintilimab may be more effective in certain patient populations and cancer types.

4. Reflections and prospects

After comprehensive analysis of clinical data and meta-analyses of sintilimab in the treatment of various tumors, we have a deeper understanding of its potential in tumor immunotherapy, as summarized in this section.

Efficacy and patient selection. The current bottleneck in ICB treatment is that efficacy and patient selection are key considerations for immunotherapy. For example, in the treatment of NSCLC, a phase III clinical trial (ORIENT-11) showed that sintilimab combined with chemotherapy significantly extended PFS and OS, particularly in patients with positive PD-L1 expression (48). This suggests that the expression level of PD-L1 is an important biomarker for predicting the efficacy of sintilimab. Another study (ORIENT-3) in patients with HCC revealed that sintilimab monotherapy showed a higher ORR in PD-L1-positive patients (34). These findings highlight the importance of evaluating PD-L1 expression before treatment to help select patients most likely to benefit from sintilimab treatment. In addition, TMB, as an emerging biomarker, has shown potential in predicting the efficacy of sintilimab, especially in MSI-H/dMMR tumors (80). However, the lack of results from head-to-head comparisons of sintilimab with other PD-1 antibodies is also a limitation of the present review.

Combination treatment strategies. As a PD-1 inhibitor, sintilimab has shown potential in combination with a variety of therapeutic methods in the treatment of cancer. The aim of the combination treatment strategy is to enhance antitumor effects by integrating drugs with different mechanisms of action, while potentially reducing resistance to monotherapy. For example, the combination of sintilimab with chemotherapy may take advantage of the immunomodulatory effects of chemotherapy drugs to enhance the immune response to tumors. In combination with anti-angiogenic drugs, the aim is to improve the tumor microenvironment and increase the penetration and activity of immune cells. In the treatment of NSCLC, a randomized, double-blind, multicenter phase III trial (ORIENT-11) revealed that combining sintilimab with chemotherapeutic agents, such as gemcitabine and cisplatin, significantly improved the PFS and OS in patients compared with chemotherapy alone (81). In addition, in another study (ORIENT-32), the combination of sintilimab and bevacizumab exhibited greater efficacy than sorafenib in patients with advanced HCC, significantly extending the PFS and OS (34). In addition, the combination of sintilimab with other ICIs, such as CTLA-4 inhibitors, may enhance efficacy by targeting different immunosuppressive pathways. These combination treatment strategies not only provide patients with more diversified treatment options, but also provide novel treatment ideas to overcome the complexity and heterogeneity of tumors. However, this combination therapy also faces several challenges, such as an increased incidence of adverse events, particularly immune-related adverse events (irAEs), which require close monitoring and management. Additionally, the high cost of combination therapy may limit its widespread application in some regions. Future research needs to further optimize the combination therapy regimen to enhance treatment efficacy and reduce adverse reactions, thereby providing more effective treatment options for patients with cancer.

Long-term efficacy and safety. The long-term efficacy and safety of sintilimab are key factors in evaluating its application in the treatment of cancer. The present review provides some data on its long-term effects and safety. For example, in a phase III clinical study in patients with advanced NSCLC, sintilimab combined with chemotherapy as first-line treatment not only showed good efficacy in the short term, but long-term follow-up results showed that patients in the combined treatment group had a significant extension in OS compared with those receiving chemotherapy alone. These findings suggested the potential of sintilimab to improve long-term survival in patients (81). In addition, in a study of patients with advanced HCC, the treatment regimen of sintilimab combined with bevacizumab showed sustained efficacy and manageable safety during long-term follow-up, which further confirmed the efficacy and safety of sintilimab in long-term treatment (34). These findings not only provide a scientific basis for the long-term application of sintilimab, but also provide important information for clinicians during treatment planning and patient consultations.

Affordability and accessibility. As an emerging PD-1 inhibitor, sintilimab has received extensive attention in terms of economic burden and accessibility. In resource-limited countries and regions, sintilimab has been considered a better economic choice due to its relatively low cost. For example, a study from China evaluated the cost-effectiveness of sintilimab in the treatment of NSCLC and found that sintilimab combined with chemotherapy had a higher cost-effectiveness ratio as first-line treatment compared with standard chemotherapy (82). In addition, the wide availability of sintilimab in China, due to its medical insurance coverage, has made this advanced immunotherapy affordable for more patients. These findings not only highlight the potential of sintilimab in global immuno-oncology therapy, but also underscore the importance of improving access to drugs to improve patient outcomes.

Treatment resistance and follow-up. Sintilimab, as a PD-1 inhibitor, has made significant progress in tumor therapy, but treatment resistance remains a major challenge. Research is currently exploring strategies to overcome this resistance and options for follow-up treatments. For example, one study examined patients with NSCLC who progressed after treatment with PD-1 inhibitors and found that the subsequent use of tyrosine kinase inhibitors may provide clinical benefit for this subset of patients (83). Another study evaluated a rechallenge treatment strategy using antiangiogenic agents in combination with ICIs in patients with HCC whose disease had progressed after treatment with PD-1 inhibitors, and showed a modest efficacy and manageable safety profile (84). These studies not only provide clues for understanding the mechanism of treatment resistance of sintilimab, but also provide a scientific basis for the selection of subsequent treatment strategies.

Future development of individualized therapy. Personalized therapy is considered the future direction of tumor immunotherapy and sintilimab shows great potential in this area. The latest research has explored how to optimize the treatment regimen of sintilimab based on the specific biomarkers and tumor characteristics of patients. For example, one study used genomic and transcriptomic data to identify specific gene expression patterns associated with sintilimab response, which may help predict the patients that are more likely to benefit from treatment (85). Another study focused on immune cell

subsets in the tumor microenvironment and found that specific patterns of immune cell infiltration were associated with the efficacy of sintilimab, providing a new perspective for individualized therapy (86). These studies not only deepen the understanding of the mechanism of action of sintilimab, but also lay the foundation for the development of new biomarkers and therapeutic strategies.

5. Conclusions

In summary, sintilimab, as a domestically developed PD-1 inhibitor in China, has demonstrated significant innovation in the field of tumor immunotherapy. Its innovative aspects are reflected in the following areas: Firstly, clinical studies of sintilimab in Asian populations have provided data different from Western populations, which is crucial for understanding the efficacy and safety of PD-1 inhibitors across different ethnicities and geographical regions. Secondly, the exploration of sintilimab in combination therapy, such as its use with chemotherapy, targeted therapy and anti-angiogenic drugs, offers new insights for enhancing treatment effects and overcoming drug resistance. Additionally, the application of sintilimab in rare or specific subtypes of cancer, such as NETs and BTC, has expanded the therapeutic scope of PD-1 inhibitors, providing new hope to patients. Finally, the pharmacoeconomic advantages of sintilimab, especially in resource-limited regions, make its global accessibility and affordability one of its benefits. These innovations have not only propelled the application of sintilimab in clinical practice, but also provide new directions for future research and development.

Acknowledgements

Not applicable.

Funding

This work was supported by the Nanjing Pharmaceutical Society-Changzhou Four-Medicine Hospital Pharmaceutical Research Fund (grant no. 2023YX024), the Bethune Charity Foundation (grant no. BCF-XD-ZL-20220118-038) and the National Health Commission of China Pharmaceutical Health Science and Technology Development Research Center - Innovative Drug Post-Marketing Clinical Research Research Project - Surface Topic (grant no. WKZX2024CX501213).

Availability of data and materials

Not applicable.

Authors' contributions

YYW wrote the main manuscript text and prepared the figure and tables. HS reviewed and revised the manuscript. Data authentication is not applicable. Both authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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