Efficacy and safety of sintilimab plus albumin-bound-paclitaxel in recurrent or metastatic cervical cancer: a multicenter, open-label, single-arm, phase II trial

Yin Wang,[a,f] Jing Zhao,[b,f] Haixi Liang,[a,f] Junxiu Liu,[c] Shenjiao Huang,[d] Guorong Zou,[e] Xin Huang,[a,g,**] and Chunyan Lan[a,g,*]

[a]Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, China
[b]Department of Medical Imaging, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, China
[c]Department of Obstetrics and Gynecology, First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshaner Road, Guangzhou 510080, China
[d]Department of Obstetrics and Gynecology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou 556599, China
[e]Department of Radiotherapy, Panyu Central Hospital, Cancer Institute of Panyu, 8 Fuyu East Road, Guangzhou 511400, China

eClinicalMedicine
2023;65: 102274
Published Online 24 October 2023
https://doi.org/10.1016/j.eclinm.2023.102274

Summary

Background Sintilimab is an antibody against programmed cell death protein 1. We assessed the efficacy and safety of sintilimab plus albumin-bound (nab)-paclitaxel for the treatment of recurrent or metastatic cervical cancer.

Methods This multicenter, open-label, single-arm, phase II study (ClinicalTrials.gov identifier NCT04341883) enrolled patients with recurrent or metastatic cervical cancer who progressed after at least one line of systemic therapy. The patients received sintilimab 200 mg and nab-paclitaxel 260 mg/m^2 body surface area every 3 weeks. The primary endpoint was objective response rate (ORR) assessed by investigators per Response Evaluation Criteria in Solid Tumors version 1.1. Key secondary endpoints were progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety.

Findings From January 13, 2020 to February 21, 2022, 27 patients were enrolled and received treatment. Median patient age was 50 years (range, 34–68 years). By data cut-off (May 22, 2022), in intention-to-treat population, ORR was 44.4% (95% CI, 24.4%–64.5%). The disease control rate was 88.9% (95% CI, 70.8%–97.6%). Median PFS was 5.2 months (95% CI, 2.7–7.7 months). Median DoR was 3.8 months (95% CI, 0.7–6.9 months), and median OS was 13.1 months (95% CI, 5.8–20.4 months). Treatment-related grade 3 or 4 adverse events (AEs) occurred in 44.4% of the patients, and the most common AEs were decreased neutrophil count (22.2%), decreased white blood cell count (14.8%), and anemia (7.4%). The most common potential immune-related AEs were grade 1–2 hypothyroidism (18.5%), neutropenia (11.1%), and rash (7.4%).

Interpretation Sintilimab plus nab-paclitaxel treatment shows promising antitumor activity and manageable toxicity in patients with advanced cervical cancer. Larger randomized controlled trials are required for validation.

Funding Innovent Biologics Co., Ltd.; Csps Holdings Co., Ltd.

Keywords: Cervical cancer; Sintilimab; Albumin-bound-paclitaxel; Immunotherapy

*Corresponding author. Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, China.
**Corresponding author. Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, China.
E-mail addresses: lanchy@sysucc.org.cn (C. Lan), pumc04wy@163.com (X. Huang).
[f]Contributed equally.
[g]Contributed equally.

Research in context

Evidence before this study

PD-1 inhibitor monotherapies have been approved as a second-line therapy for PD-L1-positive cervical cancer. However, responses are modest. Synergistic effect of chemotherapy and PD-1 inhibitors has been demonstrated in some tumor types. We searched PubMed up to August 31, 2023 with the following terms: "PD-1" OR "programmed death protein 1" OR "PD-L1" OR "programmed death-ligand 1" AND "chemotherapy" OR "albumin-bound-paclitaxel" OR "nab-paclitaxel" AND "cervical cancer [Title/Abstract]" for clinical trials. The search was not limited to the language or date. Only one trial of nab-paclitaxel combined with a PD-1 inhibitor as a second-line therapy or later for patients with PD-L1-positive advanced cervical cancer has been published. However, the overall data on the efficacy and safety of chemotherapy combined with PD-1/PD-L1 inhibitors in patients in this setting are limited. Only one phase 2 trial of chemotherapy combined with PD-1 inhibitor in patients with PD-L1-positive advanced cervical cancer was published, reporting a response rate of 57.1% and a median progression-free survival of 5.7 months. There are no data on patients with PD-L1-negative tumors in this setting.

Added value of this study

To our knowledge, this is the first study that evaluates the combination therapy of a PD-1 inhibitor and nab-paclitaxel in patients with recurrent or metastatic cervical cancer regardless of tumor PD-L1 expression. In this study, the combination of sintilimab and nab-paclitaxel demonstrated promising antitumor activity and a tolerable safety profile when administered as a second-line therapy or later treatment.

Implications of all the available evidence

Combination of chemotherapy and PD-1 inhibitors is a promising option for second-line and later treatments in patients with recurrent cervical cancer. The investigation of the combination of sintilimab and nab-paclitaxel in patients with recurrent cervical cancer is warranted in larger trials.

Introduction

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related deaths in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020.[1] Despite the long-term survival of patients with early-stage disease,[2] the prognosis of patients with metastatic and recurrent disease remains poor.[3–5] Platinum-based chemotherapy, with or without bevacizumab, is the mainstay first-line treatment.[3,4] Recently, the KEYNOTE-826 study revealed that addition of the programmed cell death-1 (PD-1) inhibitor pembrolizumab to platinum-based chemotherapy, with or without bevacizumab, as first-line treatment significantly improved progression-free survival (PFS) and overall survival (OS) as compared with placebo among patients with programmed death ligand 1 (PD-L1)-positive tumors.[5] In that trial, the median PFS was 10.4 months and the OS at 24 months was 53.0% in the pembrolizumab group, versus 8.2 months (hazard ratio [HR], 0.62; $P < 0.001$) and 41.7% (HR, 0.64; $P < 0.001$) in the placebo group.

Nevertheless, most patients have tumor progression following first-line therapy. Treatment options for patients in these settings are limited. Pembrolizumab and nivolumab have been approved by the US Food and Drug Administration as second-line therapies for PD-L1-positive advanced cervical cancer based on the KEYNOTE 158[6] and CheckMate 358 studies,[7] respectively. Other PD-1 inhibitors, such as cemiplimab[8] and balstilimab,[9] have also demonstrated antitumor effects against cervical cancer. Nevertheless, the responses to PD-1 inhibitor monotherapies are only modest, with objective response rates (ORRs) ranging from 14.6% to 26.3%.[6–9]

Chemotherapy may enhance tumor antigen release and, thereby, enhance responses to immune checkpoint inhibitors.[5] Albumin-bound (nab)-paclitaxel is a common second-line regimen for advanced cervical cancer treatment. Nab-paclitaxel has shown considerable activity with moderate toxicity in the treatment of drug-resistant, metastatic, and recurrent cervical cancer. In a study by Alberts,[10] nab-paclitaxel was administered to patients with metastatic or recurrent cervical cancer who had progressed to first-line therapy and achieved an ORR of 28.6%, with a median PFS and OS of 5.0 and 9.4 months. Growing evidence shows that taxanes regulate many aspects of immune function, including lymphocyte recruitment and activation and production of immunoenhancing cytokines, such as IL-12, IFNγ, TNFα, and GMCSF, all of which may augment the antitumor activity of immunotherapies.[11] These findings provide a rationale to combine taxanes with anti-PD-1/PD-L1 inhibitors. Moreover, nab-paclitaxel and anti-PD-L1 inhibitors have shown synergistic antitumor activity in patients with advanced triple-negative breast cancer[12] and non-small cell lung cancer.[13] Nevertheless, there're few studies on the combination therapy of nab-paclitaxel and anti-PD-1 inhibitors in cervical cancer.

Therefore, in this phase II trial, we investigated the efficacy and safety of sintilimab, a selective anti-PD-1 monoclonal antibody, in combination with nab-paclitaxel, as second-line or later therapy for recurrent and metastatic cervical cancer.

Methods

Ethics

This is a multicenter, open-label, single-arm, phase II trial (ClinicalTrials.gov identifier: NCT04341883) conducted at three hospitals in China. The study protocol was approved by Sun Yat-sen University Cancer Center Ethics Committee (Reference Number, B209-204-01) and the ethics committee at each participating site. All patients provided written informed consent before enrolment.

Study design and participants

Patients, aged 18–70 years, with histologically confirmed recurrent or metastatic cervical cancer that had progressed after at least one line of platinum-based chemotherapy were eligible for enrollment. Patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and an Eastern Cooperative Oncology Group performance status score of 0 or 1. The patients were also required to have adequate hematological and organ function.

Key exclusion criteria were previous treatment with nab-paclitaxel; previous treatment with anti-PD-1/PD-L1 or anticytotoxic T-lymphocyte-associated antigen-4 antibodies; active autoimmune disease or a history of it; active central nervous system metastases; and active hepatitis B or hepatitis C virus infection. The full eligibility and exclusion criteria are described in the protocol (see Supplementary Materials). Per protocol, concurrent administration of any other antitumor therapy not described in the protocol is prohibited.

Procedures

Patients received sintilimab 200 mg intravenously every 3 weeks for up to 2 years and nab-paclitaxel intravenously at a dose of 260 mg/m^2 of body surface area every 3 weeks for up to 6 cycles. The dose of sintilimab was determined based on the phase Ia study of sintilimab in advanced solid tumors.[14] Treatment was continued until the maximum number of cycles for each component, disease progression, unacceptable toxicity, or withdrawal of patient consent. Dose reduction of sintilimab was not permitted whereas that of nab-paclitaxel was permitted.

Outcomes

The primary endpoint was the ORR, defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) according to RECIST version 1.1. The secondary endpoints were PFS, OS, disease control rate (DCR), duration of response (DoR), tolerability, and safety.

Responses were assessed by the investigators according to RECIST version 1.1 using computed tomography or magnetic resonance imaging at baseline and every two cycles for the first six treatment cycles, and then every three cycles until disease progression or up to 2 years from the first dose. CRs and PRs had to be confirmed with a repeat scan at least four weeks after the initial response.

Adverse events (AEs) were assessed continuously from the time of the first dose until 30 days after the last dose and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Tumor PD-L1 expression was tested using the PD-L1 22C3 pharmDx assay (Dako, Agilent Technologies, Santa Clara, CA, USA) and calculated as a combined positive score (CPS), defined as the number of PD-L1-stained cells divided by the total number of vital tumor cells multiplied by 100. Positivity was defined as a CPS $\geq$1.

Statistical analysis

A Simon's optimal two-stage design was used to test the primary endpoint, ORR. The KYENOTE-158 study demonstrated that the ORR of the anti-PD-1 antibody pembrolizumab in recurrent or metastatic cervical cancer was around 17%.[6] And previous study showed the ORR of nab-paclitaxel in patients with metastatic or recurrent cervical cancer was 28.6%.[10] Thus the combination of sintilimab and nab-paclitaxel was expected to result in an improved ORR of 45%. The null hypothesis that the true ORR was 17% was tested against a one-sided alternative of 45%. In the first stage, six subjects would be accrued. If there was no response or only one response, the study would be stopped. Otherwise, 16 additional subjects would be accrued for a total of 22 subjects. This design yields a type I error rate of 5% and power of 80% when the true response rate is 45%. Assuming a dropout rate of 20%, 27 patients were required.

The ORR and 95% CIs were calculated using the Clopper–Pearson method in both the intention-to-treat (ITT) population (all enrolled patients) and the efficacy-evaluable population (patients who received at least one dose of sintilimab plus nab-paclitaxel and had at least one available post-baseline assessment). Descriptive statistics were used to summarize the clinical results and AEs. DoR, PFS, and OS were analyzed using the Kaplan–Meier method to estimate median and two-sided 95% CI values. Primary and the key secondary endpoints were evaluated in different subgroups. Statistical analysis were conducted using R software V4.0.3.

Role of the funding source

The funders had no role in the study design, collection, management, analysis and interpretation of data, writing of the report or decision to submit it for publication.

Results

Participants

From January 2020 to February 2022, 34 patients were screened, of whom 27 were enrolled in the study. All 27

patients received at least one study treatment (ITT and safety population). One (3.7%) patient with hepatitis B virus (HBV) discontinued the study after one dose of study treatment because of protocol violation. She was confirmed to have high levels of serum HBV DNA (>1 × 10^4/mL), which is not meet the inclusion criteria. Thus, 26 (96.3%) patients were included in the efficacy evaluation.

As of May 22, 2022 data cut-off, the median follow-up was 10.2 months (range, 3.0–24.5 months). At the time of analysis, the median number of treatment cycles was five (range, 1–31), with the number for nab-paclitaxel ranging from one to six and that for sintilimab ranging from 1 to 31. Seven (25.9%) patients were still receiving treatment, and 19 (70.4%) discontinued treatment because they reached the upper limit of treatment duration (n = 1, 3.7%), disease progression (n = 13, 48.1%), AEs (n = 2, 7.4%), and patient withdrawal (n = 3, 11.1%) (Fig. 1). The baseline characteristics of the study population are summarized in Table 1.

Efficacy

In the first stage, six patients were enrolled, and two patients had confirmed PR. The ORR threshold for the

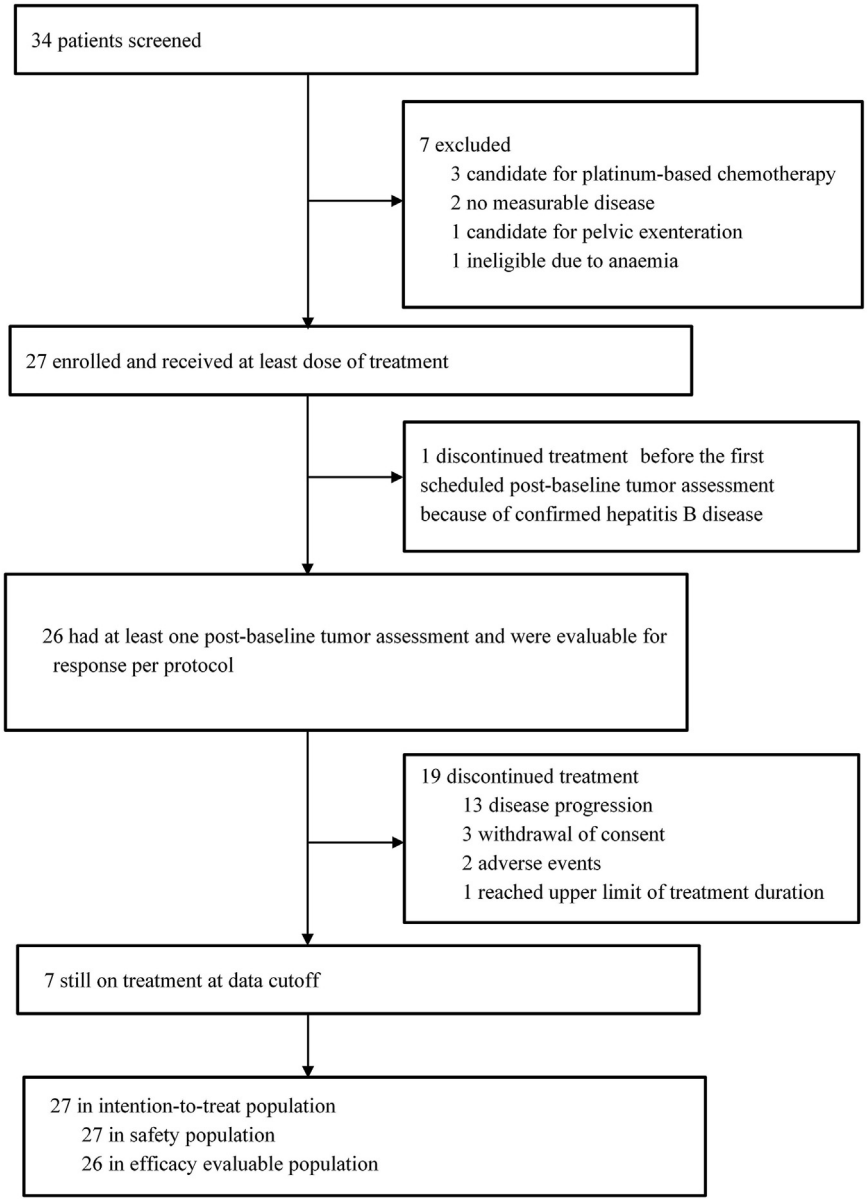

Fig. 1: **Participant flow diagram.**

first stage of Simon's two-stage was reached, and the trial continued to full accrual. Tumor responses are summarized in Table 2. In the ITT population, 12 (44.4%, 95% CI, 24.4%–64.5%) patients achieved an objective response, all of which were PRs. Stable disease was observed in 12 (44.4%) patients, and DCR was 88.9% (95% CI, 70.8%–97.6%) (Table 2). In the efficacy-evaluable population, ORR was 46.2% (95% CI, 25.6%–66.7%) (Table 2). Eighteen (66.7%) patients had PD-L1-positive tumors, and five (18.5%) patients had PD-L1-negative tumors. In the population of patients with PD-L1-positive tumors, the ORR was 55.6% (95% CI, 30.1%–81.0%); it was 20.0% (95% CI, 0.5%–71.6%) in those with PD-L1-negative tumors. Nineteen (70.4%) patients achieved a reduction from baseline in the target lesion size (Fig. 2a). Among the 12 patients with confirmed objective response, the median time to achieve response was 1.6 months (range, 1.2–3.3 months; Fig. 2b and c). Of the 12 partial responders, the responses were ongoing in eight (66.7%) patients (Fig. 2b), with three (25.0%) lasting over 12 months and five (41.7%) lasting over 6 months. The median DoR was 3.8 months (95% CI, 0.7–6.9 months) (Fig. 3a).

As of the cutoff date, 16 (59.3%) events of disease progression or death occurred. The median PFS was 5.2 months (95% CI, 2.7–7.7 months) (Fig. 3b), and the 6-month PFS rate was 49.3% (95% CI, 40.2%–70.7%). Twelve (44.4%) deaths occurred. The median OS was 13.1 months (95% CI, 5.8–20.4 months) (Fig. 3c), and 9-month OS rate was 77.6% (95% CI, 52.9%–80.8%). In the PD-L1-positive tumor population, median PFS was 5.2 months (95% CI, 2.7–7.7 months) (Fig. 4a), and median OS was 14.9 months (95% CI, 5.6–25.2 months) (Fig. 4b).

Thirteen patients (48.1%) received subsequent therapies after disease progression (Supplementary Table S1), including targeted therapy (n = 8), PD-1 inhibitors (n = 7), chemotherapy (n = 3), surgery (n = 1), and Chinese traditional medicine (n = 2). The details of the subsequent treatments were shown in Supplementary Table S2.

Safety

Treatment-related adverse events (TRAEs) of any grade occurred in all 27 patients (safety population) (Table 3), with the most common TRAEs being decreased white blood cell (WBC) count (n = 25, 92.6%), decreased neutrophil count (n = 24, 88.9%), asthenia (n = 17, 63.0%), and peripheral neuropathy (n = 16, 59.3%). A total of 12 (44.4%) patients experienced grade 3 TRAEs, including six cases (22.2%) with decreased neutrophil count, four (14.8%) with decreased WBC count, and two (7.4%) with anemia, and one (3.7%) each with asthenia and peripheral neuropathy. None of the patients experienced grade 4 TRAEs, treatment-related serious adverse events, or treatment-related death.

Characteristics	Patients
Age, years, median (range)	50 (34–68)
FIGO stage at initial diagnosis[a], No. (%)	
IB1	2 (7.4)
IB2	1 (3.7)
IIA1	3 (11.1)
IIA2	2 (7.4)
IIB	1 (3.7)
IIIB	1 (3.7)
IIIC1	9 (33.3)
IIIC2	1 (3.7)
IVB	7 (25.9)
Time from initial cancer diagnosis to first progression, months, median (range)	12 (3–70)
Time from first progression to second progression, months, median (range)	6 (2–38)
Time from initial cancer diagnosis to study enrollment, months, median (range)	26 (4–91)
ECOG performance status, No. (%)	
0	6 (22.2)
1	21 (77.8)
Histology, No. (%)	
Squamous cell carcinoma	23 (85.2)
Adenocarcinoma	2 (7.4)
Adenosquamous carcinoma	2 (7.4)
Location of metastases, No. (%)	
Lymph node	
Distant lymph nodes	11 (40.7)
Para-aortic lymph nodes	6 (22.2)
Pelvic lymph nodes	3 (11.1)
Lung	10 (37.0)
Liver	2 (7.4)
Pelvis	8 (29.6)
Bone	4 (14.8)
Pleura	10 (37.0)
Bladder	2 (7.4)
Vulva	2 (7.4)
Omentum	6 (7.4)
Other	6 (22.2)
Target lesion size, mm, median (range)	38 (12–110)
Previous radiotherapy, No. (%)	21 (77.8)
Adjuvant radiotherapy	9 (33.3)
Curative radiotherapy	5 (18.5)
Palliative radiotherapy	7 (25.9)
No. of previous system therapies[b], No. (%)	
1	15 (55.6)
2	10 (37.0)
≥3	2 (7.4)
Previous platinum, No. (%)	27 (100)
Previous paclitaxel, No. (%)	26 (96.3)
Previous bevacizumab, No. (%)	5 (18.5)
PD-L1 expression status, No. (%)	
Positive	18 (66.7)
Negative	5 (18.5)
Unknown	4 (14.8)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PD-L1, programmed cell death ligand 1. [a]Staging was according to 2018 FIGO staging for carcinoma of the cervix. [b]Per protocol, prior adjuvant therapy is not counted as a systemic chemotherapeutic regimen for the management of recurrent, persistent, or metastatic cervical cancer. However, adjuvant chemotherapy could be counted as one prior regimen in patients who experienced recurrence during or within 6 months of therapy completion.

Table 1: **Baseline characteristics (n = 27).**

Efficacy	Intention-to-treat population (*n* = 27)	Efficacy-evaluable population (*n* = 26)
ORR, No. (%)	12 (44.4)	12 (46.2)
95% CI	24.4–64.5	25.6–66.7
DCR	24 (88.9)	24 (92.3)
95% CI	70.8–97.6	74.9–99.1
Best overall response, No. (%)		
CR	0	0
PR	12 (44.4)	12 (46.2)
SD	12 (44.4)	12 (46.2)
PD	2 (7.4)	2 (7.7)
Not assessed[a]	1 (3.7)	–

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable disease. [a]One patient discontinued the study treatment before the first scheduled post-baseline scan.

Table 2: **Antitumor activity assessed using RECIST version 1.1.**

TRAEs led to sintilimab dose interruption in three (11.1%) patients, with anemia (*n* = 2, 7.4%) and asthenia (*n* = 1, 3.7%). Sintilimab was discontinued in two (7.4%) patients. The discontinuation was caused by consistent grade 2 increased blood creatinine after the 13th cycle of sintilimab in one patient whose ureters were blocked by the tumor and blood creatinine increased with time. The other one discontinued sintilimab because of the resurgence of tuberculous pneumonia after the third treatment cycle. One (3.7%) patient experienced nab-paclitaxel interruption owing to anemia. Two (11.1%) patients discontinued nab-paclitaxel, of whom one discontinued because of consistent grade 2 anemia, and delayed it for more than 6 weeks, and the other discontinued because of resurgence of tuberculous pneumonia. No dose reduction of nab-paclitaxel was needed.

Potential immune-related AEs (irAEs) assessed by the investigators occurred in ten (37.0%) of the 27 patients, and included hypothyroidism (*n* = 5, 18.6%), neutropenia (*n* = 3, 11.1%), rash (*n* = 2, 7.4%), asthenia (*n* = 1, 3.7%), increased blood creatinine (*n* = 1, 3.7%), and anemia (*n* = 1, 3.7). All patients had grade 1 or 2 irAEs, except for one patient who had grade 3 asthenia.

Discussion

In this study, we report the results of a phase 2 trial that evaluated the combination therapy of an anti-PD-1 antibody sintilimab and a chemotherapy regimen nab-paclitaxel in patients with recurrent or metastatic cervical cancer. When administered as a second- or later-line treatment, the combination of sintilimab and nab-paclitaxel demonstrated promising antitumor activity and a manageable toxicity profile. The ORR of this combination was 44.4% (95% CI, 24.4%–64.5%), median PFS was 5.2 months (95% CI, 2.7–7.7 months), and median OS was 13.1 months (95% CI, 5.8–20.4 months).

Thus far, several PD-1 and PD-L1 inhibitors have been evaluated as monotherapy or as part of combination therapy for patients with advanced cervical cancer in second-line or later treatments. In the KEYNOTE-158 trial,[6] pembrolizumab monotherapy showed an ORR of 17% (95% CI, 5%–37%), with a median PFS of 2.1 months (95% CI, 2.0–2.2 months) and a median OS of 11.1 months (95% CI, 9.1–14.1 months) in patients with PD-L1-positive cervical cancer. In the CheckMate 358 trial,[7] nivolumab demonstrated an ORR of 26.3% (95% CI, 9.1%–51.2%), with a median PFS of 5.1 months (95% CI, 1.9–9.1 months) and a median OS of 21.9 months (95% CI, 15.1 months to not reached) in the cervical cancer cohort. In a phase 3, randomised trial (EMPOWER-Cervical 1), patients with advanced cervical cancer who were treated with the PD-1 inhibitor cemiplimab, achieved an ORR of 16.4% (95% CI, 12.5%–21.1%) and a longer median OS with 12.0 months compared with those treated with chemotherapy chosen by the investigator (median OS, 8.5 months; HR, 0.69; $P < 0.001$).[8] In a phase 2 study on the safety and efficacy of the anti-PD-1 antibody balstilimab in patients with recurrent or metastatic cervical cancer, the ORR for balstilimab was 15%.[9] In our study, the response rate to sintilimab plus nab-paclitaxel seems promising. And the survival observed in the current study was comparable to that in the above-mentioned studies on anti-PD-1 therapy in patients with advanced cervical cancer. Furthermore, compared with an ORR of 28.6% for nab-paclitaxel monotherapy,[10] the response rate of 44.4% in our study supports the synergistic efficacy of combined sintilimab and nab-paclitaxel therapy.

Recently, An et al.[15] have reported a phase 2 trial of similar combination therapy. In that study, the efficacy of an anti-PD1 monoclonal antibody serplulimab plus nab-paclitaxel was evaluated in 21 patients with advanced cervical cancer. They achieved an ORR of 57.1%, with a DCR of 76.2%, a median PFS of 5.7 months, and an OS of 15.5 months. Our results are consistent with those reported by An et al. It is worth mentioning that, all the patients included in the trial by An et al. had PD-L1-positive tumors, which would have resulted in a better response to PD-1 inhibitors. In our study, patients were enrolled regardless of tumor PD-L1 expression. Moreover, both the patients with PD-L1-positive and PD-L1-negative tumors showed responses to the study treatment. In addition, 28.6% of the patients had ≥2 lines of prior therapies in the trial by An et al.,[15] compared with 44.4% of the patients in this setting in the current study. Our findings indicate that nab-paclitaxel is an attractive drug when combined with sintilimab to augment the immunotherapeutic response in cervical cancer.

The safety profile in the present study was consistent with the known toxic effects of sintilimab and nab-paclitaxel.[10,16,17] The toxicities in our study were moderate and manageable. Notably, 44.4% of the patients experienced grade 3 TRAEs, which was lower than that of the

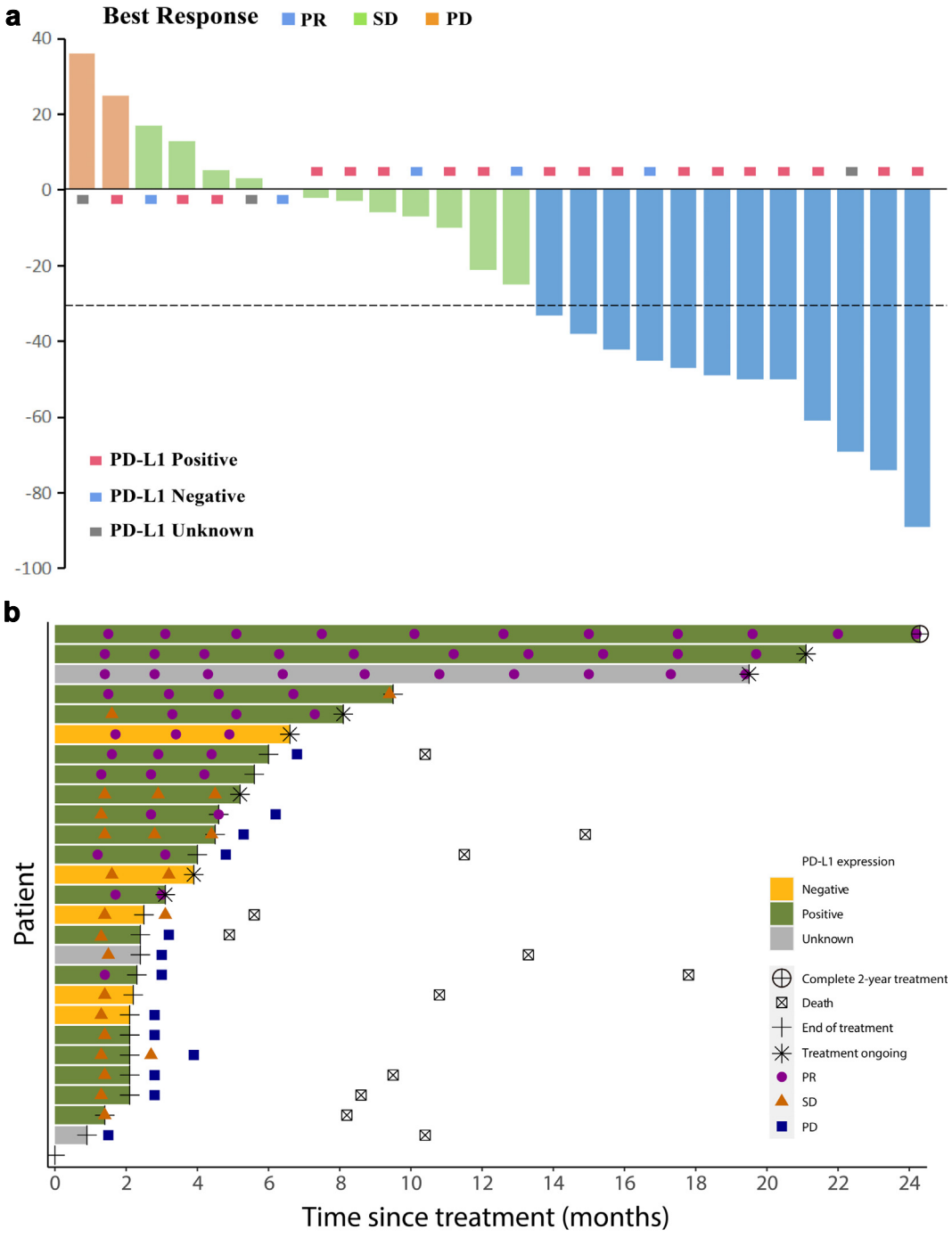

***Fig. 2:* Antitumor activity.** (a) Best percentage of change from baseline in the sum of the diameters of target lesions. Data for only those patients with available tumor assessments (efficacy-evaluable population) are shown (n = 26). The dashed line at −30% change represents the RECIST version 1.1 cutoff to define partial response. (b) Duration of responses. The length of each bar represents the treatment duration of each patient. All patients in the per-protocol population (intention-to-treat population) (n = 27) are shown. (c) Longitudinal change in tumor size from the baseline. Blue lines define objective response and red lines define non-responders. Only patients with available tumor assessment data are shown (n = 26). PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease.

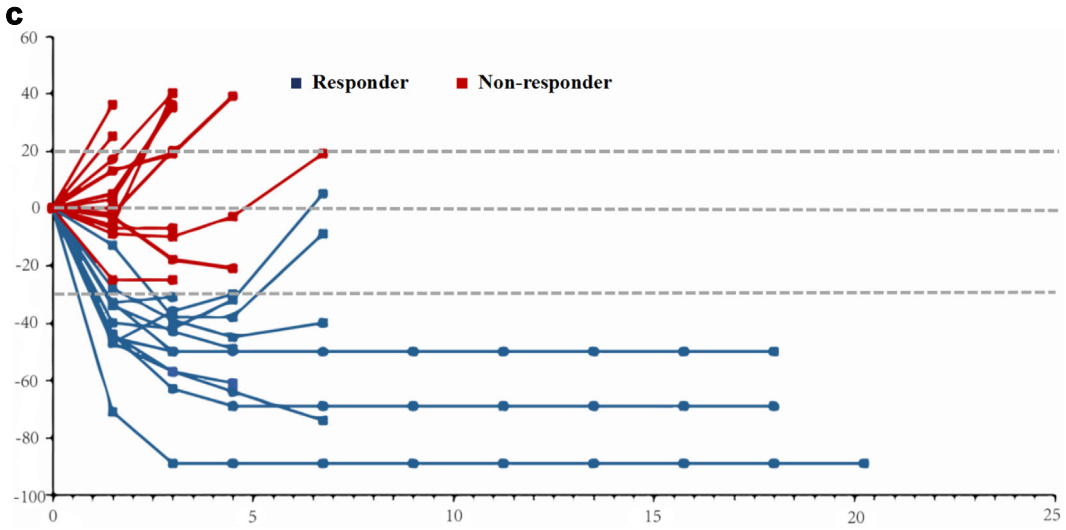

Fig. 2: (continued)

study on serplulimab plus nab-paclitaxel by An et al., with 81.0% of the patients experiencing ≥ grade 3 TRAEs.[15] Furthermore, none of the patients in the current study experienced grade 4 TRAEs, treatment-related serious adverse events, or treatment-related death. In addition, sintilimab did not compromise the nab-paclitaxel dose intensity. These findings suggest a safety advantage of sintilimab plus nab-paclitaxel.

However, the present study has some limitations. First, this was a single-arm study without a direct

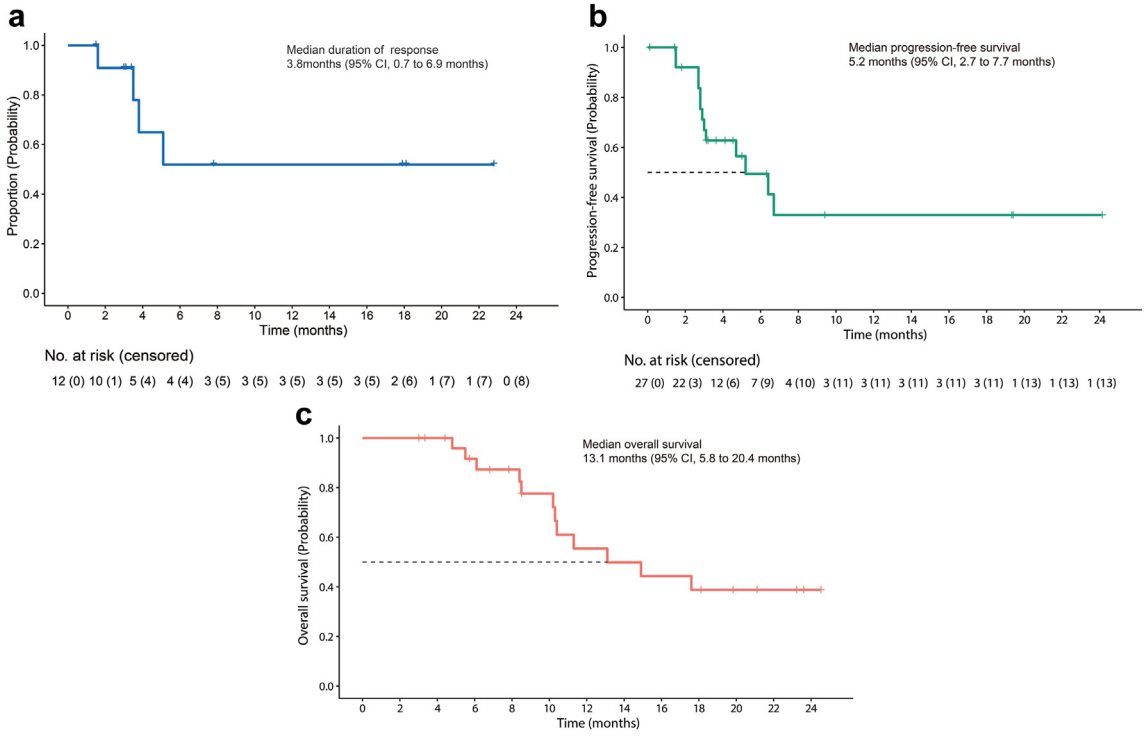

***Fig. 3:* Kaplan–Meier curves of duration of response, progression-free survival, and overall survival.** (a) Duration of response was assessed in responders (*n* = 12), and (b) progression-free survival and (c) overall survival were assessed in the intention-to-treat population (*n* = 27). No. at risk, number of subjects that were still accounted for in the study that had not yet experienced the event of interest; No. censored, number of the subjects whose survival time cannot be accurately determined.

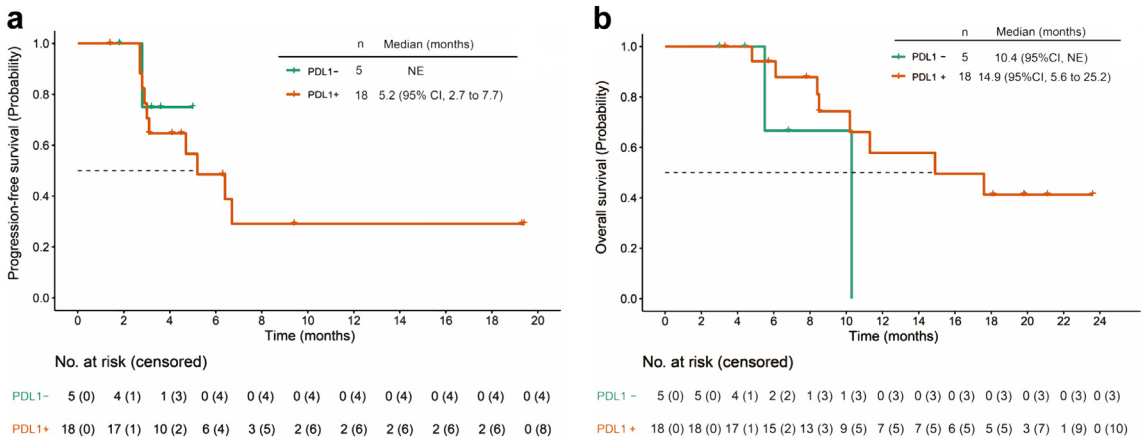

Fig. 4: **Kaplan–Meier estimates of progression-free survival and overall survival using programmed cell death ligand 1 (PD-L1) expression.** Progression-free survival (a) and overall survival (b) were assessed in patients with available PD-L1 expression (*n* = 23). NE, not estimable; PD-L1, programmed cell death ligand 1; No. at risk, number of subjects that were still accounted for in the study that had not yet experienced the event of interest; No. censored, number of the subjects whose survival time cannot be accurately determined.

	No. of patients (%)
TRAEs	
Any grade	27 (100%)
Grade 3	12 (44.4%)
Grade 4	0
Serious	0
TRAEs leading to	
Sintilimab interruption	3 (11.1%)
Sintilimab discontinuation	2 (7.4%)
Nab-paclitaxel reduction/interruption	
Nab-paclitaxel dose reduction	0
Nab-paclitaxel interruption	1 (3.7%)
Nab-paclitaxel discontinuation	2 (7.4%)
Deaths	0

TRAEs	Any grade	≥Grade 3
WBC count decreased	25 (92.6%)	4 (14.8%)
Neutrophil count decreased	24 (88.9%)	6 (22.2%)
Asthenia	17 (85.1%)	1 (3.7%)
Peripheral neuropathy	16 (59.3%)	1 (3.7%)
Anemia	12 (44.4%)	2 (7.4%)
Decreased appetite	12 (44.4%)	0
Pruritus	10 (37.0%)	0
Myalgia	10 (37.0%)	0
Arthralgia	6 (22.2%)	0
Blood creatinine increased	6 (22.2%)	0
Hypothyroidism	5 (18.5%)	0
AST increased	5 (18.5%)	0
Pyrexia	5 (18.5%)	0
Vomiting	5 (18.5%)	0
Rash	4 (14.8%)	0
Nausea	4 (14.8%)	0
Constipation	4 (14.8%)	0
Abdominal pain	4 (14.8%)	0

(Table 3 continues on next column)

TRAEs	Any grade	≥Grade 3
(Continued from previous column)		
ALT increased	3 (11.1%)	0
Diarrhea	3 (11.1%)	0
Abdominal pain	3 (11.1%)	0
Cough	2 (7.4%)	0
Insomnia	2 (7.4%)	0
Platelet count decreased	2 (7.4%)	0
Abdominal distension	1 (3.7%)	0
Stomachache	1 (3.7%)	0
Limb edema	1 (3.7%)	0
Potential immune-related adverse events		
Hypothyroidism	5 (18.5%)	0
Neutropenia	3 (11.1%)	0
Rash	2 (7.4%)	0
Asthenia	0	1 (3.7%)
Anemia	1 (3.7%)	0
Blood creatinine increased	1 (3.7%)	0

Abbreviations: TRAE, treatment-related adverse event; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3: **Treatment-related adverse events in total treated patients (*n* = 27).**

control, and thus selection bias could not be ruled out. Second, the association between biomarker (e.g., PD-L1 expression) and efficacy was not analyzed due to the small patient population, and also because it was not mandatory for patients to provide tumor samples. In addition, we acknowledge that the patient population was small and heterogenous, so the results should be interpreted with caution.

Nevertheless, in conclusion, the combination of sintilimab and nab-paclitaxel exhibited encouraging

efficacy and a tolerable safety profile, which make it a promising option for second-line or later treatments in patients with advanced cervical cancer.

Contributors

YW, JZ, and HXL contributed equally to this work. CYL and XH contributed equally to this work. Conception and design: YW, CYL, and XH; administrative support: XH, JXL, and GRZ; provision of study materials or patients: XH, JXL, GRZ, CYL, and SJH; collection and assembly of data: YW, JZ, JXL, and GRZ; data analysis and interpretation: YW, JZ, and HXL; manuscript writing: all authors; final approval of manuscript: all authors; accountable for all aspects of the work: all authors. All authors were responsible for the decision to submit the report for publication. All authors had unrestricted access to all the study data, have read and approved the version of the article to be submitted, and accept responsibility for all content and editorial decisions. YW, XH, and CYL had directly accessed and verified the underlying data.

Data sharing statement

The data of patients in this study have been recorded at Research Data Deposit public platform (http://www.researchdata.org.cn), with the approval RDD number RDDA2023541786. The data are available from Research Data Deposit but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Research Data Deposit public platform.

Declaration of interests

All authors declare no competing interests.

Acknowledgements

We thank Innovent Biologics (Suzhou) Co., Ltd., for providing sintilimab free of charge and Csps Holdings Co., Ltd., for a discount on nab-paclitaxel with a buy-one-get-one-free offer. We thank all the patients and their families who participated in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102274.

References

1 Buskwofie A, David-West G, Clare CA. A review of cervical cancer: incidence and disparities. *J Natl Med Assoc*. 2020;112(2):229–232.
2 Golia DT, Giannini A, Bogani G, et al. Prevention, screening, treatment and follow-up of gynecological cancers: state of art and future perspectives. *Clin Exp Obstet Gynecol*. 2023;50(8):160.
3 Tewari KS, Sill MW, Long HR, et al. Improved survival with bevacizumab in advanced cervical cancer. *New Engl J Med*. 2014;370(8):734–743.
4 Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 2004;22(15):3113–3119.
5 Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *New Engl J Med*. 2021;385(20):1856–1867.
6 Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37(17):1470–1478.
7 Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. *J Clin Oncol*. 2019;37(31):2825–2834.
8 Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. *New Engl J Med*. 2022;386(6):544–555.
9 O'Malley DM, Oaknin A, Monk BJ, et al. Phase II study of the safety and efficacy of the anti-PD-1 antibody balstilimab in patients with recurrent and/or metastatic cervical cancer. *Gynecol Oncol*. 2021;163(2):274–280.
10 Alberts DS, Blessing JA, Landrum LM, et al. Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;127(3):451–455.
11 Chan OT, Yang LX. The immunological effects of taxanes. *Cancer Immunol Immunother*. 2000;49:181–185.
12 Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *New Engl J Med*. 2018;379(22):2108–2121.
13 West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(7):924–937.
14 Xu JM, Jia R, Wang Y, et al. A first-in-human phase 1a trial of sintilimab (IBI308), a monoclonal antibody targeting programmed death-1 (PD-1), in Chinese patients with advanced solid tumors. *J Clin Oncol*. 2018;36(15_suppl):e15125.
15 An JS, Li XM, Wang J, et al. Efficacy and safety of serplulimab plus nab-paclitaxel in previously treated patients with PD-L1-positive advanced cervical cancer: a phase II, single-arm study. *Front Immunol*. 2023;14:1142256.
16 Shi Y, Su H, Song Y, et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2019;6(1):e12–e19.
17 Tao R, Fan L, Song Y, et al. Sintilimab for relapsed/refractory extranodal NK/T cell lymphoma: a multicenter, single-arm, phase 2 trial (ORIENT-4). *Signal Transduct Target Ther*. 2021;6(1):365.