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Efficacy and Safety of Sintilimab Plus Anlotinib for PD-L1–Positive Recurrent or Metastatic Cervical Cancer: A Multicenter, Single-Arm, Prospective Phase II Trial

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abstract

PURPOSE No combined immunotherapy and antiangiogenic therapy have been investigated in exclusively programmed death-ligand 1 (PD-L1)–positive advanced cervical cancer (CA). We investigated the efficacy and safety of sintilimab plus anlotinib as second-line or later therapy for PD-L1–positive recurrent or metastatic (R/M) CA.

PATIENTS AND METHODS Patients with PD-L1–positive (Combined Positive Score ≥ 1) R/M CA who progressed after at least one prior systemic chemotherapeutic regimen or could not tolerate chemotherapy were eligible for the phase II trial. The patients received 200 mg sintilimab once on day 1 and 10 mg anlotinib once daily on days 1-14 every 3 weeks. The primary end point was investigator-confirmed objective response rate (ORR) per RECIST v1.1. Secondary end points included progression-free survival (PFS), overall survival, and disease control rate. Biomarkers were explored.

RESULTS Forty-two patients were enrolled. The ORR was 54.8% (95% CI, 38.7 to 70.2). In 39 efficacy-evaluable patients, the ORR was 59.0% (95% CI, 42.1 to 74.4); the disease control rate was 94.9% (95% CI, 82.7 to 99.4). The median PFS was 9.4 months (95% CI, 8.0 to 14.6). The median overall survival was not reached. Furthermore, 85.8% of the patients experienced treatment-related adverse events. The most frequent treatment-related adverse events were hypothyroidism (33.3%), elevated aspartate aminotransferase levels (21.4%), and hypertension (19.0%). Patients with altered *PIK3CA*, PI3K-AKT signaling, or *KMT2D* had a higher ORR, whereas those with altered *STK11* and/or *JAK2* had a significantly shorter PFS.

CONCLUSION Sintilimab plus anlotinib as second-line or later therapy is efficacious and safe for patients with advanced CA who have failed prior chemotherapy.

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INTRODUCTION

Cervical cancer (CA) ranks fourth in incidence and cancer-related mortality globally and is the second most common malignancy in women in China.[1,2] Patients with recurrent or metastatic (R/M) CA fare poorly despite best available therapeutic regimens, with a 5-year survival of 17%.[3] Currently, platinum-based chemotherapy plus antiangiogenic therapy is the standard first-line treatment for R/M CA; however, prognosis remains dismal for advanced CA patients with the absence of standard of care in the second and later lines, in the context of resistance to platinum-based chemotherapy.[4,5] Novel therapeutic options are urgently awaited.

Pivotal trials, KEYNOTE-028 and KEYNOTE-158, have established the efficacy and safety of pembrolizumab in R/M CA with disease progression after chemotherapy.[6,7] In KEYNOTE-158, pembrolizumab monotherapy achieved an objective response rate (ORR) of 14.3% in patients with advanced CA failing at least one line of standard therapy; however, only programmed death-ligand 1 (PD-L1)–positive patients responded to pembrolizumab.[8] Although PD-L1 is expressed in 34.4%-96% of CA tissues, these trials suggest that only a small subset of PD-L1–positive patients benefit from programmed death protein-1 (PD-1)/PD-L1 inhibitor therapies, highlighting the need for more effective PD-1/PD-L1 inhibitors and/or novel effective therapies combining diverse antitumor mechanisms.[9,10]

In the GOG 240 trial, the addition of bevacizumab to chemotherapy regimens notably improved the overall survival (OS) and ORR of patients with advanced CA in the first-line setting, demonstrating that anti-angiogenic therapy could provide clinical benefits in

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The KEYNOTE 826 study has recently demonstrated significant survival benefits with first-line anti–programmed death protein-1 (PD-1) antibody pembrolizumab plus chemotherapy for recurrent/metastatic cervical cancer (recurrent or metastatic [R/M] cervical cancer [CA]). However, platinum-based chemotherapy plus antiangiogenic therapy remains the preferred first-line treatment for R/M CA; prognosis remains dismal for patients with advanced CA who are resistant to platinum-based chemotherapy. This phase II trial investigated the efficacy and safety of combined immunotherapy and antiangiogenic therapy with sintilimab plus anlotinib as second-line or later therapy for programmed death-ligand 1 (PD-L1)–positive R/M CA. To our knowledge, this is the first study to prospectively evaluate the combination of immunotherapy and antiangiogenic therapy in exclusively patients with PD-L1–positive advanced CA.

Knowledge Generated

Sintilimab plus anlotinib as a second-line or later therapy for patients with advanced CA has exhibited promising efficacy and an acceptable safety profile.

Relevance

Sintilimab plus anlotinib could provide a promising option for second-line and later treatment for PD-L1–positive advanced CA.

advanced CA.[11,12] In addition, combination treatments with immunotherapeutic agents and antiangiogenic inhibitors have exhibited synergistic antitumor effects in several cancer types, paving the way for the exploration of immunotherapy plus antiangiogenic agents for advanced CA.[13]

No combined immunotherapy and antiangiogenic therapy have been investigated in exclusively PD-L1–positive advanced CA. Sintilimab, a selective anti–PD-1 monoclonal antibody, binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. Anlotinib, a multikinase inhibitor, has demonstrated broad inhibitory effects on oncoangiogenesis and tumor growth.[14] Despite their antitumor activities in other tumor types, neither has been studied in CA. In this phase II trial, we investigated the efficacy and safety of sintilimab plus anlotinib as second-line or later therapy for PD-L1–positive R/M CA and explored novel biomarkers for predicting responses to combined immunotherapy and antiangiogenic therapy in advanced CA by integrating genomic profiling, tumor mutational burden (TMB), and PD-L1 expression.[15]

PATIENTS AND METHODS

Patients

This multicenter, open-label, single-arm, phase II trial, with a Simon two-stage optimal design, enrolled adult patients (age 18-75 years) with pathologically proven PD-L1–positive (Combined Positive Score [CPS] ≥ 1) R/M CA. Patients who had received at least one line of systemic therapy or could not tolerate chemotherapy were eligible. Patients must have at least one measurable lesion per RECIST v1.1, adequate organ function (including hemoglobin ≥ 9 g/dL), and an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients who had received anlotinib therapy or other anti–PD-1 antibodies or other therapies targeting PD-1/PD-L1 were excluded. Additional eligibility criteria are provided in the Data Supplement (online only).

The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice and approved by the Institutional Review Board of Fujian Provincial Cancer Hospital (Fuzhou, China). All patients provided written informed consent.

Treatment

Patients received sintilimab 200 mg intravenously once on day 1 every 3 weeks and anlotinib 10 mg orally once daily on days 1-14 per cycle. Treatment was continued until progressive disease (PD), treatment intolerance or death, and withdrawal or start of new antitumor therapy. Anlotinib dose determination and protocol-defined dose modification criteria are detailed in the Data Supplement. Dose modification of sintilimab was not allowed. Patients with intolerable adverse events (AEs) that caused delay or discontinuation of one drug continued treatment with the other study drug.

Assessments

Responses were evaluated by investigators per RECIST v1.1 using computed tomography or magnetic resonance imaging at baseline, every 6 weeks during the first 16 treatment cycles, and every 12 weeks thereafter. Complete response (CR) and partial response (PR) had to be confirmed radiologically at least 4 weeks later. Patients with first radiologic evidence of PD continued treatment until PD was confirmed in subsequent examinations provided that they could benefit from continuous treatment. AEs were recorded from the first day of treatment until 1 month after the end of treatment and graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

TABLE 1. Baseline Characteristics (N = 42)

Characteristic	Patients
Age, years, median (range)	53 (36-67)
FIGO stage at initial diagnosis, No. (%)	
IA	1 (2.4)
IB	5 (11.9)
IIA	5 (11.9)
IIB	9 (21.4)
IIIB	7 (16.7)
IIIC	6 (14.3)
IVB	4 (9.5)
Unknown	5 (11.9)
Median time from initial diagnosis to enrollment, months (range)	13.3 (3.6-170.5)
ECOG PS, No. (%)	
0	6 (14.3)
1	36 (85.7)
Histology, No. (%)	
SCC	35 (83.3)
Adenocarcinoma	5 (11.9)
Adenosquamous carcinoma	2 (4.8)
Local recurrence only, No. (%)	9 (21.4)
Local recurrence plus distant metastasis, No. (%)	7 (16.7)
Distant metastasis only, No. (%)	26 (61.9)
Lymph node metastasis	13 (31.0)
Organ metastasis	21 (50.0)
Liver	13 (31.0)
Lung	14 (33.3)
Others	13 (31.0)
Target lesion size, mm, median (range)	49 (15-217)
Previous radiotherapy, No. (%)	39 (92.9)
Adjuvant radiotherapy	18 (42.9)
Curative radiotherapy	16 (38.1)
Palliative radiotherapy	5 (11.9)
Time since last radiotherapy, months, No. (%)	n = 39
< 12	24 (61.5)
≥ 12	14 (35.9)
Unknown	1 (2.6)
No. of previous systemic therapies, No. (%)	
1	17 (40.4)
2	16 (38.1)
≥ 3	9 (21.4)
Previous platinum, No. (%)	42 (100.0)
PD-L1 expression (CPS), No. (%)	
< 4	14 (33.3)
≥ 4	28 (66.7)
TMB status, No. (%)	
High (≥ 7 mutations/Mb)	10 (23.8)
Low (< 7 mutations/Mb)	28 (66.7)
No somatic mutation	3 (7.1)
Unknown	1 (2.3)

Abbreviations: CPS, Combined Positive Score; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; Mb, megabase; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; TMB, tumor mutational burden.

End Points

The primary end point was ORR, defined as the proportion of patients who achieved investigator-confirmed CR or PR. The secondary end points included progression-free survival (PFS, time from the first dose to PD or death from any cause), OS (time from the first dose to death from any cause), and disease control rate (DCR, the proportion of patients who achieved CR, PR, or stable disease [SD]).

Biomarker Analysis

Tumor PD-L1 expression was assessed by immunohistochemistry (Data Supplement) and measured using CPS, defined as the number of PD-L1 staining cells divided by the total number of viable tumor cells, multiplied by 100. CPS ≥ 1 indicated PD-L1 positivity.

Next-generation sequencing–based gene panel tests are detailed in the Data Supplement. A TMB cutoff of 7 mutations per megabase, representing top 20% of CA specimens in the database (Burning Rock Dx, Guangzhou, China), was used to differentiate high from low TMB.

Statistical Analysis

A true ORR of ≤ 10% for an anti–PD-1 antibody plus anlotinib was assumed unacceptable, whereas a true ORR of ≥ 30% warranted further study. Assuming a power of 0.80 and $\alpha = .05$, target accrual was a minimum of 18 patients in Simon stage I, and if responses were confirmed in more than two patients, 17 additional patients were accrued in Simon stage II, with totally 35 patients. Assuming a dropout rate of 20%, a population of 42 patients was required.

R version 3.4.1 was used for data analyses. ORR and 95% CIs were calculated using the Clopper-Pearson method. For exploratory purpose, Fisher's exact test was used to compare ORR and other binary outcomes among different subgroups. Furthermore, we provided Kaplan-Meier plots for PFS and OS. The log-rank test was used to compare the survival functions among different subgroups. Association between time-to-event outcomes and molecular features was evaluated using a Cox proportional hazards test.

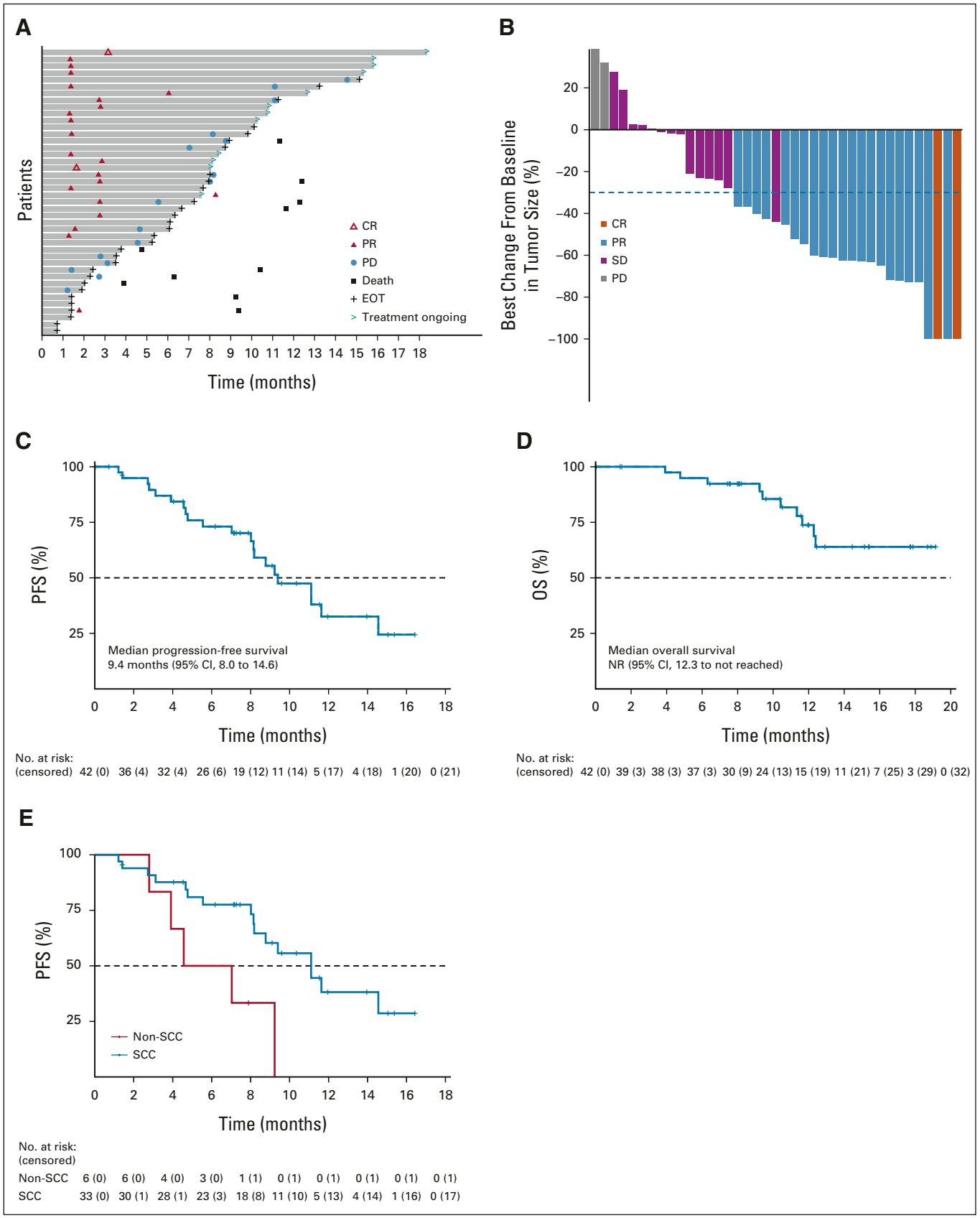

FIG 1. Antitumor activity. (A) Duration of responses of patients in the ITT population. The length of each bar represents the duration of treatment of each patient. (B) Best percentage change from baseline in target lesion size. The dashed line at –30% change represents the cutoff (continued on following page)

FIG 1. (Continued). for PR or SD per RECIST v1.1. The Kaplan-Meier curves of (C) PFS and (D) OS in the ITT population. (E) The Kaplan-Meier curves of PFS of patients stratified by squamous versus non-SCC of the cervix. CPS, Composite Positive Score; CR, complete response; EOT, end of treatment; ITT, intention-to-treat; non-SCC, nonsquamous cell carcinoma of the cervix; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SCC, squamous cell carcinoma of the cervix.

The safety set included all patients who had received at least one dose of the study medications. Safety assessments mainly used descriptive statistics.

All tests were two-tailed with a level of significance set at $\alpha \leq .05$.

RESULTS

Between December 2019 and December 2020, 51 patients were screened, of whom 42 patients were enrolled and received study treatment (intention-to-treat population and safety population; Data Supplement). Except for only one patient who failed to tolerate chemotherapy, all patients had disease recurrence. All patients had received prior platinum-based regimens, including 25 (59.5%) patients who had received two or three chemotherapy regimens before enrollment. Furthermore, 35 (83.3%) patients had squamous cell carcinoma (SCC), and 39 (92.9%) had received radiotherapy. In addition, 30 (71.4%) patients had distant metastasis, including 13 (31.0%) cases of liver metastases (Table 1).

Three patients discontinued treatment before the first scheduled postbaseline assessment because of AE (n = 1) or withdrawal (n = 2). Finally, 39 patients were included in the efficacy-evaluable population.

The data cutoff was July 13, 2021, with a median follow-up of 10.9 (range, 0.03-19.2) months. The median treatment duration was 7.0 (range, 0.03-17.7) months. At the data cutoff, 12 (23.8%) patients were still receiving treatment and 30 (71.4%) patients discontinued treatment, including 16 (38.1%) patients because of PD and 3 (7.1%) because of AEs.

Efficacy Measures

Nine patients had achieved PR when Simon stage I reached the minimum accrual target, leading to study expansion. In the intention-to-treat population, two (4.8%) patients achieved CR and 21 (50%) attained PR; the confirmed ORR was 54.8% (95% CI, 38.7 to 70.2). The median time to response was 1.7 months (95% CI, 1.4 to 2.8; Fig 1A). Fourteen (33.3%) patients had SD, and the DCR was 88.1% (95% CI, 74.4 to 96.0). In efficacy-evaluable patients, the ORR was 59.0% (95% CI, 42.1 to 74.4) and the DCR was 94.9% (95% CI, 82.7 to 99.4; Table 2). Thirty-two (82.1%) patients exhibited a reduction from baseline in target lesion size (Fig 1B). At the data cutoff, 21 (50.0%) patients had PD or died. The median PFS was 9.4 months (95% CI, 8.0 to 14.6), and the 6-month PFS rate was 73.1% (95% CI, 60.1 to 88.9; Fig 1C). OS events occurred in 10 patients (23.8%). The median OS was not reached (95% CI, 12.3 to not reached), and the 12-month OS rate was 73.8% (95% CI, 59.3 to 91.7; Fig 1D).

In efficacy-evaluable patients, compared with patients with non-SCC, patients with SCC showed a significantly higher ORR (69.7%, 23 of 33 *v* 0%, 0 of 6; Fisher's exact test, $P = .003$) and longer median PFS (11.1 months, 95% CI, 8.2 to not reached *v* 5.8 months, 95% CI, 2.8 to not reached; log-rank test, $P = .01$; Fig 1E). Notably, the ORR and median PFS were comparable between patients whose time since last radiotherapy was $<$ 12 months versus $\geq$ 12 months and between patients with liver metastasis and those with metastasis to other organs (Data Supplement).

TABLE 2. Efficacy Measures per RECIST v1.1 Guidelines

Efficacy	ITT Population (N = 42)	Efficacy-Evaluable Population (n = 39)
ORR, No. (%)	23 (54.8)	23 (59.0)
95% CI	38.7 to 70.2	42.1 to 74.4
DCR, No. (%)	37 (88.1)	37 (94.9)
95% CI	74.4 to 96.0	82.7 to 99.4
Best overall response, No. (%)		
CR	2 (4.8)	2 (5.1)
PR	21 (50.0)	21 (54.8)
SD	14 (33.3)	14 (35.9)
PD	2 (4.7)	2 (5.1)
Not assessed	3 (7.1)	—

Abbreviations: CR, complete response; DCR, disease control rate; ITT, intention-to-treat; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 3. AEs in the Safety Set

AE	Total, No. (%)	No. (%)		
		Grade 1	Grade 2	Grade 3 and above
Hypothyroidism	14 (33.3)	0 (0)	14 (33.3)	0 (0)
AST elevation	9 (21.4)	7 (16.7)	2 (4.8)	0 (0)
Hypertension	8 (19.0)	5 (11.9)	2 (4.8)	1 (2.4)
Diarrhea	7 (16.7)	4 (9.5)	2 (4.8)	1 (2.4)
ALT elevation	7 (16.7)	5 (11.9)	2 (4.8)	0 (0)
Hand-foot syndrome	7 (16.7)	3 (7.1)	4 (9.5)	0 (0)
Fistula	6 (14.3)	0 (0)	3 (7.1)	3 (7.1)
Hypertriglyceridemia	6 (14.3)	6 (14.3)	0 (0)	0 (0)
Anemia	5 (11.9)	1 (2.4)	4 (9.5)	0 (0)
Hypercholesterolemia	5 (11.9)	5 (11.9)	0 (0)	0 (0)
Rash	3 (7.1)	2 (4.8)	1 (2.4)	0 (0)
Swelling and aching of gum	2 (4.8)	2 (4.8)	0 (0)	0 (0)
Dental ulcer	2 (4.8)	2 (4.8)	0 (0)	0 (0)
Fatigue	2 (4.8)	2 (4.8)	0 (0)	0 (0)
Immune pneumonitis	2 (4.8)	0 (0)	1 (2.4)	1 (2.4)
Immune myocarditis	1 (2.4)	0 (0)	0 (0)	1 (2.4)

Abbreviation: AE, adverse event.

Safety

Thirty-six (85.8%) patients experienced at least one treatment-related adverse event (TRAE), the most common of which were hypothyroidism (33.3%), elevated aspartate aminotransferase (21.4%), and hypertension (19.0%; Table 3). Seven (16.7%) patients experienced ≥ grade 3 TRAEs, including three (7.1%) cases of fistula, and the rest occurred only once (2.4%). No treatment-related deaths occurred. Three (7.1%) patients discontinued treatment, and three (7.1%) patients discontinued anlotinib alone because of TRAEs. TRAEs led to dose reduction of anlotinib in 11 (26.2%) patients. Notably, the overall incidence of fistula of any grade was 14.3% (n = 6) among the safety set; all had received radiotherapy within the preceding 12 months. In addition, five (31.3%) patients with fistula had local recurrence versus one patient without local recurrence (P = .023).

Biomarker Analysis

In efficacy-evaluable patients, exploratory analysis showed that patients who achieved CR or PR had significantly higher mean PD-L1 CPS scores than patients who had SD or PD (P = .006; Fig 2A). In addition, patients with high TMB (n = 10, 23.8%) and low TMB (n = 28, 66.7%) exhibited no remarkable difference in ORR (90% and 50%, P = .056; Fig 2B) and PFS (HR, 1.39; 95% CI, 0.38 to 5.06; P = .585; Fig 2C).

Next-generation sequencing revealed that *PIK3CA* was the most frequently altered gene, occurring in 13 (31.7%) patients, including 10 cases with missense mutations. *FAT1* was altered in nine (22.0%) patients, followed by *PRKDC* (8 of 41, 19.5%), *KMT2D* (7 of 41, 17.1%), and *ATR* (6 of 41, 14.6%; Fig 3A). The altered genes were significantly enriched in DNA damage response pathways and the PI3K-AKT pathway (Data Supplement).

The ORR was 91.7% (11 of 12) in patients with altered *PIK3CA* versus 46.2% (12 of 26) in their wild-type counterparts (P = .012) and 82.4% (14 of 17) in patients with altered PI3K-AKT signaling versus 42.9% (9 of 21) in those without (P = .020). Furthermore, the PI3K-AKT signaling pathway was altered in 55.9% (19 of 34) of patients with SCC, whereas all (7 of 7) patients with non-SCC showed no alteration in the pathway (Fig 3B). Notably, the ORR of patients with mutated *KMT2D* was 100% (7 of 7) versus 51.6 (16 of 31) in those without (P = .029; Fig 3C). Compared with their wild-type counterparts, patients with altered *STK11* or *JAK2* had significantly shorter median PFS (*STK11*: HR, 0.09; 95% CI, 0.01 to 1.04; P = .016; *JAK2*: HR, 0.12; 95% CI, 0.02 to 0.70; P = .005; *STK11* or *JAK2*: HR, 0.08; 95% CI, 0.01 to 0.42; P < .001; Fig 3D).

DISCUSSION

To our knowledge, this is the first study to prospectively evaluate the combination of immunotherapy plus anti-angiogenic therapy in exclusively PD-L1–positive patients with advanced CA. In our study, sintilimab plus anlotinib as a second-line or later therapy for patients with advanced CA has exhibited promising efficacy and an acceptable safety

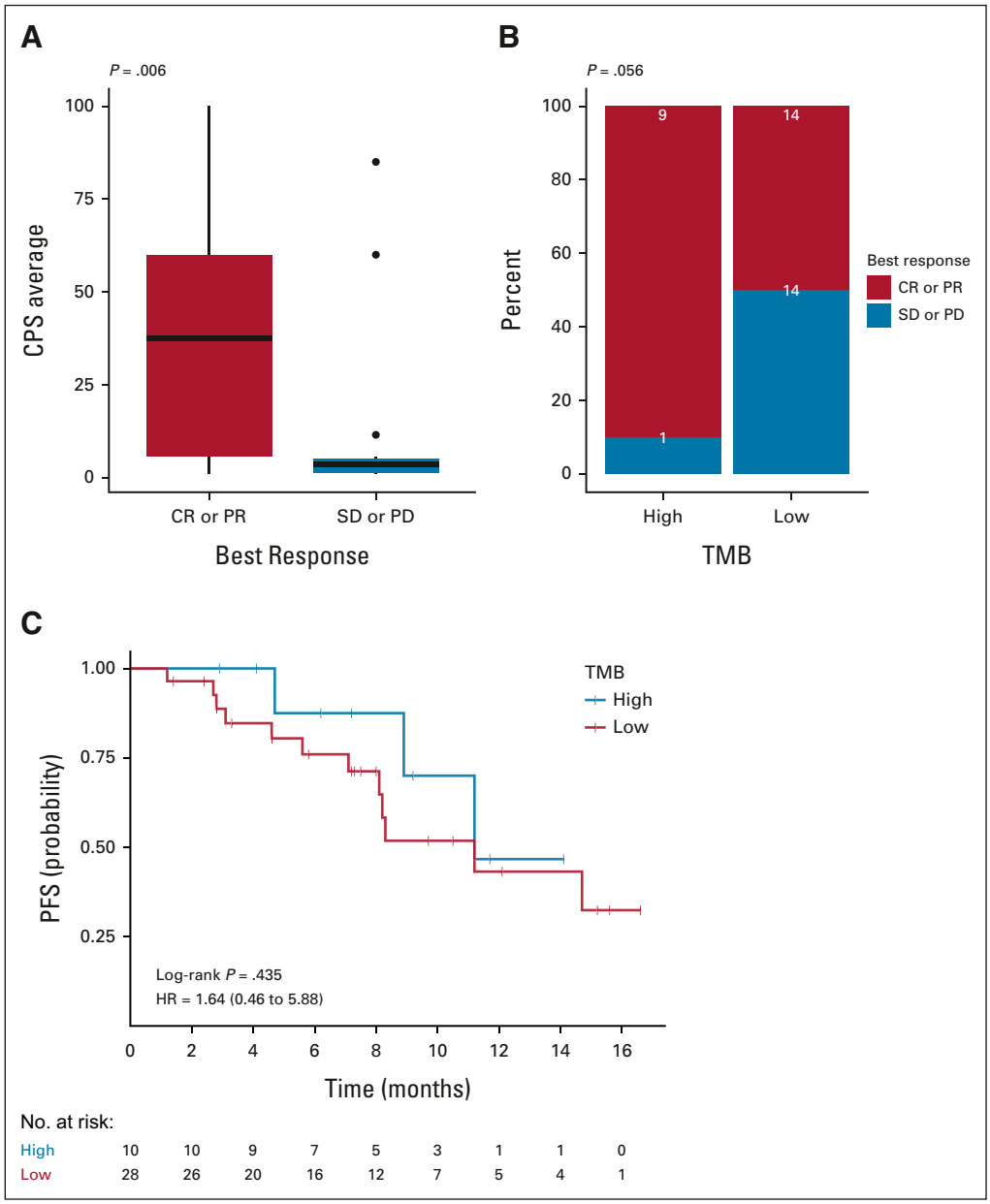

FIG 2. Boxplots showing the median CPS (A) of PD-L1 in the efficacy-evaluable patients stratified by best response (CR or PR *v* SD or PD). (B) Treatment response of efficacy-evaluable patients stratified by TMB (high *v* low). (C) The Kaplan-Meier curves of PFS of efficacy-evaluable patients stratified by TMB (high *v* low). TMB high was defined as ≥ 7 Muts/Mb, and TMB low was defined as < 7 Muts/Mb. CPS, Composite Positive Score; CR, complete response; HR, hazard ratio; Muts, mutations; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TMB, tumor mutational burden.

profile. Notably, 60% of our patients had two or more prior recurrences, suggesting that this drug combination holds promise for heavily pretreated CA.

There have been several studies on monotherapy or combination therapy with immune checkpoint inhibitors for R/M CA. Pembrolizumab monotherapy attained an ORR of 14.3% and a DCR of 30.6% and achieved a median PFS of 2.1 months with a 6-month PFS rate of 25.0% in advanced CA.[8] In the phase III EMPOWER trial involving patients with R/M CA that progressed after platinum-based chemotherapy, monotherapy with the PD-1 inhibitor cemiplimab demonstrated an increased ORR (16.4% *v* 6.3%) and significantly prolonged OS (12.0 *v* 8.5 months; HR, 0.69; 95% CI, 0.56 to 0.84) as compared with chemotherapy.[16] Notably, sintilimab plus anlotinib yielded an ORR of 54.8% with a DCR of 88.1% and a median PFS of 9.4 months with the 6-month PFS rate of 73.1%. Two other studies, one combining pembrolizumab plus GX-188E, a therapeutic

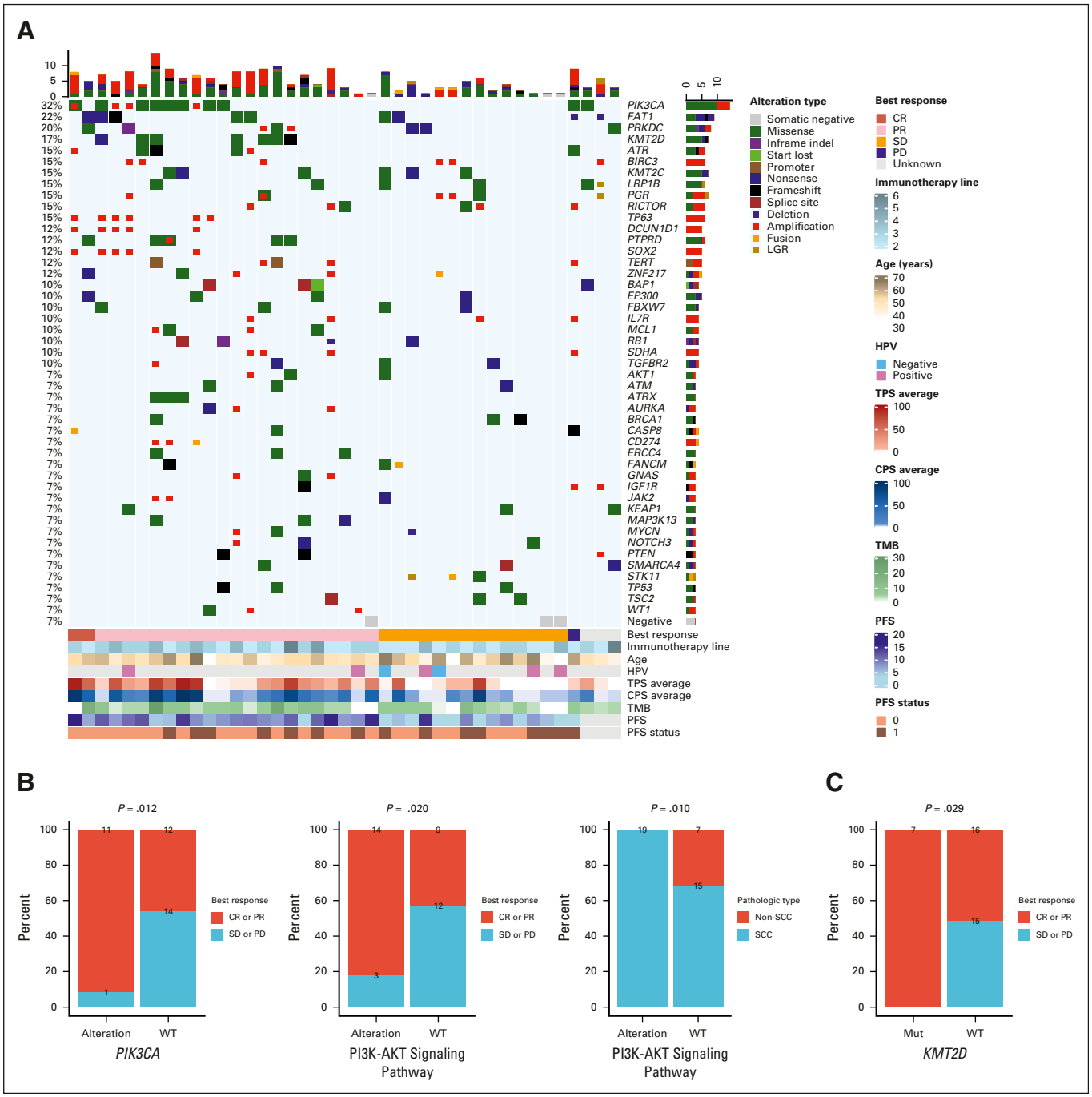

FIG 3. (A) OncoPrint of functional driver mutations in 41 patients with cervical cancer. Genes altered in at least three patients are shown. Rows represent genes, and columns represent samples. Glyphs and color coding are used to summarize distinct genomic alterations including mutations, copy number alterations (amplifications and homozygous deletions), and changes in gene expression, best response, immunotherapy line, age, HPV, TPS and CPS coverage, PFS and PFS status, and TMB. (B) Treatment response of patients with altered versus wild-type *PIK3CA* (left) or PI3K-AKT (middle). Alteration status of the PI3K-AKT signaling pathway in patients with SCC and non-SCC (right). (C) Treatment response of patients with mutated versus wild-type *KMT2D*. (D) The Kaplan-Meier curves of PFS of efficacy-evaluable patients stratified by the alteration status of *STK11* (left), *JAK2* (middle), and *STK11* or *JAK2* (right). CPS, Composite Positive Score; CR, complete response; HPV, human papilloma virus; Mut, mutant; non-SCC, nonsquamous cell carcinoma of the cervix; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SCC, squamous cell carcinoma; TMB, tumor mutational burden; TPS, tumor proportion score; WT, wild-type. (continued on following page)

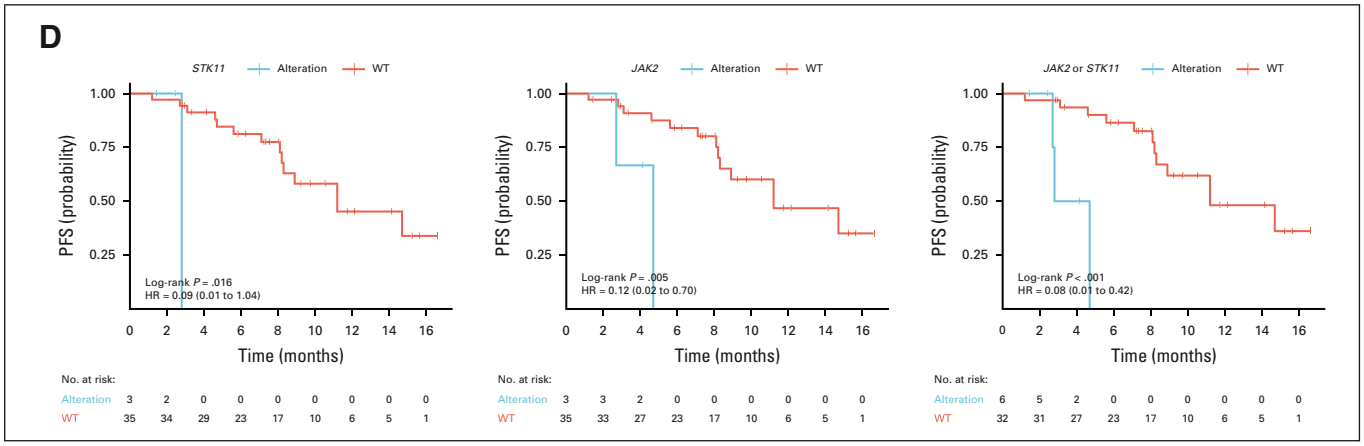

FIG 3. (Continued)

DNA vaccine, for HPV 16–positive and/or HPV 18–positive advanced CA and the other combining atezolizumab plus simlukafusp-α, an engineered interleukin-2 variant targeted to fibroblast activation protein-α for R/M CA, reported an ORR of around 30%.[17,18] Our results (ORR, DCR, and median PFS) are comparable with those of camrelizumab, a fully humanized, high-affinity monoclonal antibody against PD-1, plus apatinib, a tyrosine kinase inhibitor of VEGFR2, in second-line or later advanced CA in the CLAP trial.[19] In both studies, immunotherapy plus antiangiogenic therapy demonstrated synergistic activities and conferred greater clinical benefits than PD-L1 inhibitor monotherapy and immunotherapy combined with non-antiangiogenic agents. Our study enrolled PD-L1–positive patients, whereas the CLAP trial included both PD-L1–negative and PD-L1–positive patients. The CLAP trial showed no statistical difference in ORR between PD-L1–negative and PD-L1–positive patients; the investigators acknowledged that the study was underpowered to distinguish responses between the two groups because of the small sample size. Compared with the CLAP trial, a greater proportion of our patients had liver metastasis (31% *v* 20%) and received ≥ third-line chemotherapy (21.4% *v* 15.5%) with a shorter time from diagnosis to enrollment (13.3 *v* 21.5 months). Although the two studies cannot be compared head-to-head, our study is statistically powered to prove that the combination therapy is effective in advanced PD-L1–positive CA. A trial of pembrolizumab and lenvatinib in patients with advanced CA who had failed first-line therapy (NCT04865887) will open shortly. The result of the trial is awaited to further confirm the effects of immunotherapy plus antiangiogenic therapy for advanced CA.

The safety profile of our cohort is consistent with that reported for sintilimab and anlotinib. Of note, only 16.7% of patients were reported with ≥ grade 3 TRAEs, which is apparently better than that of the CLAP trial (54.5%) and another trial (66.9%) combining pembrolizumab and lenvatinib in advanced endometrial cancer, suggesting that sintilimab plus anlotinib might have a safety advantage over drugs with similar mechanisms of actions.[19-21] In our study, the overall incidence of any grade fistula was 14.3% and that of ≥ grade 3 fistula was 7.1%, which is comparable with that in GOG 240.[11] Notably, all fistula patients in both trials had received prior radiotherapy, and 5 of 6 patients with fistula in our study had local recurrence. Similarly, in a study of patients with recurrent CA treated with chemotherapy alone or plus bevacizumab, half (3 of 6) patients with fistulae had a local recurrence.[22] Our findings suggested that patients who have received prior radiotherapy and have local recurrence shortly before immunotherapy plus antiangiogenic therapy should be carefully evaluated for treatment benefit and risk of fistula occurrences. In addition, 5 of 6 patients with fistula had tumor cavities, suggesting a possible association between fistula occurrences and tumor cavitation. The rate of cavitation was 21.4% (9 of 42) in our study and 40.9% in a previous study of the same combination regimen in non–small-cell lung cancer.[20] Sintilimab plus anlotinib might have synergistic antitumor activities and is more likely to lead to the development of tumor cavitation.

PD-L1 levels have been shown to be predictive of response to immunotherapy.[23] Our trial showed that PD-L1 expression was higher in patients who achieved CR or PR than in those who had SD or PD. Given the small sample size in our trial, future investigations involving a larger population are warranted to determine whether PD-L1 levels could be a biomarker to stratify patients with advanced CA for the combination of immunotherapy and antiangiogenic therapy. Apart from PD-L1, TMB has been reported to correlate with response to anti–PD-1 monotherapy across multiple cancers.[24] Interestingly, our study failed to establish a significant association between ORR or PFS and TMB, consistent with the observation from the study of anti–PD-1/cytotoxic T-cell lymphocyte-4 combination immunotherapy

for solid tumors, suggesting that the TMB test might be waived in patients with PD-L1–positive R/M CA on immunotherapy plus antiangiogenic therapy.[25]

Patients with SCC in our study particularly benefited from the combination regimen, exhibiting a significantly higher ORR and longer PFS than patients with non-SCC. Interestingly, genetic alterations in the PI3K/AKT pathway are more common in patients with SCC than in patients with adenocarcinoma (55.9% *v* 0%), which is similar to the CLAP study (80.9% *v* 45.5%; $P = .05$).[26] Furthermore, significantly more patients with altered *PIK3CA* responded to sintilimab plus anlotinib than their wild-type counterparts, with a better PFS, suggesting an intimate interplay between CA histology and aberrant PI3K-AKT signaling in shaping response to antiangiogenic therapy plus immunotherapy.

This study has several limitations. First, this study has no control arm. In addition, only four of our patients received prior bevacizumab therapy as bevacizumab was not indicated for advanced CA in China at the time of the study. It remains an important issue whether our combination regimen could be effective for advanced CA that progresses despite bevacizumab treatment. There are also many other promising agents such as tisotumab vedotin, a novel tissue factor–targeting antibody-drug conjugate, combination regimens like nivolumab plus ipilimumab, and lymphocyte therapy.[27-29] They are set to change the treatment landscape of R/M CA, but the challenges will be when to incorporate these treatments. In addition, a first-line trial of carboplatin and paclitaxel plus bevacizumab versus sintilimab and anlotinib would not be out of the question in R/M PD-L1–positive CA if these findings are confirmed.

In conclusion, the combination of sintilimab plus anlotinib has exhibited encouraging efficacy and acceptable safety in this study, making it a promising option for second-line and later treatment in patients with PD-L1–positive advanced CA. Moreover, our comprehensive genomic profiling to interrogate CA gene mutational landscape will help to provide a framework in future studies involving multiple biomarkers for molecularly stratified therapy of advanced CA. Additional investigations in larger randomized controlled trials are warranted.

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DATA SHARING STATEMENT

The clinical trial data collected for the study will not be made available to others. The data set for biomarker analysis in the study has been uploaded onto NODE (http://www.biosino.org/node; Project ID OEP003082). Although restrictions are placed on access to the data set, the authors will make the data available to readers upon request.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Sintilimab Plus Anlotinib for PD-L1–Positive Recurrent or Metastatic Cervical Cancer: A Multicenter, Single-Arm, Prospective Phase II Trial

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