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Fruquintinib plus sintilimab in advanced cervical cancer: an open-label, multicenter, phase 2 study

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Glossary

AE	Adverse event
CPS	Combined positive score
CI	Confidence interval
CR	Complete response
DCR	Disease control rate
DoR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
FAS	Full analysis set
H_0	Null hypothesis
HR	Hazard ratio
ICF	Informed consent form
ICI	Immune checkpoint inhibitor
NE	Not estimable
ORR	Objective response rates
OS	Overall survival
PD	Disease progression
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
pMMR	Proficient mismatch repair
PR	Partial response
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
TRAE	Treatment-related adverse event

TREND	Transparent Reporting of Evaluations With Nonrandomized Designs
TRES	Tumour response-evaluable set
TTR	Time to response
VEGF	Vascular endothelial growth factor

Abstract

BACKGROUND

Efficacy of second-line treatments after first-line platinum-based chemotherapy in advanced cervical cancer is modest. This open-label, single-arm, multicentre, proof-of-concept phase 2 study evaluated fruquintinib plus sintilimab in advanced cervical cancer.

METHODS

Patients recruited between July 2021 and June 2022 had received at least first-line platinum-based chemotherapy or were unable to receive standard treatment in China. Patients received fruquintinib 5 mg once daily orally (2 weeks on/1 week off) plus sintilimab 200 mg intravenously every 3 weeks. Efficacy and safety analyses included patients who had received at least one dose of study drug.

RESULTS

Here we show of 34 patients who received treatment; 28 (82%) have prior systemic antitumour therapy, with 19 (68%) pretreated patients having PD-L1 combined positive score (CPS) ≥1. The objective response rate (ORR) is 32% (95% confidence interval [CI] 17–51), meeting the prespecified effective boundary, and disease control rate (DCR) is 97% (95% CI 85–100). Median progression-free survival (PFS) and overall survival (OS) are 8.3 months (95% CI 5.5–19.4) and 23.5 months (95% CI 15.8–not estimable [NE]), respectively. The most common grade ≥3 treatment-related adverse event is palmar-plantar erythrodysaesthesia syndrome (21%). In pretreated patients with CPS ≥1, ORR is 37% (95% CI 16–62), median PFS is 19.4 months (95% CI 4.0–22.1), and OS rate at 18-month is 72% (95% CI 46–87).

CONCLUSIONS

Fruquintinib plus sintilimab may indicate favourable and durable antitumour activity with manageable safety profile in advanced cervical cancer, especially in pretreated patients with CPS ≥1, warranting further investigation.

KEYWORDS

Fruquintinib, sintilimab, cervical cancer, combined positive score, PD-L1

PLAIN LANGUAGE SUMMARY

Cervical cancer is one of the deadliest forms of cancer for women and survival is poor. This study aimed to explore whether the combination of fruquintinib, a therapy that blocks the growth of new blood vessels, and sintilimab, an immunotherapy, could improve outcomes for patients with advanced cervical cancer. We treated 34 patients, 28 of whom previously received treatment. The combination was able to control disease in all but one patient. We found that the disease progressed after an average of 8.3 months, and patients survived for an average of 25.3 months. The side effects of this combination were generally manageable. These findings suggest that this combination therapy may be a useful approach in patients with advanced cervical cancer.

INTRODUCTION

Cervical cancer is the fourth most common female cancer in the world.[1] Globally, an estimated 604,127 new cases of cervical cancer and 341,831 deaths occurred in 2020, with over 18% of cases and 17% of deaths due to cervical cancer occurring in China.[2] The 5-year survival rate for metastatic cervical cancer is 19%.[3] In contrast to patients with early-stage cervical cancer and locally advanced cervical cancer, prognosis for patients with metastatic cervical cancer and those with persistent or recurrent disease after platinum-based chemoradiotherapy is poor, and second-line and later treatment options are limited after disease progression (PD).[4,5]

For patients who progressed after first-line platinum-based chemotherapy, second-line treatment options have historically shown modest efficacy. In a study of topotecan for recurrent cervical cancer, the overall response rate was 18.6% and median progression-free survival (PFS) was 2.4 months.[6] Immune checkpoint inhibitor (ICI) monotherapy has shown improvements in the second-line setting. The KEYNOTE-158 and EMPOWER-Cervical 1 studies evaluated programmed cell death protein 1 (PD-1) inhibitors (pembrolizumab and cemiplimab) in previously treated cervical cancer patients. These ICIs demonstrated efficacy in the second-line setting, with objective response rates (ORRs) ranging from 15% to 18%, median PFS from 2.1 to 3.0 months, and median overall survival (OS) from 11.0 to 13.9 months.[7,8] However, some patients still do not respond to ICI monotherapy.

Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis.[9] The anti-VEGF antibody bevacizumab is a widely prescribed antiangiogenic drug, with bevacizumab-containing regimens recommended by guidelines for the treatment of recurrent or metastatic cervical cancer, both in first- and later-line settings.[10] Building on these advances, current research is focusing on combining antiangiogenic therapies with ICIs for second-line or

subsequent advanced cervical cancer, which might result in more durable clinical benefit. Potential efficacy of this combination was demonstrated in the KEYNOTE-826 trial, which evaluated pembrolizumab plus chemotherapy with or without bevacizumab in the first-line setting. This study showed that concomitant use of bevacizumab with pembrolizumab resulted in a better hazard ratio for OS than those who did not receive bevacizumab (HR 0.61 vs. 0.67) in the subgroup analysis.[11] The BEATcc phase 3 study further confirmed the role of angiogenesis and immunosuppression in cervical cancer by demonstrating improved PFS (13.7 vs. 10.4 months) and OS (32.1 vs. 22.8 months) when atezolizumab (PD-L1 inhibitor) was added to bevacizumab plus chemotherapy.[12] However, there is an unmet need for extending these combination approaches to the second-line setting worldwide.

Fruquintinib is a potent, selective, small-molecule inhibitor of VEGF receptors 1, 2, and 3 and sintilimab is an anti-PD-1 monoclonal antibody. An open-label phase 1b/2, multi-cohort study of fruquintinib in combination with sintilimab was performed to evaluate the safety and efficacy in patients with advanced solid tumour. The combined treatment regimen of fruquintinib plus sintilimab has shown preliminary antitumour efficacy and a tolerable safety profile in multiple advanced tumours.[13] Here, we report the efficacy and safety results of the cervical cancer cohort. We show that this regimen results in an ORR of 32% and a median PFS of 8.3 months with a manageable safety profile, especially in pretreated patients with combined positive score (CPS) ≥1 (ORR 37%, median PFS 19.4 months). These findings highlight the potential of fruquintinib plus sintilimab in the treatment of advanced cervical cancer.

METHODS

Study design

This was an open-label, single-arm, phase 2 multicentre study in China (clinicaltrials.gov: NCT03903705; first submitted: 27 March 2019) of fruquintinib plus sintilimab in patients with advanced cervical cancer. The study enrolled patients at 11 clinical study sites.

Ethical approval

This study was approved by the ethics committee (approval number of the leading site Fudan University Shanghai Cancer Center is 1908205-7) and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulations and guidelines. All enrolled patients provided written informed consent. This study follows the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline.

Participants

Eligible patients were aged between 18 and 75 years and were required to have histologically or cytologically confirmed inoperable advanced cervical cancer, including recurrent or metastasised squamous cell carcinoma, adenocarcinoma, or adeno-squamous carcinoma. Patients were required to have either experienced disease progression following at least one line of platinum-based chemotherapy or be unable or unwilling to receive standard first-line treatment due to medical contraindications, intolerance, or other clinically relevant factors. Patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable tumour lesions by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1), and adequate organ functions.

Study treatment

Enrolled patients received fruquintinib 5 mg once daily orally, 2 weeks on/1 week off, plus sintilimab 200 mg intravenously, every 3 weeks, in 3-week cycles, which was already determined as the recommended phase 2 dose from a colorectal cancer cohort.[14]

Treatment continued until PD, death, intolerable toxicity, patient withdrawal, poor compliance, pregnancy, investigators' decision, loss to follow-up, or initiation of new antitumour therapy, but sintilimab was continued for a maximum of 24 months. Patients who still had clinical benefit after first observation of PD could continue the study treatment if the patient was clinically stable and at the discretion of the investigator.

Tumour tissues (either archived or fresh) were required for the detection of PD-L1 expression, which was assessed via an immunohistochemical assay using a monoclonal Mouse Anti-Human PD-L1 Clone 22C3 (Dako, Carpinteria, CA). Tumour evaluation was performed by an enhanced computed tomography/magnetic resonance imaging scan per RECIST v1.1. During the study, tumour assessments were performed at baseline, every 6 weeks from the first dose, and every 12 weeks after 48 weeks until PD, death, start of new antitumour therapy, loss to follow-up, withdrawal of informed consent form (ICF), or end of study, whichever occurred first. Complete response (CR) or partial response (PR) were confirmed at least four weeks after the first documented response.

Patients who discontinued study treatment for any reason other than PD (except withdrawal of ICF or death) continued the tumour assessment according to the protocol-specified visit schedule. Tumour assessment can be performed within 28 days at the time of end of treatment. Survival follow-up (telephone follow-up) was performed every 12 weeks after the last dose, and the subsequent antitumour therapy after PD was recorded.

Safety and tolerability assessments were based on grade and severity of treatment-related adverse events (TRAEs), laboratory examinations, vital signs, ECOG PS, electrocardiograms, and immunogenicity. All adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Only serious adverse events confirmed by the investigator to be causally related to the study drug were reported within 90 days after the last dose or the start of new antitumour therapy.

Outcomes

Primary endpoint was ORR per RECIST v1.1 assessed by the investigator. Secondary endpoints included the disease control rate (DCR), time to response (TTR), duration of response (DoR), PFS, OS, and safety. The definition of each endpoint is provided in the Supplementary Table 1.

Statistics and Reproducibility

Approximately 34 patients with cervical cancer were planned to be enrolled, and the null hypothesis (H_0) was ORR ≤15% and the alternative hypothesis was ORR >15%. Assuming the ORR of fruquintinib plus sintilimab for advanced cervical cancer to be 35%, a sample size of 34 patients had approximately 80% power to reject the H_0 (ORR ≤15%) at a 1-sided 0.025 significance level. Statistical hypothesis test was performed on the basis of a two-sided exact 95% CI. The H_0 was rejected if the lower bound of the two-sided exact 95% CI exceeded 15%.

The full analysis set (FAS) included all patients who had received at least one dose of study drug and served as the primary analysis population for ORR and other efficacy and safety endpoints. Additionally, the tumour response-evaluable set (TRES) included patients from the FAS who had measurable disease at baseline and at least one post-baseline tumour-imaging evaluation. The TRES was employed to support the analysis of efficacy endpoints, with the exception of PFS and OS, which were analysed exclusively in the FAS population. The corresponding 2-sided

95% CIs of ORR and DCR were calculated using the Clopper–Pearson method. Time-to-event outcomes were estimated by Kaplan–Meier method. Only results from tumour assessments performed prior to the initiation of new antitumour therapy were included in the analyses of ORR, DCR, DoR, TTR, PFS, and tumour shrinkage. The detailed assessment criteria are provided in Supplementary Table 2. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Trial registration: ClinicalTrials.gov Identifier: NCT03903705 (first submitted: 27 March 2019)

RESULTS

Patients

Of the 58 female patients screened for eligibility, 34 were enrolled between July 19, 2021, and June 7, 2022 (last patient signed the ICF), to receive the treatment combination of fruquintinib and sintilimab (Fig. 1). Baseline and clinical characteristics of the patients are presented in Table 1. Median (range) age of patients was 56 (26–74) years, with the main pathological diagnosis of squamous cell carcinoma (85%). Half (50%) of the patients had an ECOG PS of 1. Proficient mismatch repair (pMMR) status was preserved in 31 (91%) patients. Of the 34 patients, majority (25 [74%]) had a PD-L1 status of CPS ≥1. Twenty-three (68%) patients had prior pelvic radiotherapy, 33 (97%) patients underwent platinum-based chemotherapy, and five (15%) patients had received bevacizumab treatment (Table 1).

Six (18%) patients were treatment-naive, and 28 (82%) had received at least one or later treatment lines with platinum-based chemotherapy. As of data cut-off (November 15, 2023), all patients have ended the study treatment. The most common reason for combination treatment

discontinuation was PD occurring in 14 (41%) patients, followed by study termination in seven (21%) patients, and AE in six (18%) patients (Fig. 1).

Efficacy

Overall, among 34 patients in the FAS, the confirmed ORR was 32% (95% CI 17–51), meeting the prespecified effective boundary (ORR lower confidence limit >15%). The DCR was 97% (95% CI 85–100); the median TTR was 2.8 (95% CI 1.4–4.1) months and median DoR was 18.7 (95% CI 4.4–not estimable [NE]) months, with a 15-month DoR rate of 71% (95% CI 34–90) (Table 2, Fig. 2a, 2b, and 2c). The median PFS follow-up time was 19.5 (95% CI 11.1–22.1) months, and the median PFS was 8.3 (95% CI 5.5–19.4) months (Fig. 3), with a 12-month PFS rate of 39% (95% CI 22–56). With a median OS follow-up of 21.2 (95% CI 19.4–22.8) months, median OS was 23.5 (95% CI 15.8–NE) months (Table 2), with 12-month and 18-month OS rates of 76% (95% CI 57–87) and 64% (95% CI 45–78), respectively.

The efficacy outcomes based on the TRES (N = 33) were also provided in Supplementary Table 3. And those in patients with pMMR subgroup (N = 31) were also provided (Supplementary Table 4). Efficacy outcomes in treatment-naïve patients (N = 6) are provided in Supplementary Table 5).

Among the pretreated patients with CPS ≥1 (N = 19), more promising outcomes were observed with an ORR of 37% (95% CI 16–62) and median PFS of 19.4 (95% CI 4.0–22.1) months, as well as the 12-month PFS rate of 61% (95% CI 33–80). The OS data was not mature at the data cut-off date, and the OS rate at 18-month was 72% (95% CI 46–87) (Table 2).

Safety

In all 34 patients, the median (range) duration of combination treatment was 10.0 (0.7–24.3) months. A total of 34 patients (100%) had at least one treatment-related adverse event (TRAE), which was related to either fruquintinib or sintilimab or both treatments (Table 3). TRAEs with an incidence of ≥30% included: proteinuria (65%), hypothyroidism (62%), hyperthyroidism (44%), palmar-plantar erythrodysaesthesia syndrome (44%), anaemia (41%), asthenia (38%), hyperuricaemia (35%), and white blood cell count decreased (32%) (Table 3). Twenty-six patients (76%) had TRAEs of grade ≥3. The most frequent (≥5%) grade ≥3 TRAEs included: palmar-plantar erythrodysaesthesia syndrome (21%), urogenital fistula (12%), female genital tract fistula (12%), white blood cell count decreased (9%), hypertension (9%), lymphocyte count decreased (6%), neutrophil count increased (6%), and stomatitis (6%) (Table 3).

TRAEs leading to permanent discontinuation of fruquintinib occurred in nine (26%) patients, and permanent discontinuation of sintilimab in six (18%) patients. TRAEs leading to death occurred in two (6%) patients. One patient who developed renal failure leading to death after 14 cycles of study treatment, was presented with other important confounding factors including urinary tract obstruction due to pelvic metastasis, urinary tract infection and long-term use of cephalexin for nearly 3 months, all of which may have contributed to increased creatinine. The other patient who died of malnutrition after 14 cycles of study treatment was presented with other important confounding factors including advanced malignancy, multiple gastrointestinal reactions, and refusal to receive effective treatment. Immune-related AEs occurred in 30 (88%) patients. The most common immune-related AEs included hypothyroidism (59%), hyperthyroidism (44%), and blood thyroid-stimulating hormone increased (26%). Immune-related AEs requiring corticosteroid treatment occurred in five (15%) patients.

DISCUSSION

The management of advanced cervical cancer remains a significant challenge, particularly for patients who have progressed on or after first-line therapy. Although ICI monotherapy agents such as pembrolizumab and cemiplimab are the mainstays for second-line or subsequent treatment of advanced cervical cancer worldwide and in China,[7,8] the efficacy of these monotherapies has proven to be limited. Our trial met the prespecified primary endpoint (lower confidence limit of ORR >15%), showing encouraging antitumour activity of fruquintinib plus sintilimab in patients with advanced cervical cancer who had progression after first-line platinum-based chemotherapy or were unable to tolerate standard treatment.

Keeping in mind the caveats associated with indirect cross-trial comparisons, it is informative to consider the outcomes in the context of other studies of ICI in combination of antiangiogenic agents in a patient population of similar disease characteristics. The median PFS of 8.3 months and 19.4 months in the total population and pretreated patients with CPS ≥1, respectively, from our study, were very similar to those demonstrated with other combination therapies of ICIs and antiangiogenics, such as a median PFS of 10.3 months in a study of camrelizumab plus famitinib and a median PFS of 8.8 months in a study of camrelizumab plus apatinib.[15,16] Several ICI combinations have also been studied in recent years. The ORR using dual PD-1 and CTLA-4 blockade with balstilimab and zalifrelimab was 25.6%, and median PFS and OS were 2.7 months and 12.8 months, respectively.[17] Elsewhere, nivolumab plus ipilimumab in the CheckMate 358 study reported an ORR of 38%.[18] In this context, the combination of fruquintinib and sintilimab in our study showed comparable efficacy profile to the combination regimens mentioned above, especially in pretreated patients with CPS ≥1 (ORR of 37%, median PFS of 19.4 months, and OS rate at 18-month of 72%).

Loss of mismatch repair proteins is a common event in cancer and has been proposed as a marker for response to ICIs for several cancer types. It is clear that pMMR is extremely common in cervical cancer.[19] In endometrial cancer, treatment options have limited efficacy for patients with pMMR status.[20] The prognostic impact of differential mismatch repair expression has not previously been clinically explored in cervical cancer. Results in our study suggest that the pMMR status did not affect the treatment efficacy.

The safety profile of the fruquintinib-sintilimab combination was generally manageable. The types of TRAEs that occurred with fruquintinib plus sintilimab in our study were generally similar to those reported in other studies of antiangiogenic agents in combination with PD-1/PD-L1 antibodies.[15,16] The incidence of most common AEs was comparable to those observed in prior studies in other solid tumours,[14,21-23] and no new safety signals were identified. Proteinuria was the most common TRAE in our study, with only one patient reporting grade ≥3. The most frequent grade ≥3 TRAEs included palmar-plantar erythrodysaesthesia syndrome, urogenital fistula, and female genital tract fistula, of which palmar-plantar erythrodysaesthesia syndrome was a common skin toxicity associated with fruquintinib.[14] Most immune-related AEs were grade 1 to 2 and included hypothyroidism, hyperthyroidism, and blood thyroid-stimulating hormone increased, which was in line with that reported for other PD-L1 inhibitors.[7,15]

A limitation of this study is the non-randomised design and the lack of a comparator arm. The analyses were also limited by small sample size, and a large, prospective phase 3 trial would be required to further understand the baseline patient characteristics that predict better outcomes with the combination of fruquintinib and sintilimab in pretreated patients with CPS ≥1. The number of enrolled patients who had previously received bevacizumab was limited (only 5

patients), making it difficult to evaluate the efficacy of rechallenge of anti-angiogenic TKIs in patients. It is also worth noting that none of the enrolled patients received immunotherapy, as immune-combined chemotherapy for first-line treatment of cervical cancer was not yet approved in China during the implementation of the study. As enrolment was exclusively in China, its applicability to other populations remains unknown.

CONCLUSION

In conclusion, fruquintinib plus sintilimab may indicate favourable and durable antitumour activity and manageable safety profile in advanced cervical cancer in this phase 2 study, especially in pretreated patients with CPS ≥1, which may warrant further investigation in a larger study.

DECLARATIONS

AUTHOR CONTRIBUTIONS

X.W., P.T., S.F., and W.S. conceptualised and designed the study. All authors acquired, analysed, and interpreted the data. K.C. performed the statistical analysis. X.W., K.C., P.L., H.S., P.T., and S.F. drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content. P.T., S.F., M.M.S., and W.S. obtained funding for the study. X.W., D.W., Ji.W., Y.H., T.Y., G.L., J.Z., K.W., Y.K., A.L., X.H., X.R., L.L., R.Y., Q.L., Q.Y., B.Z., Ju.W., H.Y., and Y.T. providing administrative, technical, and material support. X.W. had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY

De-identified participant data that underlie Figure 2 and 3 are accessible from Supplementary Data 1. Any additional information (including trial protocol or statistical analysis plan) is available to investigators for research purposes on a case-by-case basis after the time of this publication. Requests for access to data should be addressed to SF (songhuaf@hutch-med.com) for consideration. The response to data access requests will be made within 4 weeks of receipt.

CONFLICT OF INTEREST

KC, PL, HS, PT, SF, MMS, and WS are employees of HUTCHMED. All other authors have declared no conflicts of interest.

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Figures and Tables

Table 1. Baseline and clinical characteristics (full analysis set)

Patient characteristics	Fruquintinib plus sintilimab N = 34
Age, median (range), y	56 (26–74)
ECOG PS, *n* (%)	
0	17 (50)
1	17 (50)
Pathological diagnosis, *n* (%)	
Squamous cell carcinoma	29 (85)
Adenocarcinoma	5 (15)
PD-L1 status, *n* (%)	
CPS ≥1	25 (74)
CPS <1	8 (24)
Missing	1 (3)
MMR status, *n* (%)	
pMMR	31 (91)
dMMR	0
Unknown	3 (9)
Prior pelvic radiotherapy, *n* (%)	
Yes	23 (68)
No	11 (32)
Number of prior lines of systemic treatment, *n* (%)	
0	6 (18)
1	21 (62)
2	7 (21)
Adjuvant/neoadjuvant therapy, *n* (%)	
Yes	14 (41)
No	20 (59)
Prior systemic treatment type, *n* (%)	
Platinum-containing doublet chemotherapy	33 (97)
Bevacizumab containing therapy	5 (15)
Number of organ sites involved, *n* (%)	
1	13 (38)
2	10 (29)
≥3	11 (32)
Prior antitumour surgery and procedures, *n* (%)	22 (65)
Radical	16 (47)
Palliative	2 (6)

CPS, combined positive score; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; pMMR, mismatch repair proficient.

Table 2. Efficacy outcomes (full analysis set)

	Patients with prior treatments		
	CPS ≥1 n = 19	Total n = 28	Total N = 34
Best overall response, *n* (%)			
CR	1 (5)	1 (4)	1 (3)
PR	6 (32)	7 (25)	10 (29)
SD	11 (58)	19 (68)	22 (65)
PD	0	0	0
Not evaluable	1 (5)	1 (4)	1 (3)
ORR, % (95% CI)	37 (16–62)	29 (13–49)	32 (17–51)
DCR, % (95% CI)	95 (74–100)	96 (82–100)	97 (85–100)
Median DoR, month (95% CI)	18.7 (4.2–NE)	18.7 (4.2–NE)	18.7 (4.4–NE)
6-month DoR rate (95% CI), %	86 (33–98)	88 (39–98)	81 (42–95)
9-month DoR rate (95% CI), %	86 (33–98)	75 (32–93)	71 (34–90)
12-month DoR rate (95% CI), %	86 (33–98)	75 (32–93)	71 (34–90)
15-month DoR rate (95% CI), %	86 (33–98)	75 (32–93)	71 (34–90)
Median TTR, month (95% CI)	3.4 (1.6–4.1)	3.1 (1.4–4.1)	2.8 (1.4–4.1)
Number of patients with PFS events, *n* (%)	10 (53)	19 (68)	22 (65)
Median PFS, month (95% CI)	19.4 (4.0–22.1)	8.2 (4.0–19.4)	8.3 (5.5–19.4)
6-month PFS rate (95% CI), %	68 (39–85)	59 (37–76)	64 (44–78)
9-month PFS rate (95% CI), %	61 (33–80)	42 (23–61)	47 (28–63)
12-month PFS rate (95%CI), %	61 (33–80)	38 (19–56)	39 (22–56)
Median PFS follow-up, month (95% CI)	19.4 (16.5–22.1)	19.5 (16.5–NE)	19.5 (11.1–22.1)
Number of patients with OS events, *n* (%)	6 (32)	11 (39)	14 (41)
Median OS, month (95% CI)	23.5 (16.0–NE)	23.5 (12.1–NE)	23.5 (15.8–NE)
6-month OS rate (95% CI), %	94 (67–99)	89 (69–96)	91 (74–97)
12-month OS rate (95% CI), %	78 (51–91)	74 (53–87)	76 (57–87)
18-month OS rate (95% CI), %	72 (46–87)	63 (42–78)	64 (45–78)

	Patients with prior treatments		
	CPS ≥1 n = 19	Total n = 28	Total N = 34
Median OS follow-up, month (95% CI)	22.1 (19.2–22.8)	21.2 (19.2–22.3)	21.2 (19.4–22.8)

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

Table 3. Treatment-related adverse events (fruquintinib or sintilimab or both)

	Total N = 34	
TRAE, *n* (%)	34 (100)	
TRAE of grade ≥3, *n* (%)	26 (76)	
TRAE leading to discontinuation of fruquintinib, *n* (%)	9 (26)	
TRAE leading to discontinuation of sintilimab, *n* (%)	6 (18)	
TRAE leading to dose reduction of fruquintinib, *n* (%)	20 (59)	
TRAE leading to death, *n* (%)	2 (6)	
	All grades	Grade ≥3
TRAE by PT (incidence in total ≥25% or ≥5% of grade ≥3)	34 (100)	26 (76)
Proteinuria	22 (65)	1 (3)
Hypothyroidism	21 (62)	0
Hyperthyroidism	15 (44)	0
Palmar-plantar erythrodysaesthesia syndrome	15 (44)	7 (21)
Anaemia	14 (41)	1 (3)
Asthenia	13 (38)	1 (3)
Hyperuricaemia	12 (35)	1 (3)
White blood cell count decreased	11 (32)	3 (9)
Hypertension	10 (29)	3 (9)
Lymphocyte count decreased	10 (29)	2 (6)
Blood thyroid stimulating hormone increased	10 (29)	0
Hypertriglyceridemia	9 (26)	1 (3)
Urinary tract infection	9 (26)	1 (3)
Platelet count decreased	9 (26)	1 (3)
Aspartate aminotransferase increased	9 (26)	0
Hypercholesterolemia	9 (26)	0
Stomatitis	6 (18)	2 (6)
Female genital tract fistula	5 (15)	4 (12)
Urogenital fistula	4 (12)	4 (12)
Neutrophil count increased	4 (12)	2 (6)

PT, preferred term; TRAE, treatment-related adverse event.

Fig 1. Patient dispositions

Fig 2. Tumour responses of fruquintinib plus sintilimab in the treatment of advanced cervical cancer assessed by the investigator per RECIST v1.1. (a) Best change in target sum of lesions from baseline, (b) Time and duration of response, (c) Percentage change from baseline in target tumour burden over time. The waterfall, swimmer, and spider plots show the tumour responses based on the tumour response-evaluable set (*N* = 33) who had at least one post-baseline tumour-imaging evaluation. CPS, combined positive score; CR, complete response; NA, not applicable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Fig 3. Kaplan–Meier Curve of progression-free survival in the overall population (*N* = 34). CI, confidence interval; CPS, combined positive score; mPFS, median progression-free survival; PFS, progression-free survival.

ED Summary

Wu et al. investigated the efficacy and safety of fruquintinib plus sintilimab in 34 Chinese patients with advanced cervical cancer. The study finds that 32% of patients responded to the combination treatment and disease was controlled in 97%; side effects were manageable.

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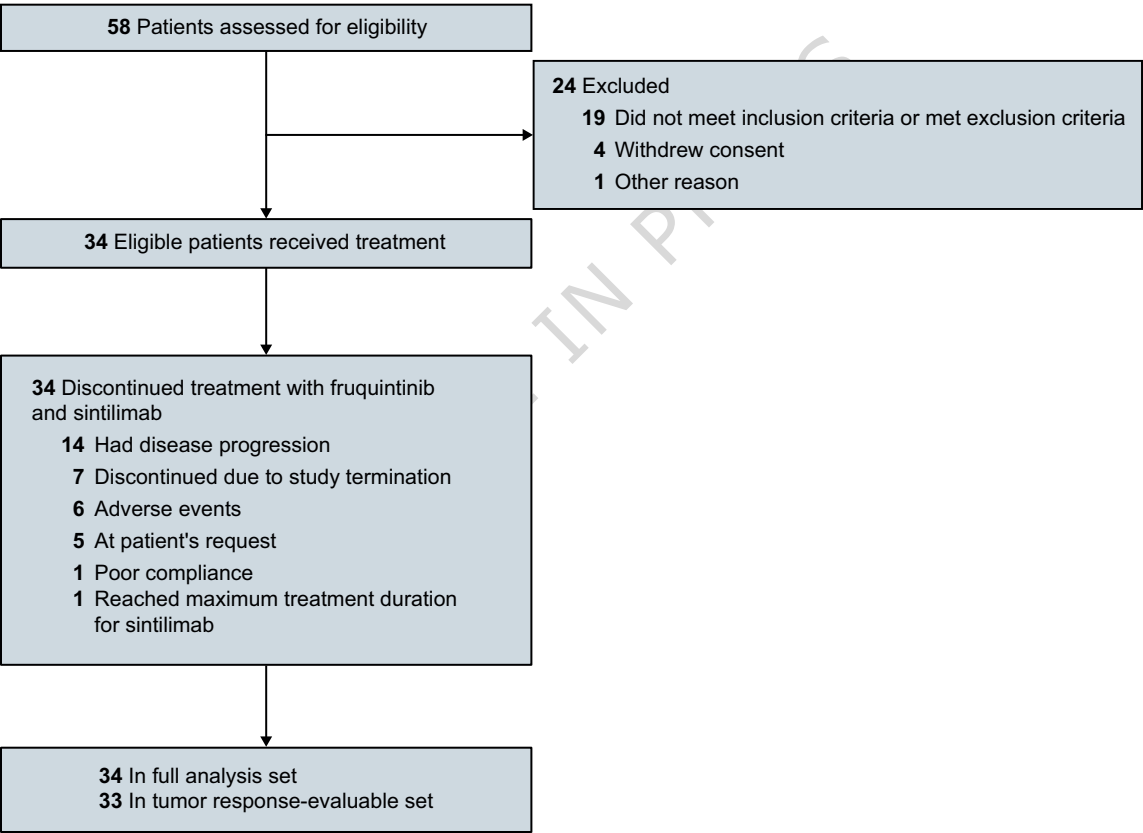

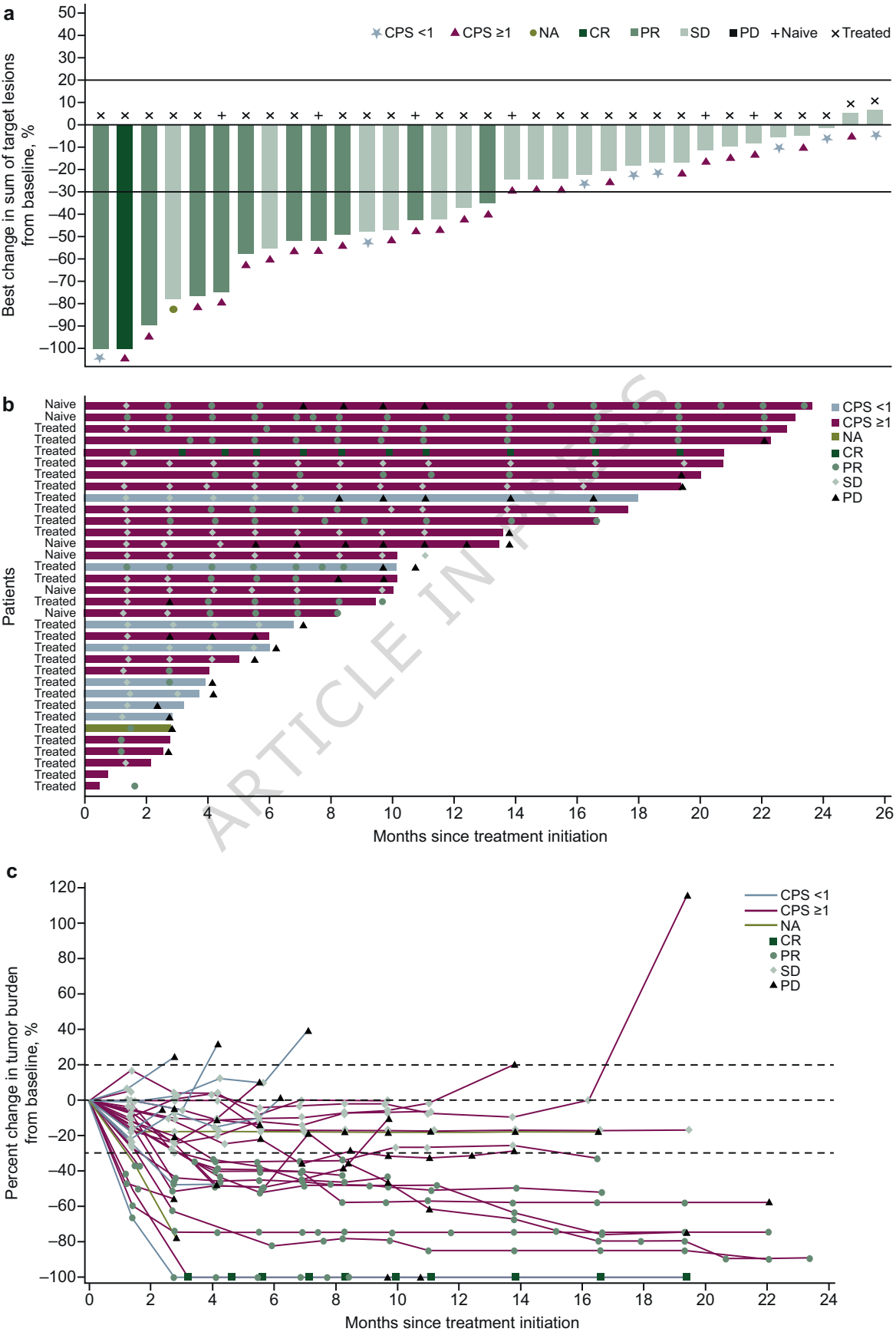

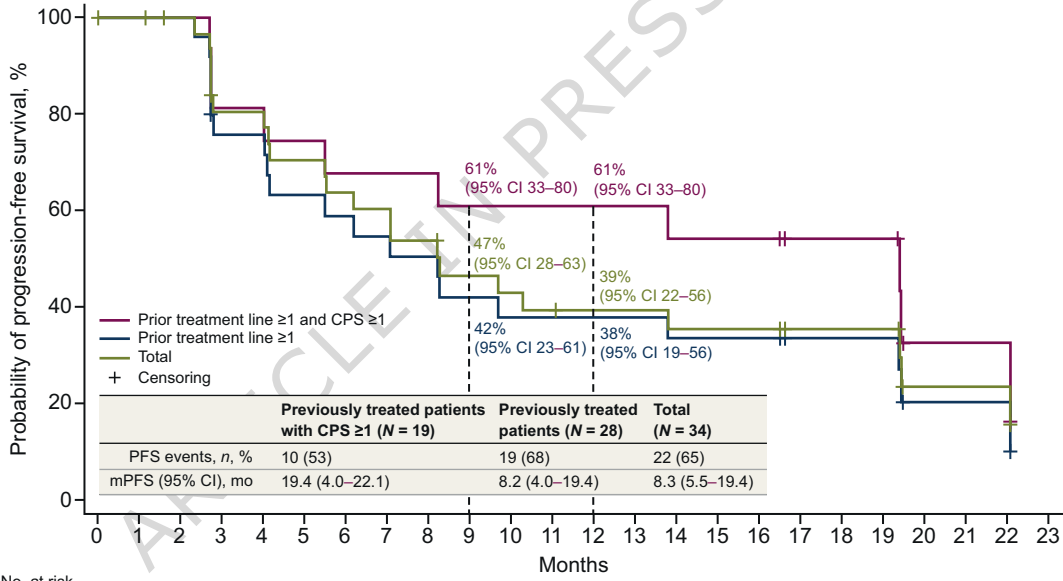

	Previously treated patients with CPS ≥1 (*N* = 19)	Previously treated patients (*N* = 28)	Total (*N* = 34)
PFS events, *n*, %	10 (53)	19 (68)	22 (65)
mPFS (95% CI), mo	19.4 (4.0–22.1)	8.2 (4.0–19.4)	8.3 (5.5–19.4)

No. at risk

Prior treatment line ≥1 and CPS ≥1	19	18	16	12	12	11	10	10	10	9	9	9	9	9	8	8	8	6	6	6	2	2	2	0
Prior treatment line ≥1	28	27	25	18	18	15	14	13	12	10	9	9	9	9	8	8	8	6	6	6	2	2	2	0
Total	34	33	31	24	24	21	19	18	16	13	12	11	10	10	9	9	9	7	7	7	3	3	3	0