Efficacy and Safety of the Anti–PD-L1 mAb Socazolimab for Recurrent or Metastatic Cervical Cancer: a Phase I Dose-Escalation and Expansion Study

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ABSTRACT

Purpose: This study (ClinicalTrials.gov identifier, NCT03676959) is an open, phase I dose-escalation and expansion study investigating the safety and efficacy of the recombinant, fully human anti–programmed death ligand 1 (PD-L1) mAb socazolimab in patients diagnosed with recurrent or metastatic cervical cancer.

Patients and Methods: Patients received socazolimab every 2 weeks until disease progression. The study was divided into a dose-escalation phase and a dose-expansion phase. Safety and tolerability were primary endpoints of the dose-escalation phase. The primary endpoints of the dose-expansion phase were safety and the objective response rate (ORR) of the 5 mg/kg dose. Efficacy was assessed by the third-party independent review committee (IRC) using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Results: 104 patients were successfully enrolled into the study. Twelve patients were included in the dose-escalation phase, with one complete response and two partial responses in the 5 mg/kg treatment group. Ninety-two patients (5 mg/kg) were enrolled in the dose-expansion phase. Fifty-four patients (59.3%) had baseline PD-L1–positive tumor expression (combined positive score ≥1). ORR was 15.4% [95% confidence interval (CI), 8.7%–24.5%]. Median PFS was 4.44 months (95% CI, 2.37–5.75 months), and the median OS was 14.72 months (95% CI, 9.59–NE months). ORR of PD-L1–positive patients was 16.7%, and the ORR of PD-L1–negative patients was 17.9%. No treatment-related deaths occurred.

Conclusions: Our study demonstrates that socazolimab has durable safety and efficacy for the treatment of recurrent or metastatic cervical cancer and exhibits a safety profile similar to other anti–PD-1/PD-L1 mAbs.

Introduction

Cervical cancer is a common malignant tumor of the female reproductive system. Globally, it is ranked the fourth leading cause of cancer-related death among women (1). Despite the widespread adoption of human papillomavirus (HPV) vaccination and cervical cancer screening, mortality rates remain high. In contrast to patients with early-stage and locally advanced cervical cancer, the treatment options for recurrent or metastatic cervical cancer are limited, thus increasing the clinical need for new and innovative second-line and later treatment options (2).

Platinum-based chemotherapy is currently the standard first-line treatment for patients with recurrent or metastatic cervical cancer. Early studies of single-agent cisplatin treatments have reported objective response rates (ORR) ranging from 20% to 25% in advanced cervical cancer, which were often accompanied with poor responses due to cisplatin resistance (3). In contrast to first-line treatments, current second-line, single-agent treatments have demonstrated much lower ORRs. In a meta-analysis utilizing the results from different earlier clinical studies, including treatments such as bevacizumab, docetaxel, paclitaxel, gemcitabine, and epirubicin (4–12), the combined ORR was 12.8% [95% confidence interval (CI), 8.7% to 14.3%], with a median progression-free survival (PFS) of 3 months, and a median overall survival (OS) of 7 months upon meta-analysis. Cisplatin-combinations have also demonstrated improvements in responses and survival times, and more recently, the combination of cisplatin, paclitaxel, and bevacizumab was explored in the GOG-240 study for the treatment of advanced cervical cancer, resulting in an increase of 3.7 months for the median OS (13–15). High toxicities, however, have limited the safety and efficacy of these treatments, and therefore have accelerated the need for novel second-line treatments to treat patients with recurrent or metastatic cervical cancer.

Immunotherapy has been gaining significant relevance as an alternate treatment method for cancer (16). Programmed cell death

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Translational Relevance

Socazolimab is a second-line treatment for patients with cervical cancer, equipped with a dual anti–programmed death ligand 1 (PD-L1)/antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism that enhances its antitumor activity beyond other drugs. As there are limited standard second-line and later treatment options to date, our findings are significant because (i) objective response rate (ORR) was reported in PD-L1–negative patients (17.9%), and 16.7% for PD-L1–positive patients. Unlike pembrolizumab, whose efficacy had only been reported in PD-L1–positive patients, socazolimab is effective in patients regardless of PD-L1 expression, enhancing patient access. (ii) Longer progression-free survival (PFS) and overall survival (OS) rates, with a median PFS of 4.44 months, and a median OS of 14.72 months. By comparison, the phase III cemiplimab GOG-3016 study reported a median PFS of 2.8 months and a median OS of 12.0 months. (iii) Excellent pharmacokinetic/pharmacodynamic and safety profile: therapeutic blood levels were achieved at the lowest dose (5 mg/kg). MTD was not determined at the highest dose (15 mg/kg), demonstrating good safety and tolerability.

receptor-1 (PD-1) and its associated programmed cell death receptor-ligand 1 (PD-L1), are key immune checkpoints overexpressed in several cancer types, including breast cancer, cervical cancer, and ovarian cancer (17). This implies that the PD-1/PD-L1 association is critical for cancer progression and is a potential target for achieving antitumor activity (18). In June 2018, the FDA approval of pembrolizumab marked an important milestone in immunotherapy for recurrent or metastatic cervical cancer with PD-L1–positive tumors (19–21). As one of the first anti–PD-1 mAbs, pembrolizumab in combination with platinum-based chemotherapy with or without bevacizumab has already been approved by the FDA in 2021 as a standard first-line treatment in PD-L1–positive recurrent or metastatic cervical cancer, as reported in the KEYNOTE-826 study (22). Results from the KEYNOTE-826 study revealed a median PFS of 10.4 months, with an unreached median OS. However, PD-1/PD-L1 inhibitor therapies have been shown to only benefit patients with recurrent or metastatic cervical cancer with PD-L1–positive tumors, and thus, more effective PD-1/PD-L1 inhibitors with novel mechanisms are needed.

Socazolimab is a novel, highly specific, fully human recombinant anti–PD-L1 mAb that is equipped with two mechanisms acting synergistically for its antitumor activity. Supporting preclinical data can be found in the Supplementary Data. Ongoing human studies with socazolimab include extensive-stage small-cell lung cancer in combination with carboplatin and etoposide (NCT04878016), advanced urothelial carcinoma in combination with albumin-bound paclitaxel (NCT04603846), and esophageal squamous cell carcinoma with neoadjuvant chemotherapy (NCT04460066). Here we report the results of this clinical trial that explores the safety and efficacy of socazolimab as a second-line treatment for patients with recurrent or metastatic cervical cancer.

Patients and Methods

Study design and enrollment

The study was conducted in two stages through a dose-escalation phase and a dose-expansion phase. Eligible patients were diagnosed with recurrent or metastatic cervical cancer and had previously failed or were intolerant to the first-line platinum-based regimen. Key eligibility criteria included histopathologically or cytologically confirmed cervical cancer; failed first-line platinum-based regimen; measurable disease with at least one evaluable lesion as assessed by the Response Evaluation Criteria in Advanced Solid Tumors version 1.1 (RECIST 1.1); Eastern Cooperative Oncology Group performance status of 0 or 1; and an expected OS of at least 3 months. Key exclusion criteria included suspected or known autoimmune disease; prior treatments with immune checkpoint inhibitors; allergic reactions to macromolecular protein inhibitors; and central nervous system metastases. Written informed consent was obtained from all patients.

The dose-escalation phase adopted the traditional 3+3 dose-escalation design, at three different doses: 5, 10, and 15 mg/kg, with 14 days as a treatment cycle. Patients received socazolimab every 2 weeks until disease progression. Dose-limiting toxicities (DLT) were observed within 28 days of the first administration. DLTs were defined as grade 3 or higher adverse events (AE) occurring within 28 days after the first dose of the study drug, excluding tumor burning reactions, grade 3 adverse infusions characterized by local pain, irritation, known or suspected tumor site rash, or transient events (remission within 6 hours). Each treatment group included 3 or 6 patients depending on DLT occurrence and were monitored for the MTD. Serum concentration and receptor occupancy tests for socazolimab were included in the dose-escalation phase. Results of the dose-escalation phase determined the recommended target dose for the dose-expansion phase. Immunogenicity testing for anti-drug antibodies were conducted in both phases. Similar dosing schedules and discharge standards had been implemented. All patients were required to complete the follow-up period. The longest follow-up period recorded for this study was one year. No control group had been set up. Informed consent was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki (2013), the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice, and approval by an Independent Ethics Review Committee and the China's Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA).

Assessments

Tumor PD-L1 expression was analysed using E1L3N antibodies. The measure of expression was the combined positive score (CPS), representing the ratio of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) to the total number of tumor cells. PD-L1 positivity was defined as CPS≥1. Tumor imaging examinations were performed every 8 weeks using CT or MRI (chest, abdomen, pelvis, and brain). To provide objective, neutral, and reproducible data, a third-party independent review committee (IRC) was established to comprehensively evaluate antitumor efficacy per the RECIST 1.1. Evaluations were performed during the last week of each treatment cycle. Pharmacokinetic and pharmacodynamic assessments were conducted using validated electrochemiluminescence assays (ECLIA) and flow cytometry. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0.3). Patients discontinuing treatment for reasons other than disease progression remained evaluated until disease progression, commencement of further antitumor treatment, or death.

Statistical analysis

Primary endpoints of the dose-escalation phase were the safety and tolerability of socazolimab upon administration once every two weeks. Results would determine the MTD, DLTs, and the recommended dose

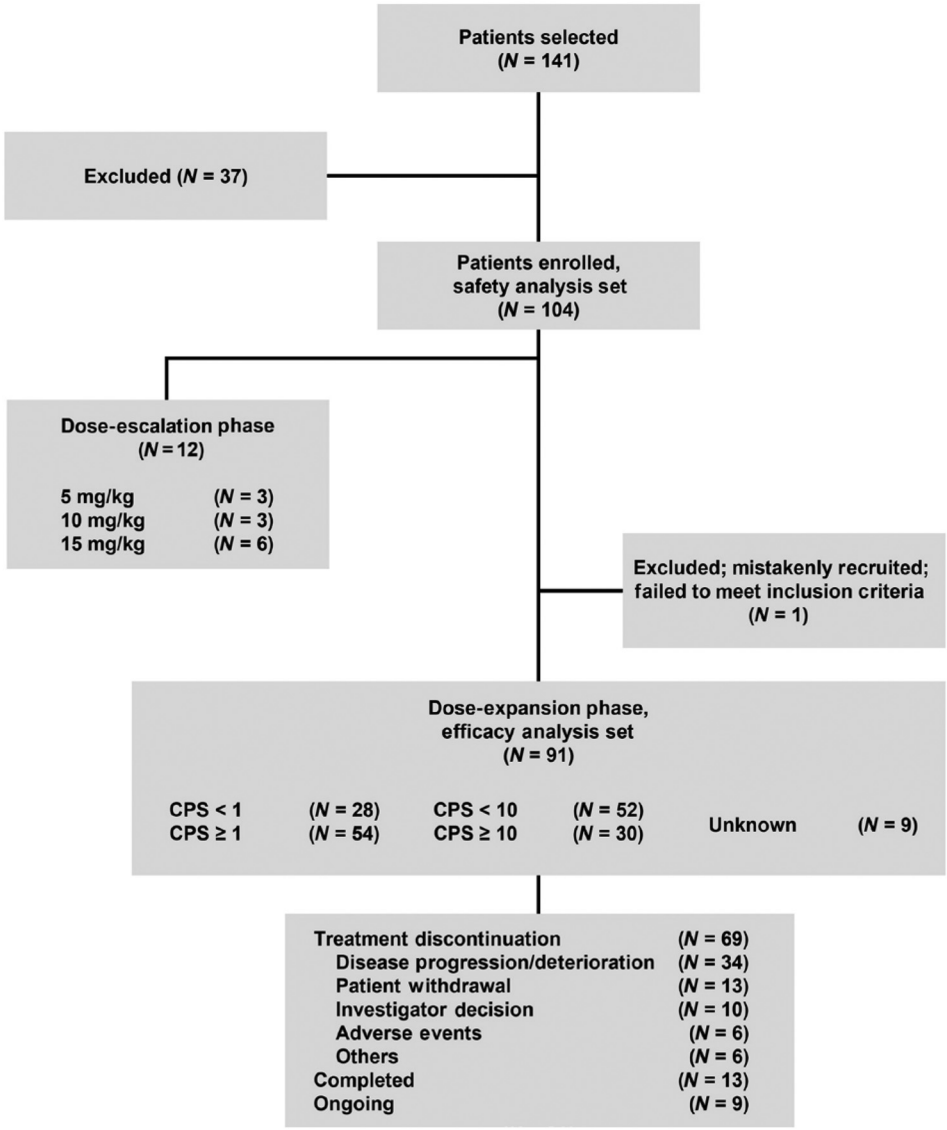

Figure 1.
CONSORT Diagram of patient disposition.

for use as a single-agent in subsequent phase II clinical trials. Pharmacokinetic and pharmacodynamic profiles were also studied.

The primary endpoints of the dose-expansion phase were safety and the ORR of the target socazolimab dose, defined as the proportion of patients with complete response (CR) or partial response (PR). Secondary endpoints included: PFS, defined as the time from the first dose to disease progression or death as assessed by RECIST 1.1, whichever occurred first; duration of response (DOR), defined as the time from the first CR or PR to disease progression; OS, defined as the time from the first dose to death; and best overall response (BOR). Efficacy was assessed using RECIST 1.1 by IRC. The ORR 95% CIs were based on the Clopper–Pearson method. PFS, DOR and OS were estimated by the Kaplan–Meier method.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

Results

Patients

From September 19, 2018 (enrollment date) to March 31, 2021 (data cutoff), 104 of 141 selected patients were enrolled in 16 sites across China and were administered with at least one dose of socazolimab (**Fig 1**). Twelve patients were enrolled in the dose-escalation phase and were allocated accordingly into the 5 mg/kg, 10 mg/kg, and 15 mg/kg treatment groups. Ninety-two patients were enrolled in the 5 mg/kg group for the dose-expansion phase. Only 91 patients were included in the efficacy analysis set as one patient failed to meet the target population criteria; the disease did not meet the progression criteria when this patient was enrolled, and thus had been excluded. Twelve patients in the dose-expansion phase were tested for complete PD-1 receptor occupancy. All 104 patients were included in the safety analysis set. Patient demographics and baseline characteristics are listed in **Table 1**.

Table 1. Patient demographics and baseline characteristics (full analysis set, $n = 103$).

Characteristics	5 mg/kg ($N = 94$)	10 mg/kg ($N = 3$)	15 mg/kg ($N = 6$)	Total ($N = 103$)
Age (years)				
No. of patients	94	3	6	103
Mean (SD)	49.9 (9.31)	40.7 (1.53)	53.0 (4.43)	49.9 (9.11)
Median	51.5	41	52.5	51
Range	31–73	39–42	47–60	31–73
ECOG performance status				
0	39 (41.5%)	2 (66.7%)	6 (100%)	47 (45.6%)
1	55 (58.5%)	1 (33.3%)	0	56 (54.4%)
PD-L1 expression (CPS)				
<1%	29 (30.9%)	1 (33.3%)	2 (33.3%)	32 (31.1%)
≥1%	56 (59.6%)	2 (66.7%)	2 (33.3%)	60 (58.3%)
Unknown	9 (9.6%)	0	2 (33.3%)	11 (10.7%)
Pathology				
Squamous cell carcinoma	90 (95.7%)	2 (66.7%)	4 (66.7%)	96 (93.2%)
Adenocarcinoma	2 (2.1%)	1 (33.3%)	1 (16.7%)	4 (3.9%)
Adenosquamous	1 (1.1%)	0	1 (16.7%)	2 (1.9%)
Other	1 (1.1%)	0	0	1 (1.0%)
Site of metastasis				
Lymph node	51 (54.3%)	2 (66.7%)	3 (50.0%)	56 (54.4%)
Lung	33 (35.1%)	0	4 (66.7%)	37 (35.9%)
Liver	14 (14.9%)	0	0	14 (13.6%)
Peritoneum	2 (2.1%)	0	2 (33.3%)	4 (3.9%)
Brain	2 (2.1%)	0	1 (16.7%)	3 (2.9%)
Pleural	2 (2.1%)	0	1 (16.7%)	3 (2.9%)
Colorectum	1 (1.1%)	0	1 (16.7%)	2 (1.9%)
Adrenal	2 (2.1%)	0	0	2 (1.9%)
Other	49 (52.1%)	1 (33.3%)	3 (50.0%)	53 (51.5%)
No. of prior lines of treatment				
1	49 (52.1%)	3 (100%)	2 (33.3%)	54 (52.4%)
2	27 (28.7%)	0	3 (50.0%)	30 (29.1%)
≥3	18 (19.1%)	0	1 (16.7%)	19 (18.4%)

Note: Data noted as *n* (%) unless stated otherwise.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Safety

One hundred and four patients were included in the safety analysis set. In the dose-escalation phase, all 12 patients did not experience any DLTs within 28 days after single administration. The MTD was not reached in the highest treatment group (15 mg/kg). One hundred and one patients (97.1%) reported AEs and 66 patients (63.5%) experienced treatment-related adverse events (TRAE; **Table 2**). The most common TRAEs were hypothyroidism (17.3%), leukopenia (11.5%), elevated alanine aminotransferase and aspartate aminotransferase levels (9.6%, respectively), and anemia (8.7%). Most TRAEs were grade 1–2, with only 8 patients (8.4%) in the 5 mg/kg group reporting grade 3 events or higher. No treatment-related deaths occurred. Forty patients (38.5%) experienced immune-mediated AEs. The most common immune-mediated AEs were hypothyroidism (17.3%), elevated rheumatoid factor (7.7%), hyperthyroidism (5.8%), and leukopenia (4.8%).

Efficacy

In the dose-escalation phase, one patient experienced CR and two patients experienced PR in the 5 mg/kg group. CR and PR were not reported in the 10 mg/kg and 15 mg/kg group. In addition to these results, as receptor occupancy saturation (88.03%) had already been achieved at 5 mg/kg before the second treatment cycle, the 5 mg/kg dose was selected as the recommended target dose.

In the dose-expansion phase (5 mg/kg), the ORR was 15.4% (95% CI, 8.7 to 24.5%), and the disease control rate (DCR) was 49.5% (95% CI, 38.8%–60.1%; **Table 3**). ORR was 18.1% (95% CI, 10.9%–27.4%) when the three 5 mg/kg patients from the dose-escalation phase were included. Patients were divided into two subgroups based on their PD-L1 expression (CPS). ORRs were 17.9% and 16.7% for the CPS<1 and CPS≥1 subgroups, respectively. Further analysis at the CPS≥10 and 1≤CPS<10 cutoffs reported ORRs of 20.0% and 12.5%, respectively. Median time to response was 2.00 months. Median DOR had not been reached (**Fig. 2A**). Reductions from baseline in target lesions were reported in 29 of 91 evaluable patients (31.9%), with 16 patients (17.6%) reporting a reduction of more than 30% (**Fig. 2B**).

Median PFS was 4.44 months (95% CI, 2.37–5.75 months). The estimated PFS at 6 and 12 months were 38.0% and 28.4%, respectively (**Fig. 2C**). At the time of data cutoff, 36 evaluable patients (39.6%) experienced death. Median OS was 14.72 months (95% CI, 9.59–NE). For the CPS≥1 subgroup, median OS was not reached (**Table 3**). The estimated OS at 6 and 12 months were 78.6% and 58.2%, respectively (**Fig. 2D**).

Additional analyses were conducted per the immune-related RECIST (iRECIST; Supplementary Table S1). iORR was 16.5% (95% CI, 9.5%–25.7%), and the iDCR was 50.5% (95% CI, 39.9%–61.2%). Median iPFS was 4.44 months (95% CI, 2.37–7.43 months).

Pharmacokinetics

In the dose-escalation phase, pharmacokinetic characteristics were observed within the dose range of 5 mg/kg to 15 mg/kg (**Table 4**). For the 5 mg/kg group, the serum concentration of

Table 2. Summary of patient AEs (safety analysis set, $N = 104$).

AEs	5 mg/kg ($n = 95$)		10 mg/kg ($n = 3$)	15 mg/kg ($n = 6$)	Total ($N = 104$)
	Any grade	Grade 3 or above			
TRAEs	59 (62.1%)	8 (8.4%)	2 (66.7%)	5 (83.3%)	66 (63.5%)
TRAE-related treatment interruption	19 (20.0%)		0	0	19 (18.3%)
TRAE-related dose discontinuation	9 (9.5%)		0	0	9 (8.7%)
Hypothyroidism	16 (16.8%)	0	0	2 (33.3%)	18 (17.3%)
Leukopenia	9 (9.5%)	0	1 (33.3%)	2 (33.3%)	12 (11.5%)
Elevated alanine aminotransferase	9 (9.5%)	1 (1.1%)	1 (33.3%)	0	10 (9.6%)
Elevated aspartate aminotransferase	9 (9.5%)	0	1 (33.3%)	0	10 (9.6%)
Anemia	7 (7.4%)	0	1 (33.3%)	1 (16.7%)	9 (8.7%)
Elevated rheumatoid factor	5 (5.3%)	0	1 (33.3%)	2 (33.3%)	8 (7.7%)
Nausea	5 (5.3%)	1 (1.1%)	2 (66.7%)	1 (16.7%)	8 (7.7%)
Hyperthyroidism	5 (5.3%)	0	0	1 (16.7%)	6 (5.8%)
Intestinal obstruction	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)
Elevated γ-glutamyltransferase	1 (1.1%)	1 (1.1%)	0	0	3 (2.9%)
Abnormal liver function	1 (1.1%)	1 (1.1%)	0	0	3 (2.9%)
Pharyngitis	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)
Elevated conjugated bilirubin	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)
Immune-mediated myocarditis	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)
Vomiting	1 (1.1%)	1 (1.1%)	1 (33.3%)	1 (16.7%)	4 (3.8%)
Immune-mediated AEs	34 (35.8%)	4 (4.2%)	1 (33.3%)	5 (83.3%)	40 (38.5%)
Hypothyroidism	16 (16.8%)	0	0	2 (33.3%)	18 (17.3%)
Elevated rheumatoid factor	5 (5.3%)	0	1 (33.3%)	2 (33.3%)	8 (7.7%)
Hyperthyroidism	5 (5.3%)	0	0	1 (16.7%)	6 (5.8%)
Leukopenia	3 (3.2%)	0	1 (33.3%)	1 (16.7%)	5 (4.8%)
Elevated alanine aminotransferase	3 (3.2%)	1 (1.1%)	0	0	3 (2.9%)
Elevated aspartate aminotransferase	3 (3.2%)	1 (1.1%)	0	0	3 (2.9%)
Elevated blood thyroid stimulating hormone	3 (3.2%)	0	0	0	3 (2.9%)
Abnormal liver function	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)
Pharyngitis	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)
Immune-mediated myocarditis	1 (1.1%)	1 (1.1%)	0	0	1 (1.0%)

Note: Data noted as *n* (%) unless stated otherwise. TRAEs (with ≥ 5% incidence rates); immune-related AEs (with ≥ 2% incidence rates).

socazolimab reached maximum at 1.98 hours and decreased at a clearance rate of 10.75 mL/hour. A dose-dependent, linear pharmacokinetic behavior was observed. After four treatment cycles (8 weeks), steady-state concentrations of socazolimab were reached. The mean serum half-life of socazolimab was 317.0 hours (13.2 days). Five patients were anti-drug-antibody–positive before treatment. During treatment, anti-drug antibodies were detected in an additional 11 of 104 evaluable patients (10.6%) in the safety analysis set, of which two patients experienced PR. Most patients tested negative for anti-drug antibodies after the 12th treatment cycle, with an exception for one patient who remained positive (1.0%).

Table 3. Antitumor efficacy assessment by IRC evaluation (efficacy analysis set, $N = 91$).

Efficacy	5 mg/kg dose expansion ($N = 91$)	PD-L1 expression		
		CPS < 1 ($N = 28$)	1 ≤ CPS < 10 ($N = 24$)	CPS ≥ 10 ($N = 30$)
ORR	14 (15.4%)	5 (17.9%)	3 (12.5%)	6 (20%)
95% CI	8.7%–24.5%	6.1%–36.9%	2.7%–32.4%	7.71%–38.57%
DCR	45 (49.5%)	12 (42.9%)	11 (45.8%)	21 (70.00%)
95% CI	38.8%–60.1%	24.5%–62.8%	25.6%–67.2%	50.60%–85.27%
PFS, months				
Median duration (95% CI)	4.44 (2.37–5.75)	2.79 (1.81–5.72)	3.58 (2.00–7.66)	7.56 (2.56–NE)
OS, months				
Median duration (95% CI)	14.72 (9.59–NE)	15.84 (7.10–NE)	NE (8.54–NE)	NE (13.34–NE)
OS (%)				
6 months (95% CI)	78.6% (68.5–85.8)	74.7% (54.1–87.1)	74.2% (51.3–87.5)	93.3% (75.9–98.3)
12 months (95% CI)	58.2% (45.4–69.0)	59.3% (36.6–76.3)	53.0% (23.3–75.8)	77.0% (55.3–89.1)
DOR, months				
Median duration (range)	NE (3.32–14.92)	NE (3.81–12.88)	NE (3.32–14.92)	NE (3.32–14.92)

Note: Data noted as *n* (%) unless stated otherwise.

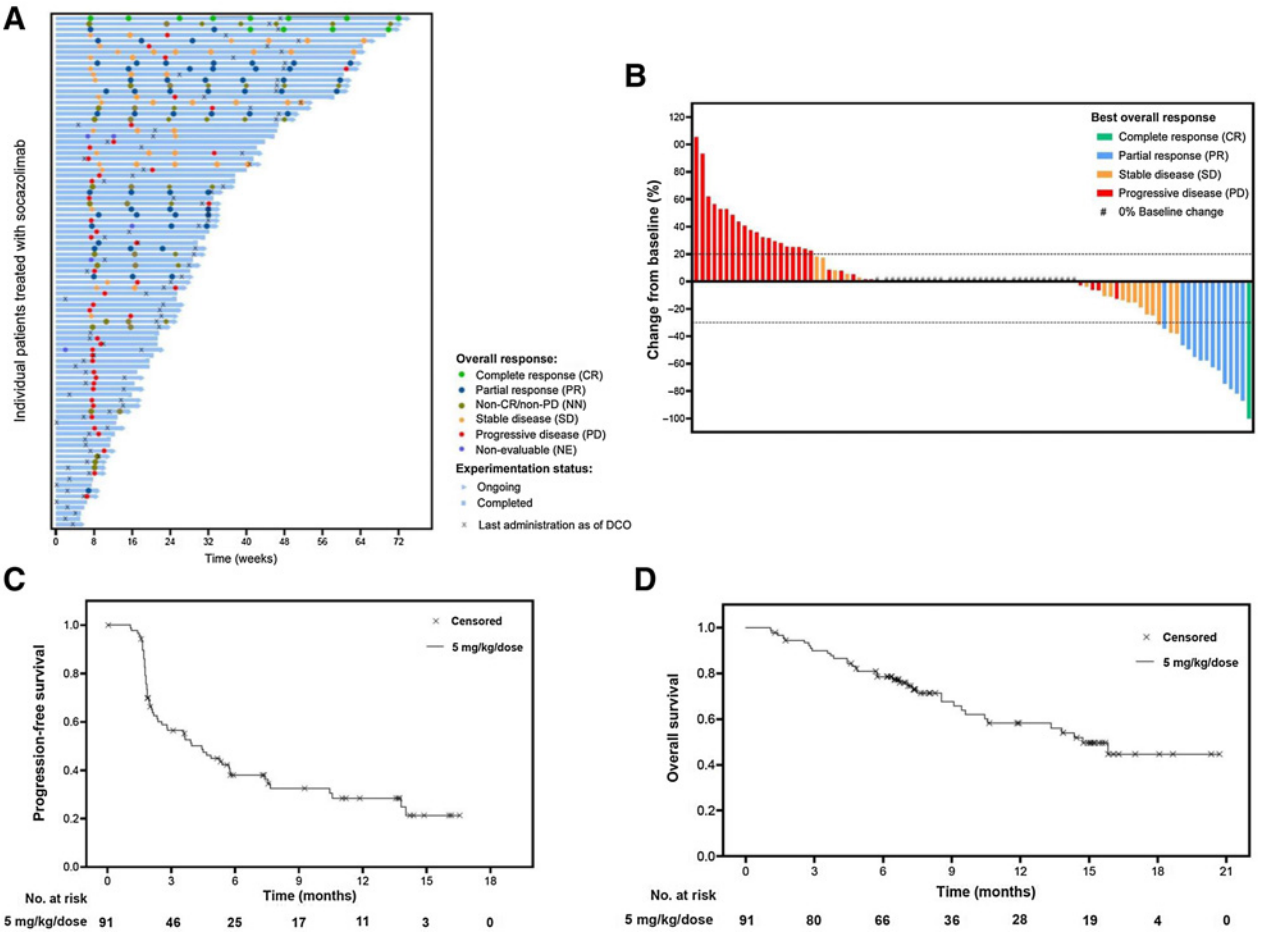

Figure 2.

A, Duration of response for individual patients in the efficacy analysis set, by IRC evaluation ($N = 91$). The 12-month DOR is 83.3% (95% CI, 27.3%–97.5%). **B,** Change from baseline in target lesions (%), by IRC evaluation. Best overall response of each evaluable patient is represented by different color-coded bars. Dotted lines at 20% and −30% indicate progressive disease (PD) and partial response (PR). **C,** Kaplan–Meier estimates of progression-free survival (PFS), by IRC evaluation. **D,** Kaplan–Meier estimates of overall survival (OS), by IRC evaluation.

Pharmacodynamics

All patients maintained complete PD-1 receptor occupancy upon single administration for at least 16 weeks. Before the second treatment cycle, the mean receptor occupancy was 88.03%, which remained consistent at levels of 88.44% on the first day of the 9th treatment cycle. Complete PD-1 receptor occupancy was defined by an occupancy of 80% to 120%.

Discussion

Prognosis for recurrent or metastatic cervical cancer has been poor, especially for those who progress after first-line chemotherapy that have few treatment options. As a result, PD-1/PD-L1 immunotherapies have been explored as second-line or later treatments in patients with cervical cancer with advanced recurrence after first-line failure.

Table 4. Pharmacokinetic characteristics of each treatment group in the dose-escalation phase ($N = 12$).

Pharmacokinetic parameters	5 mg/kg ($N = 3$)	10 mg/kg ($N = 3$)	15 mg/kg ($N = 3$)
C_{max} (μg/mL) ($\times 10^2$)	1.23 ± 0.07	2.22 ± 0.59	3.51 ± 0.53
T_{max} (h)	1.98 ± 0.27	1.98 ± 1.04	2.67 ± 1.37
$AUC_{0\text{-}t}$ (μg/mL/h) ($\times 10^4$)	2.42 ± 0.04	4.15 ± 0.9	6.84 ± 1.39
AUC_{inf} (μg/mL/h) ($\times 10^4$)	3.15 ± 0.08	4.92 ± 1.37	8.51 ± 1.81
$t_{1/2}$ (h) ($\times 10^2$)	3.17 ± 0.14	2.61 ± 0.31	2.98 ± 0.70
CL_t (mL/h)	10.75 ± 2.20	12.40 ± 0.82	12.36 ± 3.56
Vd (mL) ($\times 10^3$)	4.88 ± 0.80	4.65 ± 0.50	5.27 ± 1.76

Abbreviations: AUC_{inf}, area under concentration-time curve (time 0 to infinity); $AUC_{0\text{-}t}$, area under concentration-time curve (time 0 to t); C_{max}, maximum concentration of drug in the blood; CL_t, drug clearance rate; T_{max}, time to maximum; $t_{1/2}$, half-life; Vd, volume of drug distribution.

In the phase II pembrolizumab KEYNOTE-158 study, the first-in-class, anti–PD-1 drug, 98 patients were enrolled with advanced or metastatic cervical cancer failed first-line treatment, of which 82 patients were PD-L1–positive and had an ORR of 14.6%, and in contrast to an ORR of 0% for the remaining PD-L1–negative patients (21). On the basis of this, pembrolizumab was approved by the FDA for the second-line treatment of recurrent or metastatic cervical cancer with disease progression during or after chemotherapy, in patients with a positive PD-L1 expression (CPS≥1). In 2021, the phase III cemiplimab EMPOWER-Cervical1/GOG-3016 randomized controlled trial revealed that patients in the cemiplimab group had a reduced risk of death, regardless of PD-L1 expression status or histology, in contrast to second-line chemotherapy, with a 31% reduction in the risk of death among patients in the cemiplimab group, a 25% lower risk of disease progression, and significantly higher ORR (16.4% vs. 6.3%; ref. 23).

Socazolimab offers two mechanisms of action for its anti-tumor activity. The first mechanism involves direct binding to the PD-L1 that blocks its interaction with the PD-1 receptor to activate the T-cell response, hinder the immune evasion mechanism, and inhibit subsequent tumor growth. As the second mechanism, socazolimab is equipped with an IgG1 Fc region to stimulate an antibody-dependent cell-mediated cytotoxicity (ADCC) response, which binds the Fc receptors on NK cells to release cytokines and cytotoxic molecules, and thus, both mechanisms have contributed to the results presented in this study.

Results from this study have revealed that socazolimab exhibits durable efficacy and safety for patients with recurrent or metastatic cervical cancer. The ORR was 15.4%, with a DCR of 49.5%. ORR was enhanced to 18.1% when the three 5 mg/kg patients from the dose-escalation phase were included. In our study, patients were included regardless of baseline tumor PD-L1 expression, with 54 patients (59.3%) expressing PD-L1–positive tumors. Antitumor efficacy was observed in PD-L1–negative patients with an ORR of 17.9%, which was similar to the ORR of 16.7% reported in PD-L1–positive patients. Comparable ORRs of 20.0% and 12.5% were also reported for CPS≥10 and 1≤CPS<10 subgroups, which provides further evidence that socazolimab is effective in patients with varying PD-L1 expression levels. In patients with low PD-L1 expression levels, key antitumor activity could be attributed to its dual anti–PD-L1/ADCC mechanism, where in instances of low PD-L1 expression, the IgG1 Fc region is employed instead of the anti–PD-L1 binding region to initiate the additional ADCC response.

As several anti–PD-1/PD-L1 mAbs known to date have only demonstrated efficacy in PD-L1–positive patients, socazolimab is set to increase patient access to cervical cancer immunotherapy treatment. In the phase II pembrolizumab KEYNOTE-158 study, no observable efficacy was observed in patients with PD-L1–negative advanced cervical cancer in contrast to an ORR of 14.6% in PD-L1–positive patients (21). In KEYNOTE-826, the efficacy for CPS<1 patients was unclear due to its small subgroup size, but noted that the efficacy, if any, was small (22). More recently, another phase II study of the latest anti–PD-1 balstilimab antibody revealed ORRs of 20.0% and 7.9% for PD-L1–positive and PD-L1–negative patients, respectively (24). In EMPOWER-Cervical1/GOG-3016, objective responses to cemiplimab were observed in 15 of 82 patients with a PD-L1 expression of 1% or greater (18%; 95% CI, 11%–28%), and in 5 of 44 patients with a PD-L1 expression of less than 1% (11%; 95% CI, 4%–25%; ref. 23). In comparison, socazolimab has an ORR of 17.9% in PD-L1–negative patients, and an ORR of 16.7% in PD-L1–positive patients. Therefore, there are limited immunotherapy options for cervical cancer patients with negative PD-L1 expression, and thus socazolimab will make a key advancement in the field by enhancing patient access to cervical cancer–related immunotherapy treatment, regardless of baseline tumor PD-L1 expression.

Patient responses to socazolimab were durable, with a median time to response of 2.00 months. Median DOR was not reached, which constitutes a lasting benefit to patients administered with socazolimab as the tumor continues to respond to the treatment without growing or metastasizing. Response results were comparable to those reported in KEYNOTE-158, with a median time to response of 2.1 months and an unreached median DOR (21). For an additional comparison, the phase I/II nivolumab study (CheckMate 358) reported a median time to response of 1.7 months, as well as an unreached median DOR in its cervical cancer cohort ($n = 19$; ref. 25).

Median PFS was 4.44 months, and the estimated PFS at 6 months was 38%. Median OS was 14.72 months. For the 1≤CPS<10 and CPS≥10 subgroups, median OS was not reached. As a single agent, these results are significant as they exceed the benchmark set by other second-line treatments. In the phase Ib pembrolizumab study (KEYNOTE-028), results revealed a median PFS of only 2 months, an estimated PFS at 6 months of 21%, and a median OS of 11 months (20). In another phase II anti–PD-L1 atezolizumab and bevacizumab combination study, results revealed a median PFS of 2.9 months and a median OS of 8.9 months (26). More recently, the phase III cemiplimab EMPOWER-Cervical1/GOG-3016 study had also reported a median PFS of 2.8 months and a median OS of 12.0 months in the overall study population (23). In the squamous cell carcinoma population, socazolimab reported a median PFS of 4.44 months (95% CI, 2.33–5.78 months), and a median OS of 14.72 months (95% CI, 9.59–NE). In contrast, cemiplimab only reported a median PFS of 2.8 months (95% CI, 2.6–4.0 months), and a median OS of 11.1 months (95% CI, 9.2–13.4 months). In the socazolimab study, only 4.4% (4 of 91) patients with non–squamous cell carcinoma were enrolled, and thus the efficacy had not been analyzed statistically. As a result, these exemplify that socazolimab, as a single agent, already presents an extensive PFS and OS for patients with recurrent or metastatic cervical cancer.

Results upon RECIST 1.1 and iRECIST assessment were also comparable. iORR was 16.5%, which remained similar to the ORR of 15.4%. Median PFS and iPFS were both reported as 4.44 months. It is important to note that pseudoprogression was accounted for under the iRECIST criteria, a common phenomenon observed in patients administered with immune checkpoint inhibitors with an initial enlargement of target tumor lesions as the result of elevated immune cell entry. In particular, one patient that had continued treatment albeit being assessed as immune unconfirmed progressive disease (iUPD), due to the absence of observable clinical deterioration during the fourth treatment cycle, was reevaluated as a confirmed iPR during the 12th treatment cycle due to shrinkage in tumor lesions, and thus confirming pseudoprogression. As suitable treatment planning is dependent on accurate pseudoprogression diagnosis, reporting similar results under both the RECIST 1.1 and iRECIST criteria is a good initial measure of result reliability and validity.

Socazolimab is well tolerated and exhibits a safety profile similar to other anti–PD-1/PD-L1 mAbs. We observed that no DLTs occurred in any of the treatment groups within 28 days after the first administration. For the 5 mg/kg group, the serum concentration of socazolimab reached maximum at 1.98 h. The mean half-life was 317.0 hours, which is considerably higher than that reported in the phase I, anti–PD-1 toripalimab study (212.0 hours, 10 mg/kg) which also had a full Chinese patient cohort (27). Anti-drug antibodies to socazolimab were

detected in 10.6% of patients, with only one patient remaining positive after the 12th treatment cycle. Complete PD-1 receptor occupancy was observed in all patients with the recommended 5 mg/kg dose. The MTD was not reached in the highest treatment group (15 mg/kg). Only 8 patients (8.4%) in the 5 mg/kg group reported grade 3 events or higher, in contrast to KEYNOTE-826 and GOG-3016 of which 81.8% and 45.0% of patients had reported grade 3–5 AEs, respectively (22, 23). All TRAEs were previously reported in other anti–PD-1/PD-L1 mAbs.

Overall, these pharmacokinetic, pharmacodynamic, and safety profiles have provided good evidence that the 5 mg/kg dose is an appropriate dose for further clinical studies. On the basis of these findings, a phase III, randomized clinical study is being approved at the date of submission, which evaluates the safety and efficacy of socazolimab versus chemotherapy as a second-line treatment for patients with recurrent or metastatic cervical cancer.

Authors' Disclosures

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Authors' Contributions

J. An: Validation, investigation, visualization. **J. Tang:** Validation, investigation, visualization. **B.X. LI:** Conceptualization, resources, funding acquisition. **H. Xiong:** Validation, investigation, visualization. **H. Qiu:** Validation, investigation, visualization. **L. Luo:** Validation, investigation, visualization. **L. Wang:** Validation, investigation, visualization. **D. Wang:** Validation, investigation, visualization. **Q. Zhou:** Validation, investigation, visualization. **Q. Xu:** Validation, investigation, visualization. **H. Song:** Validation, investigation, visualization. **Y. Zhang:** Validation, investigation, visualization. **H. Zhang:** Validation, investigation, visualization. **Y. Li:** Conceptualization, resources, supervision, methodology, writing–original draft, project administration, writing–review and editing. **X. Yu:** Conceptualization, resources, supervision, methodology, project administration. **J. Zhang:** Conceptualization, resources, supervision, methodology, project administration. **R. Ng:** Resources, formal analysis, writing–original draft, writing–review and editing. **W. Zhao:** Resources, writing–original draft, writing–review and editing. **M. Wong:** Conceptualization, resources, supervision, methodology, project administration. **X. Dai:** Conceptualization, resources, supervision, methodology, project administration. **G. Li:** Supervision, validation, investigation, visualization. **L. Wu:** Supervision, validation, investigation, visualization.

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Note

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