J Gynecol Oncol. 2025 May;36(3):e44
https://doi.org/10.3802/jgo.2025.36.e44
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Toripalimab combined with bevacizumab plus chemotherapy as first-line treatment for refractory recurrent or metastatic cervical cancer: a single-arm, open-label, phase II study (JS001-ISS-CO214)

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Received: Jul 19, 2024
Revised: Sep 25, 2024
Accepted: Oct 3, 2024
Published online: Oct 25, 2024

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ABSTRACT

Objective: To evaluate the efficacy and safety of adding toripalimab to bevacizumab and platinum-based chemotherapy as first-line treatment for refractory recurrent or metastatic (R/M) cervical cancer (CC).
Methods: Patients were administered toripalimab (240 mg) + bevacizumab (7.5 mg/kg) combined with platinum-based chemotherapy once every three weeks for six cycles, followed by the maintenance therapy involving toripalimab + bevacizumab once every 3 weeks for 12 months or when disease progression or intolerable toxicity occurred. The primary endpoint was the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1. The secondary endpoints were safety profiles, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
Results: Twenty-four patients were enrolled in this study and in the final analysis. The median follow-up duration was 18.6 (range, 3.3–28.5) months. The ORR was 83.3% (95% confidence interval [CI]=62.6–95.3) and the DCR was 95.8% (95% CI=78.9–99.9); 9 (37.5%) patients achieved complete response, 11 (45.8%) achieved partial response, and 3 (12.5%) had stable disease. The median PFS was 22.6 (95% CI=10.4–34.7) months and the median OS was not reached. The most common grade 3 treatment-related adverse events (AEs) were neutropenia (41.7%) and leukopenia (16.7%). The most common immune-related AEs (irAEs) were thyroid dysfunction (37.5%) and increased adrenocorticotropic hormone (37.5%) and serum cortisol levels (33.3%). No grade ≥3 irAEs were observed.
Conclusion: Toripalimab combined with bevacizumab and platinum-based chemotherapy show promising clinical efficacy and favorable safety profile, providing an alternative first-line treatment option for patients with R/M CC.

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Trial Registration
ClinicalTrials.gov Identifier: NCT04973904

Funding
The study was supported by the National Natural Science Foundation of China (grant number 82371757) and Junshi Biosciences.

Presentation
This research was presented at the Korean Society of Gynecologic Oncology 2024 Annual Meeting, April 26, 2024, in Busan, Korea. The preliminary results were presented at the Society of Gynecologic Oncology 2023 Annual Meeting on Women's Cancer, March 26, in Tampa, Florida (preprint link: https://ssrn.com/abstract=4760493).

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: P.P., X.Y.; Data curation: L.C., H.Y.; Formal analysis: H.Y., Y.J.; Funding acquisition: X.Y.; Investigation: L.C., L.S., Y.H., Y.Z., Y.J., C.N.; Methodology: P.P.; Project administration: L.S., X.Y.; Resources: L.S., Y.H., Y.J., C.D., C.N., Y.J., P.P.; Software: L.C., H.Y., Y.Z.; Supervision: X.Y.; Validation: L.S., P.P.;

Trial Registration: ClinicalTrials.gov Identifier: NCT04973904

Keywords: Cervical Cancer; Toripalimab; PD-1 Inhibitor; Bevacizumab; Chemotherapy

Synopsis
We evaluated efficacy and safety of toripalimab + bevacizumab + platinum-based chemotherapy as first-line therapy in Chinese patients with refractory recurrent or metastatic cervical cancer. This combination showed promising objective responses and long-term median progression-free survival. The safety profile was also manageable.

INTRODUCTION

Cervical cancer (CC) is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related deaths in females, with an estimated 661,000 new cases and 348,000 deaths worldwide in the 2022 updated data [1]. Patients with recurrent or metastatic (R/M) CC represent a poor prognostic group, with a 5-year survival rate of approximately 17% [2]. Treatment options for R/M CC were limited, and platinum-based chemotherapy was the standard treatment.

With the development of targeted therapy and immunotherapy, the efficacy of anti-angiogenic drugs and immune checkpoint inhibitors in patients with R/M CC was established. The GOG-240 trial provided evidence that the addition of bevacizumab to the first-line treatment improves the efficacy of chemotherapy extended the median overall survival (OS) to 17 months [3-5]. Subsequently, the KEYNOTE-826 trial demonstrated that the first-line regimen of programmed cell death protein 1 (PD-1) inhibitor (pembrolizumab) in combination with standard chemotherapy with or without bevacizumab further extended the median OS to 26 months [6,7]. However, the role of PD-1 inhibitor with bevacizumab was inferred only from subgroup analyses.

Toripalimab, a recombinant humanized IgG4K monoclonal antibody against PD-1, has exhibited clinical efficacy and manageable toxicity in combination with standard chemotherapy regimens as first-line treatment in patients with various advanced cancers [8-10]. It has been approved by the Food and Drug Administration in 2023 as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma in combination with gemcitabine–cisplatin based on the JUPITER-02 study [11]. Currently, no evidence is available that supports the efficacy of toripalimab for CC treatment.

Therefore, in the present study, we conducted a phase II trial to evaluate the efficacy and safety of toripalimab in combination with bevacizumab and platinum-based chemotherapy as first-line treatment for refractory R/M CC, thus aiming to provide a novel first-line treatment alternative for patients with R/M CC.

Visualization: Y.H., P.P.; Writing - original draft: L.C.; Writing - review & editing: L.C., X.Y.

MATERIALS AND METHODS

1. Patients

Eligible patients were 18 years of age or older, were diagnosed and histologically confirmed with squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous carcinoma of the cervix, had not received systemic therapy previously and were not amenable to curative treatment (surgery and/or radiotherapy) but platinum-based chemoradiotherapy was permitted previously, had a 2018 International Federation of Gynecology and Obstetrics (FIGO) stage IVB or persistence or progression of any FIGO stage or recurrence of any FIGO-stage after-response more than six months after treatment, had an Eastern Cooperative Oncology Group performance status score of 0 or 1 within 2 weeks before enrollment, had at least one measurable disease as assessed by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), exhibited adequate organ function, and had no history of autoimmune diseases.

Patients were excluded from the study if they had received radiotherapy within 2 weeks, had active central nervous system metastases, suffered from uncontrolled pleural effusion, pericardial effusion, and cirrhosis of any cause, underwent surgery, open biopsy, or major trauma within 28 days, had received an agent directed against PD-1, programmed death-ligand 1 (PD-L1)/2, cytotoxic T-lymphocyte associated protein 4, or any other agent used for immunotherapy and antiangiogenic therapy (including bevacizumab) previously, and were allergic to toripalimab, bevacizumab, paclitaxel, cisplatin, and other drug components. The full eligibility criteria are provided in the protocol of the appendix.

Informed consent was obtained from all participants before enrollment. The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital (Beijing, China; approval No. HS-2536).

2. Study design and treatment

This single-arm, open-label, phase II (JS001-ISS-CO214) trial was conducted at Peking Union Medical College Hospital and Cangzhou Central Hospital. All regimes were administered intravenously every three weeks on day 1 of each cycle, and doses were as follows: toripalimab, 240 mg; bevacizumab, 7.5 mg/kg; paclitaxel, 175 mg/m^2; and the investigator's choice of cisplatin, 50 mg/m^2 or carboplatin, (area under curve=5). After 6 cycles of treatment, chemotherapy was discontinued in patients who achieved complete response (CR), partial response (PR), and stable disease (SD). Then, the patients received maintenance therapy of toripalimab (240 mg) + bevacizumab (7.5 mg/kg) once every 3 weeks for 1 year or until disease progression (PD) or intolerable toxicity occurred. Patients with PD discontinued treatment and entered survival follow-up. This study was registered at ClinicalTrials.gov (NCT04973904).

3. Endpoints

The primary endpoint was the objective response rate (ORR), which was determined by the investigator using RECIST v1.1. The secondary endpoints included safety profiles, disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and OS. ORR was defined as the proportion of patients with CR or PR according to tumor volume reduction as per RECIST v1.1. DCR was defined as the proportion of patients who achieved CR, PR, or SD. The DoR was defined as the time from the first observation of CR or PR to the first documented PD or death. PFS was defined as the time from medication administration to the first documented PD or death. OS was defined as the time from enrollment to death

because of any cause. The complete list of endpoints and statistical analysis details is available in the protocol and statistical analysis plan.

4. Assessments

Tumors were assessed at baseline every 6 weeks (2 cycles) in the first 18 months and then every 12 weeks (4 cycles) with the help of computed tomography or magnetic resonance imaging. If these patients achieved CR, PR, or SD, they were reassessed within 3–4 weeks of the first evaluation for confirmation. Clinical response was assessed by the investigator according to RECIST v.1.1 at the end of each cycle, and then, it was decided whether treatment needed to be continued.

Safety and tolerability were assessed in all patients who received any dose of the study drug. Adverse events (AEs) were monitored throughout treatment and for 28 days thereafter and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events v.5.0 (NCI-CTCAE v5.0).

5. Statistical analysis

This trial was conducted using Simon's 2-stage minimax design [12,13]. The sample size was calculated as per the 48% ORR of chemotherapy + bevacizumab as first-line therapy for patients with R/M CC in the GOG-240 study [3,4]. The null hypothesis was an ORR of less than 48%, and the alternative hypothesis was an ORR of more than 76%. The one-sided α=0.025 and β=0.2 were considered, target accrual was a minimum of 13 patients in Simon stage I, and if responses were confirmed in more than 6 patients, 11 additional patients were recruited in Simon stage II, with totally 24 patients. During the clinical trial, no patients withdrew from the clinical trial except patients who failed to enroll during the screening period. IBM SPSS Statistics v27 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, USA) were used for data analyses. The ORR and 95% confidence intervals (CIs) were calculated using the Clopper–Pearson method. Kaplan–Meier plots were generated for PFS and OS. The log-rank test was used to compare patient survival between the SCC and adenocarcinoma groups.

The safety set included all intention-to-treatment (ITT) patients who had received at least 1 cycle of the treatment medications. Safety assessments mainly used descriptive statistics.

6. Role of the funding source

The funder provided the drugs and participated in data collection, analysis, and interpretation but did not participate in manuscript writing. The corresponding authors had full access to all data in this study and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

Between November 12, 2021 and December 23, 2022, 24 adult patients were enrolled, received treatment (ITT population), and were included in the final analysis. The median age was 55 (range, 33–75) years. Histopathological diagnosis showed 19 (79.2%) patients with SCC and 5 (20.8%) patients with adenocarcinoma. None of the patients had previously received systemic chemotherapy; however, systemic platinum-based therapy with concurrent radiation was permitted. Among these, 8 (33.3%) patients had undergone surgery combined

with chemoradiotherapy, radiotherapy, or chemotherapy, 9 (37.5%) patients had received chemoradiotherapy or radiotherapy, 3 (12.5%) patients had undergone surgery, and 3 (12.5%) patients had not received any treatment. Additionally, 10 (41.7%) patients showed distant metastasis, 6 (25%) patients showed local recurrence, and 8 (33.3%) patients showed both (**Table 1**).

As of the data cutoff of December 26, 2023, the median follow-up duration was 18.6 months (range, 3.3–28.5). Thirteen (54.2%) patients completed all treatment plans, and 2 (8.3%) patients terminated treatment early because of coronavirus disease 2019. Nine (37.5%) patients discontinued treatment for the following reasons: PD (n=6, 25.0%) and AEs (n=3, 12.5%). The median treatment duration was 11.1 (range, 0.8–12.2) months.

1. Antitumor activity

In the final assessment of the ITT population (n=24), ORR was 83.3% (95% CI=62.6–95.3) as assessed by RECIST v1.1 per investigator, and 9 (37.5%) patients achieved CR, and 11 (45.8%) patients achieved PR. Three (12.5%) patients had SD, and the DCR was 95.8% (95% CI, 78.9–99.9) (**Table 2**). Representative images of complete responses in supraclavicular lymph node metastasis and pelvic recurrence are shown in **Fig. 1**. The median time to respond in 20 patients who achieved CR and PR was 1.5 (range, 1.2–9) months. The median DoR was not reached (**Fig. 2A**).

Table 1. Baseline characteristics in the ITT population*

Characteristics	Patients (n=24)
Age (yr)	55 (33–75)
ECGO performance-status score†	
0	10 (41.7)
1	14 (58.3)
FIGO stage at initial diagnosis‡	
IA	1 (4.2)
IB	8 (33.3)
IIB	2 (8.3)
IIIB	2 (8.3)
IIIC	8 (33.3)
IVB	3 (12.5)
Histology	
Squamous cell carcinoma	19 (79.2)
Adenocarcinoma	5 (20.8)
Prior treatment§	
Surgery + chemotherapy/radiotherapy/chemoradiotherapy	10 (41.7)
Chemoradiotherapy or Radiotherapy	8 (33.3)
Surgery	3 (12.5)
None‖	3 (12.5)
Local recurrence only	6 (25.0)
Distant metastasis only	10 (41.7)
Local recurrence plus distant metastasis	8 (33.3)

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; ITT, intention-to-treatment.
*The ITT population included all the patients who underwent treatment. Percentages may not total 100 because of rounding.
†ECOG performance-status scores range from 0 to 5, with 0 indicating normal functional capacity and higher scores indicating greater disability.
‡Disease stage was determined with the use of the FIGO 2018.
§Patients with no previous systemic chemotherapy were eligible, but systemic platinum-based therapy treated with concurrent radiation was permitted.
‖Patients who were initially diagnosed with stage IVB with metastatic disease and without any previous treatment were enrolled in the trial.

https://doi.org/10.3802/jgo.2025.36.e44

Table 2. Best overall response assessed by investigator review per RECIST v1.1

Efficacy	ITT population (n=24)
Best overall response	
CR	9 (37.5)
PR	11 (45.8)
SD	3 (12.5)
PD	1 (4.2)
ORR	20 (83.3)
95% CI	62.6–95.3
DCR	23 (95.8)
95% CI	78.9–99.9
Time to response (mo)	1.5 (1.2–9.0)
Duration of response (mo)	NR

Values are presented as number (%) not otherwise specified.
CI, confidence interval; CR, complete response; DCR, disease control rate; ITT, intention-to-treatment; ORR, objective response rate; PD, disease progression; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

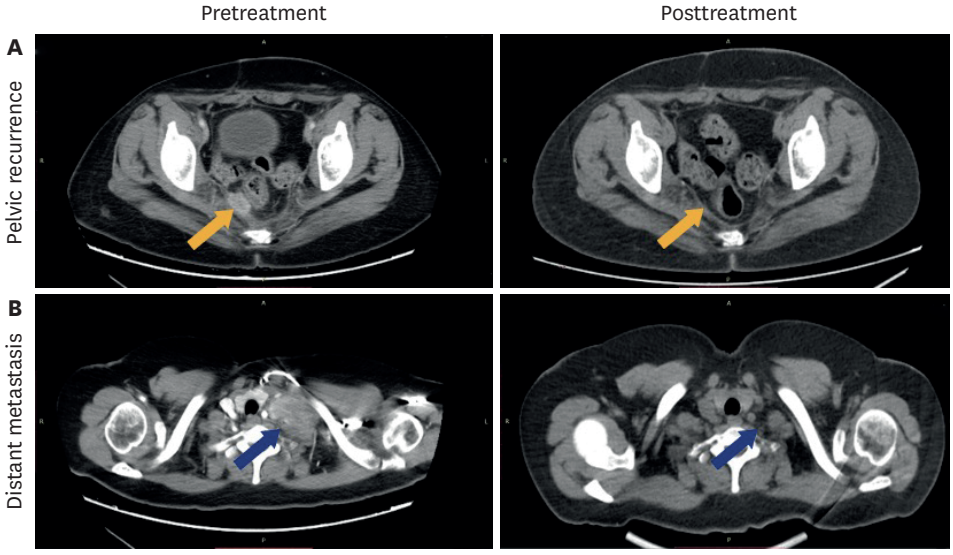

Fig. 1. The representative imaging of pelvic recurrent lesion and supraclavicular lymph node metastasis of pretreatment and posttreatment in 1 patient who evaluated with complete response. (A) The image of pelvic recurrent lesion before treatment (left), and disappearance after treatment (right). (B) The image of enlarged supraclavicular lymph node before treatment (left), and normal lymph node after treatment (right).

Regarding the data cutoff, 12 (50.0%) patients had PD or died. The median PFS was 22.6 (95% CI=10.4–34.7) months (**Fig. 2B**). OS events occurred in 5 (20.8%) patients. The median OS was not reached (95% CI=not reached) (**Fig. 2C**). Based on subgroup analysis, the median PFS was not considerably affected by pathology, with no significant difference between patients with SCC and adenocarcinoma. No significant difference was observed in median PFS (95% CI) between SCC and adenocarcinoma subgroups (22.6 [12.7–31.4] vs. 13.3 [7.0–19.5], log-rank test, p=0.591; **Fig. 2D**). Moreover, the ORR of 80% (95% CI=28.4–99.5) and the DCR of 100% (95% CI=47.8–100.0) was obtained in the adenocarcinoma group (**Table S1**).

2. Safety

Twenty-two (91.7%) patients experienced at least one treatment-related adverse event (TRAE), the most common being neutropenia (n=14, 58.3%), leukopenia (n=13, 54.2%), anemia (n=9, 37.5%), and liver dysfunction (n=7, 29.2%). Fourteen patients experienced grade 3 TRAEs, including 10 (41.7%) with neutropenia and 4 with leukopenia (16.7%). TRAEs

https://doi.org/10.3802/jgo.2025.36.e44

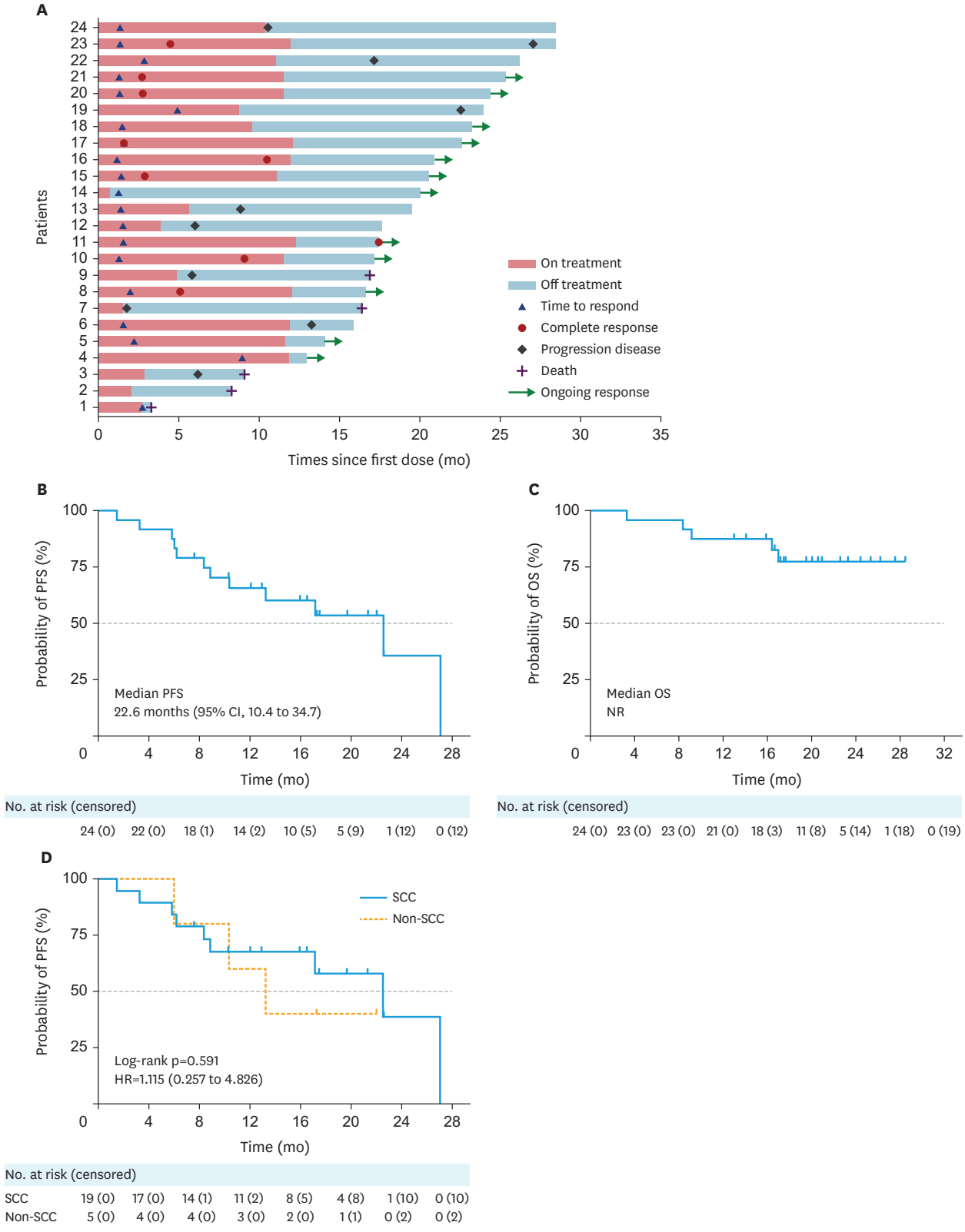

Fig. 2. Antitumor activity in the ITT population. (A) Swimmer plot for all patients in final analysis (n=24). The Kaplan-Meier curves of (B) PFS and (C) OS in the ITT population. (D) PFS in the subgroup of SCC and non-SCC patients, The p-values of comparing the Kaplan-Meier curves were computed using the log-rank test stratified by the pathology type.
ITT, intention-to-treatment; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma.

https://doi.org/10.3802/jgo.2025.36.e44

Table 3. Adverse events in the total treated population (n=24)

Event	Any grade	Grade ≥3
TRAEs		
Any event	22 (91.7)	14 (58.3)
Neutropenia	14 (58.3)	10 (41.7)
Leukopenia	13 (54.2)	4 (16.7)
Anemia	9 (37.5)	0 (0.0)
Liver dysfunction	7 (29.2)	0 (0.0)
Thrombocytopenia	3 (12.5)	0 (0.0)
Nausea	3 (12.5)	0 (0.0)
Rectovaginal fistula	2 (8.3)	1 (4.2)
Increased creatinine	1 (4.2)	0 (0.0)
Proteinuria	1 (4.2)	0 (0.0)
Neurotoxicity	1 (4.2)	0 (0.0)
Vomiting	1 (4.2)	0 (0.0)
Heart failure	1 (4.2)	1 (4.2)
Blood pressure increased	1 (4.2)	1 (4.2)
Sudden deafness	1 (4.2)	1 (4.2)
Numbness	1 (4.2)	0 (0.0)
Acute kidney injury	1 (4.2)	0 (0.0)
irAEs		
Any event	13 (54.2)	0 (0.0)
Thyroid dysfunction	9 (37.5)	0 (0.0)
Adrenocorticotropic hormone increased	9 (37.5)	0 (0.0)
Serum cortisol increased	8 (33.3)	0 (0.0)
Rash	2 (8.3)	0 (0.0)

Values are presented as number (%).
irAE, immune-related adverse event; TRAE, treatment-related adverse event.

that resulted in the discontinuation of treatment occurred in 3 (12.5%) patients, of whom 2 (8.3%) had a rectovaginal fistula and 1 (4.2%) experienced heart failure. TRAE-related death occurred in 1 (4.2%) patient, which was not related to toripalimab as per the investigator's opinion. The most common immune-related adverse events (irAEs) were thyroid dysfunction (37.5%), increased adrenocorticotropic hormone levels (37.5%), and increased serum cortisol levels (33.3%). No grade ≥3 irAEs were observed (**Table 3**).

DISCUSSION

This phase II trial of toripalimab combined with bevacizumab and platinum-based chemotherapy showed promising clinical efficacy and a favorable safety profile as first-line therapy for patients with refractory R/M CC. The primary endpoint ORR was 83.3%, which comparable to the BEATcc trial (84%) [14] and higher than the KENOTE-826 (69.6%) [6]. Nine (37.5%) patients achieved CR in this trial, which lead to slightly higher CR rate than the BEATcc trial (32%) [14]. Of note, the long-term response was observed with a median PFS of 22.57 months in this trial, which much longer than KENOTE-826 (10.4 months) and BEATcc trials (13.7 months) [6,14]. The median OS was not reached but follow-up continues, and final results are expected in 2025.

The safety profile of toripalimab adding bevacizumab and platinum-based chemotherapy was manageable and mostly occurred during the initial phase of administration. The safety profile was consistent with previous trials of toripalimab combined with chemotherapy in other types of cancer. Neutropenia, leukopenia and anemia were the most predominantly grade 1–2 TRAEs [10,11]. Besides, fistula is one of the most concerning TRAE in patients with cervical

https://doi.org/10.3802/jgo.2025.36.e44

cancer treated with bevacizumab [15,16]. In this trial, the incidence of grade ≥3 rectovaginal fistula was 4.2%, which comparable to the BEATcc (3%) [14] and GOG240 (6%) trials [4]. In addition, we provide some clarification on a reported case of death following heart failure. This patient had a sudden and unrelieved chest tightness 4 hours after completing the fifth treatment regimen, then transferred to the intensive care unit due to progressive dyspnea and blood pressure decline and died 2 weeks later. Nevertheless, due to the unknown cause of her death, it was classified as a TRAE-related death, despite the patient exhibiting no significant discomfort throughout all 5 sessions and demonstrating responsiveness to treatment.

Until recently, various PD-1/PD-L1 inhibitors (including pembrolizumab [6,17], atezolizumab [14], nivolumab [18,19], balstilimab [20], and cemiplimab [21]) showed efficacy in R/M CC patients in the way of monotherapy or combination therapy. The National Comprehensive Cancer Network guidelines has been recommended pembrolizumab plus chemotherapy with/without bevacizumab as first-line therapy for R/M CC patients with PD-L1-positive tumors (KENOTE-826) [7], and cemiplimab used after progression on platinum-based chemotherapy irrespective tumor PD-L1 status (EMPOWER-Cervical 1–GOG-3016–ENGOT-cx9) [21]. However, there are 2 aspects are still controversial: 1) Whether bevacizumab is mandatory in combination therapy; 2) Whether PD-L1 expression is used as a biomarker for the use of immune checkpoint inhibitors.

In this trial, the use of bevacizumab was mandatory, given that the benefit of bevacizumab for patients with R/M CC was definitive based on the GOG-240. In particular, the results of the BEAT trial confirmed the effect of immunotherapy combined with bevacizumab and platinum-containing therapy. However, the dosage of bevacizumab was 7.5 mg/kg, which was different from 15 mg/kg in other clinical trials. At present, there are 3 recommended dosages of bevacizumab in tumor therapy: 1) 15 mg/kg, every 3 weeks (q3w); 2) 7.5 mg/kg, q3w; and 3) 5 mg/kg q2w. At the same time, consider that the subjects in this study were all Asian women with lower body weight. Therefore, the dosage of bevacizumab was adjusted to 7.5 mg/kg q3w in this combination therapy. Nevertheless, this trial with lower dose bevacizumab achieved an ORR results comparable to the BEATcc trial. It is meaningful to further conduct a comparative analysis of varying dosages of bevacizumab within combination regimens for the treatment of cervical cancer.

This clinical trial enrolled only 24 patients with no biomarker selection, which could be considered a limitation for subgroup analysis. However, the BEATcc trial also enrolled an all-comer population with no biomarker selection, in which also demonstrated significantly efficacy of respond and clinically meaningful improvements of PFS and OS [14]. The KEYNOTE-826 trial showed that patients with PD-L1 combined positive score (CPS) ≥10 did not benefit more from pembrolizumab combination regimes than those with PD-L1 CPS ≥1 [6]. Meanwhile, several other PD-1 inhibitors (including nivolumab, balstilimab, and cemiplimab) have shown definite efficacy in PD-L1 negative patients, whether administered alone or in combination. Additionally, mechanistic studies have also shown that chemotherapeutic drugs induce immune cell death and increase antitumor immune responses to enhance the tumor-inhibitory effect of PD-1 inhibitors [22]. Furthermore, in previous clinical trial of toripalimab in combination with chemotherapy or the target drug, PD-L1 overexpression is not correlated to a remarkable survival benefit of toripalimab [23,24]. Herein, the value of enrolling a PD-L1 biomarker-selected population remain uncertain at least in context of combination chemotherapy regimens.

https://doi.org/10.3802/jgo.2025.36.e44

Although lacking a randomized control, limiting sample size, and single ethnic group in the present trial, the comparable respond rate and safety profile were observed. The subgroup analysis of squamous cell carcinoma and adenocarcinoma demonstrated comparable benefits from this treatment regimen. Notably, this trial demonstrated an extended median PFS, which require further validation through additional phase III trial. Long-term follow-ups will be continued to investigate the OS data.

In conclusion, the efficacy of toripalimab plus bevacizumab and platinum-based chemotherapy as first-line therapy for patients with R/M CC was promising in SCC and adenocarcinoma. Given the lack of effective salvage therapies, coupled with a high recurrence rate and low survival rate once first-line treatment fails, the present findings have significant clinical application value in patients with R/M CC. Furthermore, the findings of the current study emphasize the importance of administering a combination of standard chemotherapy, an appropriate dose of bevacizumab, and immune checkpoint inhibitors as early as possible once the initial occurrence of recurrence or metastasis.

ACKNOWLEDGEMENTS

We thank all the patients, their families, and the personnel of the institution for their participation in this trial.

SUPPLEMENTARY MATERIAL

Table S1

The best overall response in the subgroup based on pathology

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