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ORIGINAL ARTICLE

Long-term survival outcomes and immune checkpoint inhibitor retreatment in patients with advanced cervical cancer treated with camrelizumab plus apatinib in the phase II CLAP study

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Abstract

Background: Camrelizumab plus apatinib have demonstrated robust anti-tumor activity and safety in patients with advanced cervical cancer (CLAP study; NCT03816553). We herein present the updated long-term results of the CLAP study and explore potential biomarkers for survival. The outcomes of patients who underwent immune checkpoint inhibitor (ICI) retreatment were also reported.

List of abbreviations: AEs, adverse events; BOR, best overall response; CI, confidence interval; CNV, copy-number variation; CPS, combined positive score; CR, complete response; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; GOG, Gynecologic Oncology Group; HR, hazard ratio; ICIs, immune checkpoint inhibitors; ITT, intention-to-treat; mut/Mb, mutations per megabase; NCCN, National Comprehensive Cancer Network; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; *PIK3CA*, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden; TRAE, treatment-related adverse events; VEGFR2, vascular endothelial growth factor receptor 2; vs., versus..

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Methods: In this phase II trial, eligible patients received camrelizumab 200 mg intravenously every two weeks and apatinib 250 mg orally once daily in 4-week cycles for up to two years. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Results: Between January 21 and August 1, 2019, a total of 45 patients were enrolled. Data were analyzed as of July 31, 2023, representing > 48 months since treatment initiation for all patients. Nine (20.0%) patients completed the 2-year study. The median duration of response (DOR) was 16.6 months, and 45.0% of patients achieved a DOR of ≥ 24 months. The 12-month progression-free survival (PFS) rate was 40.7% (95% confidence interval [CI], 25.2-55.6), with an 18-month PFS rate of 37.8% (95% CI, 22.7-52.8). The median overall survival (OS) was 20.3 months (95% CI, 9.3-36.9), and the 24-month OS rate was 47.8% (95% CI, 31.7-62.3). Age > 50 years, programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 (versus [vs.] < 1), CPS ≥ 10 (vs. < 1), high tumor mutational burden, and *PIK3CA* mutations were associated with improved PFS (hazard ratio [HR] < 1) and longer OS (HR < 1). Eight patients who initially responded in the CLAP trial but later experienced disease progression were retreated with ICIs. Among them, 2 (25.0%) achieved a partial response, while 5 (62.5%) had stable disease. Notably, four patients who received retreatment with ICIs survived for more than 45 months. No new safety signals were identified in the present study.

Conclusion: Long-term survival follow-up data demonstrated that camrelizumab plus apatinib has robust, sustained, and durable efficacy in patients with advanced cervical cancer who progress after first-line platinum-based chemotherapy. No new safety signals were noted with long-term treatment.

KEYWORDS
Cemrelizumab, apatinib, programmed cell death-1 (PD-1), programmed death-ligand 1 (PD-L1), tumor mutational burden (TMB), *PIK3CA*, advanced cervical cancer

1 | BACKGROUND

Cervical cancer is the fourth leading cause of cancer-related deaths in women worldwide, with an estimated 604,000 new cases and 342,000 deaths reported in 2020 [1]. In the United States, projections for 2023 estimate 13,963 new cases and 4,310 deaths [2]. China has been reported to have an estimated 111,820 new cases and 61,579 deaths related to cervical cancer in 2022 [3]. Advances in therapy have improved the outcomes of patients with cervical cancer over the years. The first-line treatment for patients with metastatic, recurrent, or persistent cervical cancer includes a platinum compound (cisplatin or carboplatin) plus paclitaxel, with or without bevacizumab. In the GOG 240 trial, bevacizumab in addition to chemotherapy improved the median overall survival (OS) by 3.7 months [4]. In the more recent KEYNOTE-826 trial, the programmed cell death-1 (PD-1) inhibitor pembrolizumab significantly prolonged progression-free survival (PFS) and OS compared with the placebo among patients with programmed death-ligand 1 (PD-L1)-positive tumors who received chemotherapy with or without bevacizumab as a first-line treatment. In the pembrolizumab group of that trial, the median PFS was 10.4 months, and the OS at 24 months was 53.0%, compared to 8.2 months (hazard ratio [HR], 0.62; $P < 0.001$) and 41.7% (HR, 0.64; $P < 0.001$) in the placebo group [5].

Nevertheless, many patients experienced tumor progression following first-line therapy. Several PD-1/PD-L1 inhibitors have been evaluated as second-line or later treatments for patients with advanced cervical cancer [6–10]. In the KEYNOTE-158 trial, pembrolizumab monotherapy demonstrated a median progression-free survival (PFS) of 2.1 months and a median OS of 11 months in patients with PD-L1-positive tumors [7]. Additionally, in a phase III trial,

patients with advanced cervical cancer who were treated with the PD-1 inhibitor cemiplimab achieved a longer median OS compared to those treated with chemotherapy chosen by the investigator (median OS, 12.0 months vs. 8.5 months; HR, 0.69; $P < 0.001$) [10].

Furthermore, PD-1/PD-L1 inhibitor combination therapy exhibits enhanced antitumor efficacy in certain types of tumors. In our previous CLAP study (NCT03816553), combination treatment with the PD-1 inhibitor camrelizumab plus the vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor apatinib achieved an objective response rate (ORR) of 55.6% and a median PFS of 8.8 months in patients with advanced cervical cancer who progressed after first-line platinum-based chemotherapy [11]. Similar outcomes were reported in a phase II study by Xu *et al.* [12], where 42 patients with PD-L1-positive advanced cervical cancer treated with the PD-1 inhibitor sintilimab and multikinase inhibitor anlotinib achieved an ORR of 54.8% and a median PFS of 9.4 months. In addition, we conducted an analysis of genomic profiles based on efficacy data from the CLAP study to identify potential predictive biomarkers for treatment response [13]. It' is worth noting that the OS data were immature in our previous reports; therefore, we present the updated results of the CLAP study, reporting long-term survival outcomes and exploring potential biomarkers for survival. Furthermore, the outcomes of patients who underwent immune checkpoint inhibitor (ICI) retreatment are also reported.

2 | METHODS

2.1 | Patients

The CLAP trial (NCT03816553) is a multicenter, single-arm, phase II study on patients with metastatic, recurrent, or persistent cervical cancer. The eligibility criteria have been previously reported [11]. Briefly, eligible patients aged 18-70 years with confirmed metastatic, recurrent, or persistent cervical cancer who had progressed on at least one line of platinum-based systemic therapy; had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); and had no history of treatment with anti-PD-1/PD-L1, or anti-CTLA-4 antibodies were included.

The trial protocol was approved by the central and local institutional review boards of all participating centers and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent prior to enrollment.

2.2 | Treatment and assessments

Patients received camrelizumab 200 mg intravenously every two weeks and apatinib 250 mg orally once daily in four-week cycles for up to two years. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. For patients who tolerated treatment well and had potential to benefit from treatment continuation, a one-year treatment extension was provided at the discretion of the investigators and based on the patient's desire. Tumor response was assessed by investigators every eight weeks for the first 40 weeks and every 12 weeks thereafter according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

2.3 | Outcomes

The primary endpoint was the ORR according to RECIST 1.1 assessed by investigators. The secondary endpoints were PFS, OS, duration of response (DOR), disease control rate (DCR), and safety and tolerability. The exploratory endpoints reported in this analysis were antitumor activity according to PD-L1 status, tumor mutational burden (TMB), and *PIK3CA* mutation status.

2.4 | PD-L1 expression

Tumor PD-L1 expression was detected using the 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA, USA) and measured by the combined positive score (CPS), defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

2.5 | Biomarker analysis

As previously reported [13], we conducted an analysis of genomic profiles to identify potential predictive biomarkers of treatment response. Briefly, formalin-fixed paraffin-embedded (FFPE) tumor samples were collected, and genomic profiling was performed by targeted next-generation sequencing of 425 cancer-related genes. All non-synonymous mutations, including missense, nonsense, indel, splicing, copy-number variation (CNV) and fusion mutations, were analyzed. The TMB was assessed for its ability to predict treatment efficacy. In that report, *PIK3CA* was the most commonly altered gene and was associated with treatment efficacy. Furthermore, we found that the cutoff value of 5 mutations per megabase

(mut/Mb) of TMB could be used to effectively separate patients with different treatment responses. Therefore, the association between *PIK3CA* mutation status and updated survival outcomes was investigated in the present study, and a cutoff value of 5 mut/Mb for TMB was used to classify patients into the TMB-high and TMB-low groups.

2.6 | Statistical analysis

Efficacy was analyzed in the intention-to-treat (ITT) population, and safety was analyzed in all patients who received at least one dose of the study treatment. The previous analysis was performed on the data cutoff date of April 30, 2020. The current analysis had an updated cutoff date of July 31, 2023. The ORR and 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. Fisher's exact test was used to compare proportions between subgroups. The Kaplan-Meier method was used to estimate DOR, PFS, and OS. Kaplan-Meier curves of PFS and OS were generated based on different biomarker statuses. The Cox proportional hazards model was used to analyze survival data among subgroups. A two-sided $P < 0.05$ was considered to indicate statistical significance unless stated otherwise. All statistical tests were performed using SAS software version 9.4.

3 | RESULTS

3.1 | Patient characteristics

In the CLAP study, 45 patients were enrolled between January 21 and August 1, 2019 [11]. The data were analyzed as of July 31, 2023, representing more than 48 months since treatment initiation for all patients. The median duration of treatment exposure was 6 (range, 0.9-37.4) months. Nine (20.0%) patients completed the 2-year study treatment period, and 36 (80.0%) patients discontinued treatment within two years because of disease progression ($n = 24$, 53.3%), adverse events (AEs) ($n = 4$, 8.9%), patient refusal ($n = 5$, 11.1%), and withdrawal of consent ($n = 3$, 6.7%). Patient characteristics for the entire population and of the patients who completed the two-year treatment are summarized in Table 1.

Per protocol, patients were allowed a one-year treatment extension. Of the 9 patients who completed the two-year treatment, 8 patients opted to continue treatment. Among these 8 patients, 5 (5/8, 62.5%) completed the one-year treatment extension, and 3 (3/8, 37.5%) discontinued because of disease progression (Supplementary Figure S1).

3.2 | Response to treatment

The previous analysis was conducted using data up to April 30, 2020 [11]. For the current analysis, we updated the cutoff date to July 31, 2023. With extended follow-up periods in this study, 4.4% ($n = 2$) of the ITT population achieved a best overall response (BOR) of complete response (CR), and 51.1% ($n = 23$) achieved partial response (PR), which is consistent with the previously reported ORR [11] (Table 2). The best response and treatment duration are shown in a three-dimensional waterfall plot (Supplementary Figure S2). Most tumor reductions occurred soon after treatment initiation, with 72% (18/25) of responses documented at the initial 8-week assessment. The median DOR was 16.6 months (95% CI, 5.6-33.7; Supplementary Figure S3A), and 63.1% (95% CI, 40.9-78.8) of patients had a DOR of ≥ 12 months, as determined by a Kaplan–Meier estimate, and 45.0% (95% CI, 24.6-63.6) of patients achieved a DOR of ≥ 24 months. At the data cutoff date, six of the 25 responses were ongoing, with the longest response being 40.8 months. The treatment duration is summarized in a swimmer plot (Figure 1). The response rates according to PD-L1 CPS status, TMB, and *PIK3CA* mutation status are shown in Table 2.

3.3 | PFS and OS in ITT population and subgroups

With extended follow-up, 30 patients in the ITT population died or experienced disease progression. The median PFS was 8.9 months (95% CI, 5.6-18.1). The 12-month PFS rate was 40.7% (95% CI, 25.2-55.6), and the 18-month PFS rate was 37.8% (95% CI, 22.7-52.8; Supplementary Figure S3B). The median OS was 20.3 months (95% CI, 9.3-36.9). The 12-month OS rate was 56.2% (95% CI, 39.8-69.7), and the 24-month OS rate was 47.8% (95% CI, 31.7-62.3; Supplementary Figure S3C).

In the previous study [11], archival tumor tissue samples were collected from 40 patients. Among these 40 patients, 10 (25.0%) had a PD-L1 CPS < 1, 30 (75.0%) had a PD-L1 CPS ≥ 1, and 21 (52.5%) had a PD-L1 CPS ≥ 10. The median PFS was 11.9 months (95% CI, 5.8-31.0) and 13.5 months (95% CI, 5.8-31.0) among patients with a CPS ≥1 and patients with a CPS ≥ 10, respectively, compared to 5.3 months (95% CI, 1.8-31.7) among those with a CPS < 1 (Figure 2A-B). The median OS was 26.3 months (95% CI, 11.7– not estimable [NE]) and 21.1 months (95% CI, 8.9–NE) among patients with a CPS ≥ 1 and ≥ 10, respectively, as compared to 10.3 months (95% CI, 2.8–NE) in patients with a CPS < 1 (Figure 3A-B). The 18-month PFS and 24-month OS rates of patients with a CPS ≥ 1, ≥ 10 and < 1 are shown in Table 2.

TABLE 1 Patient baseline characteristics.

Characteristics	All patients ($n = 45$)	Patients who completed the two-year treatment ($n = 9$)
Median age, years (range)	51 (33-67)	55 (39-62)
FIGO stage at initial diagnosis[a], *n* (%)		
IB1	10 (22.2)	0 (0)
IB2	3 (6.7)	0 (0)
IIA1	7 (15.6)	2 (22.2)
IIA2	7 (15.6)	1 (11.1)
IIB	7 (15.6)	1 (11.1)
IIIB	7 (15.6)	3 (33.3)
IVB	4 (8.9)	2 (22.2)
Median time from initial cancer diagnosis to study enrollment, months (range)	21.5 (3.7-92.1)	15.6 (6.6-66.9)
ECOG performance status, *n* (%)		
0	10 (22.2)	0 (0)
1	35 (77.8)	9 (100.0)
Histology, *n* (%)		
Squamous cell carcinoma	30 (66.7)	9 (100.0)
Adenocarcinoma	15 (33.3)	0 (0)
Location of metastases[b], *n* (%)		
Lung	20 (44.4)	4 (44.4)
Liver	9 (20.0)	0 (0)
Pelvis	20 (44.4)	3 (33.3)
Lymph node[b]		
Distant lymph nodes	24 (53.3)	7 (77.8)
Para-aortic lymph nodes	12 (26.7)	1 (11.1)
Pelvic lymph nodes	14 (31.1)	2 (22.2)
Bone	4 (8.9)	1 (11.1)
Pleura	4 (8.9)	2 (22.2)
Bladder	2 (4.4)	1 (11.1)
Spleen	2 (4.4)	1 (11.1)
Other	5 (11.1)	0 (0)
Target lesion size, mm		
Median (range)	41 (15-131)	41 (29-95)
Previous radiotherapy, *n* (%)	40 (88.9)	9 (100.0)
Adjuvant radiotherapy	25 (55.6)	2 (22.2)
Curative radiotherapy	10 (22.2)	4 (44.4)
Palliative radiotherapy	5 (11.1)	3 (33.3)
Number of previous systemic therapies, *n* (%)		
1	19 (42.2)	6 (66.7)
2	19 (42.2)	1 (11.1)
≥ 3	7 (15.6)	2 (22.2)
Previous platinum, *n* (%)	42 (93.3)	9 (100.0)
Previous paclitaxel, *n* (%)	42 (93.3)	9 (100.0)
Previous bevacizumab, *n* (%)	10 (22.2)	1 (11.1)

(Continues)

TABLE 1 (Continued)

Characteristics	All patients ($n = 45$)	Patients who completed the two-year treatment ($n = 9$)
PD-L1 CPS, *n* (%)		
< 1	10 (22.2)	2 (22.2)
1 to < 10	9 (20.0)	1 (11.1)
≥ 10	21 (46.7)	6 (66.7)
Unknown	5 (11.1)	0 (0)
TMB, *n* (%)		
< 5 mut/Mb	20 (44.4)	3 (33.3)
≥ 5 mut/Mb	19 (42.2)	5 (55.6)
Unknown	6 (13.3)	1 (11.1)
MSI, *n* (%)		
MSI-H	1 (2.2)	0 (0)
MSS	24 (53.3)	5 (55.6)
Unknown	20 (44.4)	4 (44.4)
PIK3CA, *n* (%)		
Mutation	14 (31.1)	5 (55.6)
Wildtype	18 (40.0)	2 (22.2)
Unknown	13 (28.9)	2 (22.2)

Some of these baseline data have been previously reported [11].

[a]Staging was according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging for carcinoma of the cervix.

[b]Some patients had more than 1 metastasis and several locations lymph node metastasis.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; mut/Mb, mutations per megabase; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; CPS, combined positive score.

Nineteen and 20 patients were in the TMB-high (TMB ≥ 5 mut/Mb) and TMB-low (TMB < 5 mut/Mb) groups, respectively. The median PFS was 18.5 months (95% CI, 7.4–NE) and 5.8 months (95% CI, 3.6-9.4) in the TMB-high and TMB-low groups, respectively (Figure 2C). The median OS was not reached (95% CI, 11.9–NE) in the TMB-high group, whereas the median OS was 9.4 months (95% CI, 8.1-36.9) in the TMB-low group (Figure 3C). The 18-month PFS and 24-month OS rates of the TMB-high and TMB-low groups are shown in Table 2.

PIK3CA mutations were detected in 14 patients. The median PFS was 18.5 months (95% CI, 7.6–NE) in patients with *PIK3CA* mutations, as opposed to 9.4 months (95% CI, 4.1-19.5) in patients with *PIK3CA* wildtype (Figure 2D). The median OS was not reached (95% CI, 15.9–NE) in *PIK3CA* mutation, whereas the median OS was 11.9 months (95% CI, 8.7–NE) in patients with *PIK3CA* wildtype (Figure 3D). The 18-month PFS and 24-month OS rates for patients with *PIK3CA* mutations and wildtype are shown in Table 2. Additionally, all the patients (100%) with *PIK3CA* mutations were PD-L1 positive, compared with 66.7% of the patients with *PIK3CA* wildtype had PD-L1 expression ($P = 0.028$, Supplementary Table S1).

Associations of baseline patient characteristics and tumor features with PFS and OS were assessed (Figure 4). Age > 50 years (hazard ratio [HR] = 0.60 and 0.57, respectively), squamous cell carcinoma (HR = 0.32 and 0.67, respectively), response to treatment (HR = 0.12 and 0.16, respectively), CPS ≥ 1 (HR = 0.55 and 0.62, respectively), CPS ≥ 10 (HR = 0.55 and 0.74, respectively), TMB-high (HR = 0.36 and 0.41, respectively), and *PIK3CA* mutation (HR = 0.39 and 0.46, respectively) were associated with improved PFS and longer OS. The multivariate Cox regression analyses for PFS and OS among the subgroups are provided in Supplementary Table S2.

3.4 | Safety

The treatment-related adverse events (TRAEs) in this study are summarized in Supplementary Table S3. TRAEs of any grade occurred in 45 patients, and 32 (71.1%) patients experienced grade 3-4 TRAEs, which was consistent with previously reported results [11]. With extended treatment duration, TRAEs leading to treatment discontinuation included uveitis ($n = 1$, grade 2); abdominal pain ($n = 1$,

TABLE 2 Summary of efficacy

Efficacy	Intention-to-treat population ($n = 45$)	PD-L1 CPS				TMB		*PIK3CA*	
		< 1 ($n = 10$)	≥ 1 ($n = 30$)	1–9 ($n = 9$)	≥ 10 ($n = 21$)	< 5 mut/Mb ($n = 20$)	≥ 5 mut/Mb ($n = 19$)	Mutation ($n = 14$)	Wildtype ($n = 18$)
CR	2 (4.4)	0 (0)	2 (9.5)	0 (0)	2 (9.5)	1 (5.0)	1 (5.3)	1 (7.1)	1 (5.6)
PR	23 (51.1)	5 (50)	18 (60.0)	6 (66.7)	12 (57.1)	6 (30.0)	15 (78.9)	12 (85.7)	7 (38.9)
SD	12 (26.7)	1 (10)	9 (30.0)	3 (33.3)	6 (28.6)	8 (40.0)	3 (15.8)	1 (7.1)	8 (44.4)
PD	4 (8.9)	4 (40)	0 (0)	0 (0)	0 (0)	4 (20.0)	0 (0)	0 (0)	2 (11.1)
No assessment	4 (8.9)	0 (0)	1 (3.3)	0 (0)	1 (4.8)	1 (5.0)	0 (0)	0 (0)	0 (0)
ORR (95% CI), %	55.6 (40.0-70.4)	50.0 (18.7-81.3)	66.7 (49.8-83.5)	66.7 (29.9-92.5)	66.7 (43.0-85.4)	35.0 (12.1-57.9)	84.2 (60.4-96.6)	92.9 (66.1-99.8)	44.4 (21.5-69.2)
DCR (95% CI), %	82.2 (70.6-93.8)	60.0 (26.2-87.8)	96.7 (90.2-100.0)	100.0 (66.4-100.0)	95.2 (76.2-99.9)	75.0 (50.9-91.3)	100.0 (82.4-100.0)	100.0 (76.8-100.0)	88.9 (65.3-98.6)
DOR, months									
Median (range)	16.6 (5.6-33.7)	29.9 (2.2–NE)	16.6 (5.6–NE)	11.1 (1.9–NE)	17.6 (6.6–NE)	29.9 (3.8–NE)	16.6 (5.6–NE)	16.6 (5.6–NE)	17.6 (2.2–NE)
PFS									
Median (95% CI), months	8.9 (5.6-18.1)	5.3 (1.8-31.7)	11.9 (5.8-31.0)	7.6 (3.7–NE)	13.5 (5.8-31.0)	5.8 (3.6-9.4)	18.5 (7.4–NE)	18.5 (7.6–NE)	9.4 (4.1-19.5)
12-month PFS rate (95% CI), %	40.7 (25.2-55.6)	30.0 (7.1-57.8)	48.4 (28.9-65.4)	43.8 (10.1-74.2)	50.0 (27.1-69.2)	26.1 (8.6-47.9)	58.8 (32.5-77.8)	61.5 (30.8-81.8)	36.1 (13.9-59.2)
18-month PFS rate (95% CI), %	37.8 (22.7-52.8)	30.0 (7.1-57.8)	44.3 (25.4-61.7)	43.8 (10.1-74.2)	44.4 (22.5-64.4)	26.1 (8.6-47.9)	52.3 (26.8-72.7)	53.9 (24.8-76.0)	36.1 (13.9-59.2)
OS									
Median (95% CI), months	20.3 (9.3-36.9)	10.3 (2.8–NE)	26.3 (11.7–NE)	36.9 (12.0–NE)	21.1 (8.9–NE)	9.4 (8.1-36.9)	Not reached (11.9–NE)	Not reached (15.9–NE)	11.9 (8.7–NE)
12-month OS rate (95% CI), %	56.2 (39.8-69.7)	40.0 (12.3-67.0)	65.5 (45.4-79.7)	88.9 (43.3-98.4)	55.0 (31.3-73.5)	39.0 (17.6-60.1)	73.7 (47.9-88.1)	84.6 (51.2-95.9)	44.4 (21.6-65.1)
24-month OS rate (95% CI), %	47.8 (31.7-62.3)	40.0 (12.3-67.0)	54.1 (34.3-70.3)	61.0 (20.2-85.8)	50.0 (27.1-69.2)	39.0 (17.6-60.1)	61.4 (35.4-79.5)	69.2 (37.3-87.2)	44.4 (21.6-65.1)

The data are presented as *n* (%), unless otherwise specified. Some of the data have been reported previously [11]. Responses were assessed in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1. Only confirmed responses were included.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; DOR, duration of response; CI, confidence interval; PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival; CPS, combined positive score; TMB, tumor mutational burden; NE, not estimable.

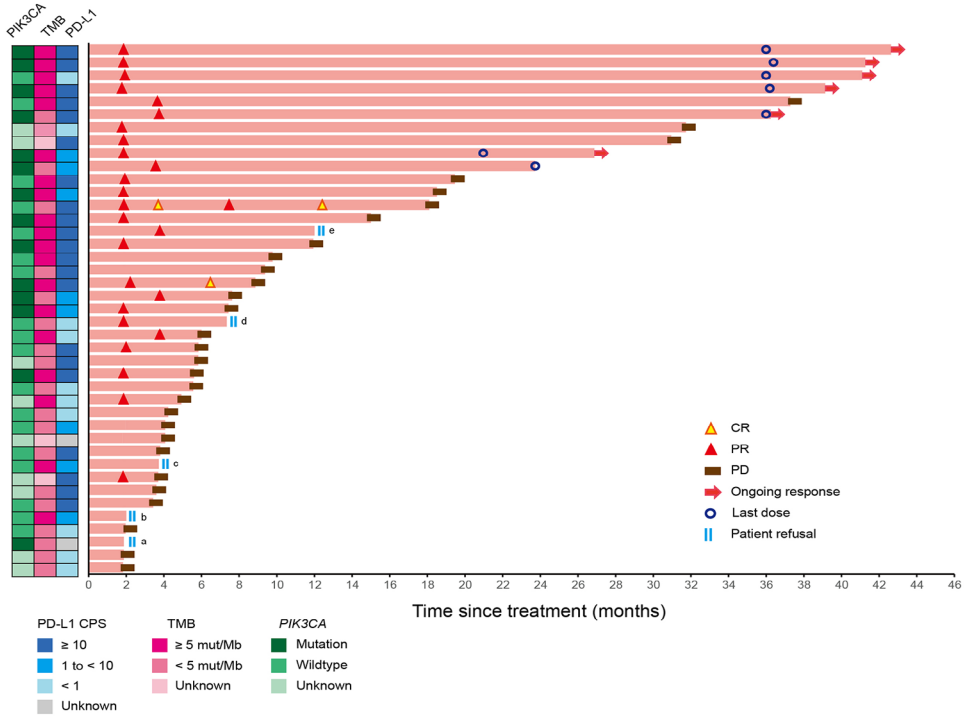

FIGURE 1 Swimmer plot of response duration. Each bar represents an individual patient, and the length of each bar represents the duration of response for each patient. (a) Patient declined further treatment, citing inconvenience due to frequent travel between Sichuan and Guangdong provinces. (b) Patient withdrew from the study to seek alternative treatment options, as per the family's wishes. (c) Patient opted for traditional Chinese medicine exclusively, leading to withdrawal from the study after four treatment cycles. (d) Patient refused treatment in mid-January 2020 due to the travel restrictions imposed following a Covid-19 outbreak. (e) Patient declined treatment due to the inconvenience caused by edema in both lower limbs. Abbreviations: CR, complete response; PR, partial response; PD, progressive disease; PD-L1, programmed death-ligand 1; CPS, combined positive score; TMB, tumor mutational burden; mut/Mb, mutations per megabase.

grade 3); thrombocytopenia ($n = 1$, grade 4); and fatigue, stomatitis, arthralgia, and myalgia (same patient; grade 3). None of the patients experienced treatment-related death.

3.5 | Subsequent therapies following study discontinuation because of disease progression

Ten patients received subsequent therapies after disease progression (Supplementary Table S4), including ICIs ($n = 8$), targeted therapy ($n = 5$), chemotherapy ($n = 4$), radiotherapy ($n = 4$), and surgery ($n = 1$). Out of these 10 patients, 9 initially responded to the initial study treatment, with only one displaying primary resistance to our PD-1 inhibitor combination therapy. In the follow-up treatment after discontinuation from the CLAP study due to disease progression, three (30.0%) of the 10 patients achieved a response, including 2 CR and 1 PR. Additionally, four (40%) out of the 10 patients had a subsequent treatment duration exceeding 12 months. As of the data cutoff, four patients survived beyond 45 months. The details of the subsequent treatments are shown in Figure 5 and Supplementary Table S5.

Among these 10 patients, eight underwent subsequent treatment with the same or different ICIs (Table 3). All 8 patients initially responded to treatment in the CLAP trial, with one achieving CR and seven achieving PR. However, they later experienced disease progression. Regarding their response to subsequent ICIs therapy, 2 (25.0%) out of the 8 patients achieved a BOR of PR, while 5 (62.5%) exhibited stable disease (SD).

Four patients were primarily resistant to camrelizumab, with only one receiving subsequent chemotherapy. All patients died soon after disease progression.

4 | DISCUSSION

In this study, we provide long-term survival data on combination therapy with the PD-1 inhibitor camrelizumab and the VEGFR2 inhibitor apatinib in patients with advanced cervical cancer. In the analysis, the ORR was 56%, which was the same as that in previous reports of this trial. Most tumor reductions occurred soon after treatment initiation,

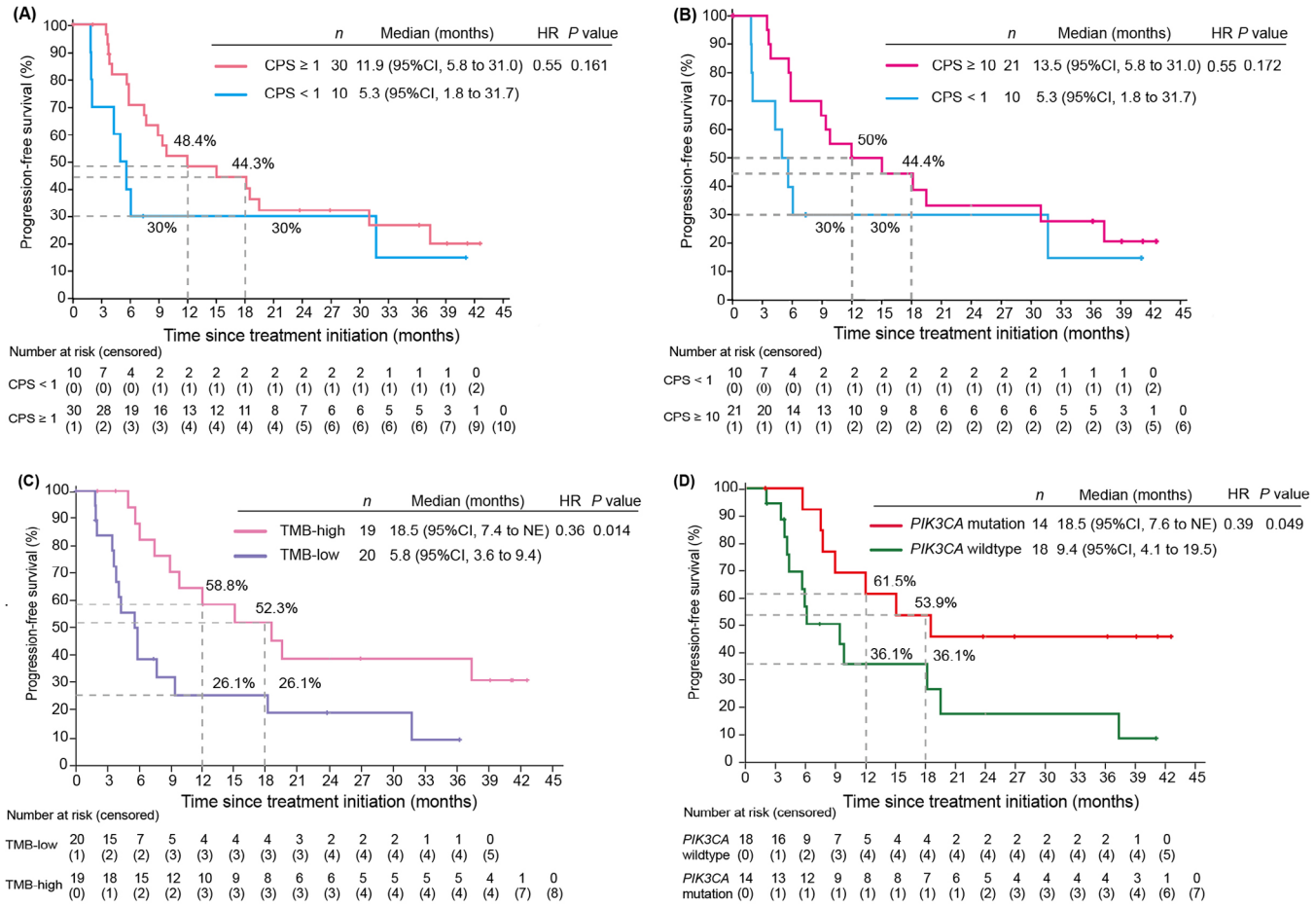

FIGURE 2 Kaplan-Meier curves of progression-free survival. Progression-free survival according to the Kaplan-Meier method in patients with (A) a PD-L1 CPS ≥ 1 and a CPS < 1, (B) a CPS ≥ 10 and a CPS < 1, (C) TMB-high and TMB-low, and (D) *PIK3CA* mutation and wildtype. Abbreviations: PD-L1, programmed death-ligand 1; CPS, combined positive score; TMB, tumor mutational burden; mut/Mb, mutations per megabase; HR, hazard ratio; CI, confidence interval; NE, not estimable.

with 72% of the responses documented within the initial 8-week assessment. This may be attributed to the rapid kinetics of concurrent PD-1 and angiogenesis blockade.

Importantly, most of the responses were durable: the median DOR was 16.6 months, and 45% of patients maintained a DOR for at least 2 years. The median OS in our study was 20.3 months, with 12- and 24-month OS rates of 56.2% and 47.8%, respectively. The OS curve exhibited a prolonged rightward plateau, with 10 patients surviving beyond 45 months, still under follow-up at the data cutoff date (Supplementary Figure S3C). These findings highlight the synergistic effect of anti-PD-1 and anti-angiogenic combination therapy, indicating sustained benefits. In a study by Xu *et al.* [14], sintilimab plus anlotinib, another anti-PD-1 antibody combined with anti-angiogenic therapy, demonstrated comparable results in patients with PD-L1 positive tumors, with 12- and 24-month OS rates of 71.8% and 49.1%, respectively. Numerous clinical trials have demonstrated the enhanced efficacy of combining anti-angiogenic treatments with immunotherapy across multiple cancer types, including non-small cell lung cancer (NSCLC) [15], hepatocellular carcinoma [16], and renal cell carcinoma [17]. A recent randomized, open-label, phase II trial by Wu *et al.* [18] revealed that the combination of a PD-1 inhibitor with anti-angiogenic treatment was associated with better efficacy than the PD-1 inhibitor alone in advanced cervical cancer. Camrelizumab plus famitinib, a multitargeted tyrosine kinase inhibitor (TKI) against VEGFR2/3, showed improved antitumor activity (ORR, 42.9%; median PFS, 8.1 months) compared with camrelizumab alone (ORR, 22.2%; median PFS, 4.1 months), or chemotherapy alone (ORR, 14.3%; median PFS, 2.9 months) [18]. Patients in our study who had PD-1 inhibitor combination therapy achieved longer PFS and OS than those treated with PD-1 inhibitor monotherapy, experiencing a median PFS of 2-3 months and OS of 11-12 months [6, 7, 10]. However, cross-trial comparisons should be made with caution, and the lack of comparison precludes a definitive conclusion in our study. Notably, after an extended follow-up period, the safety profile of our

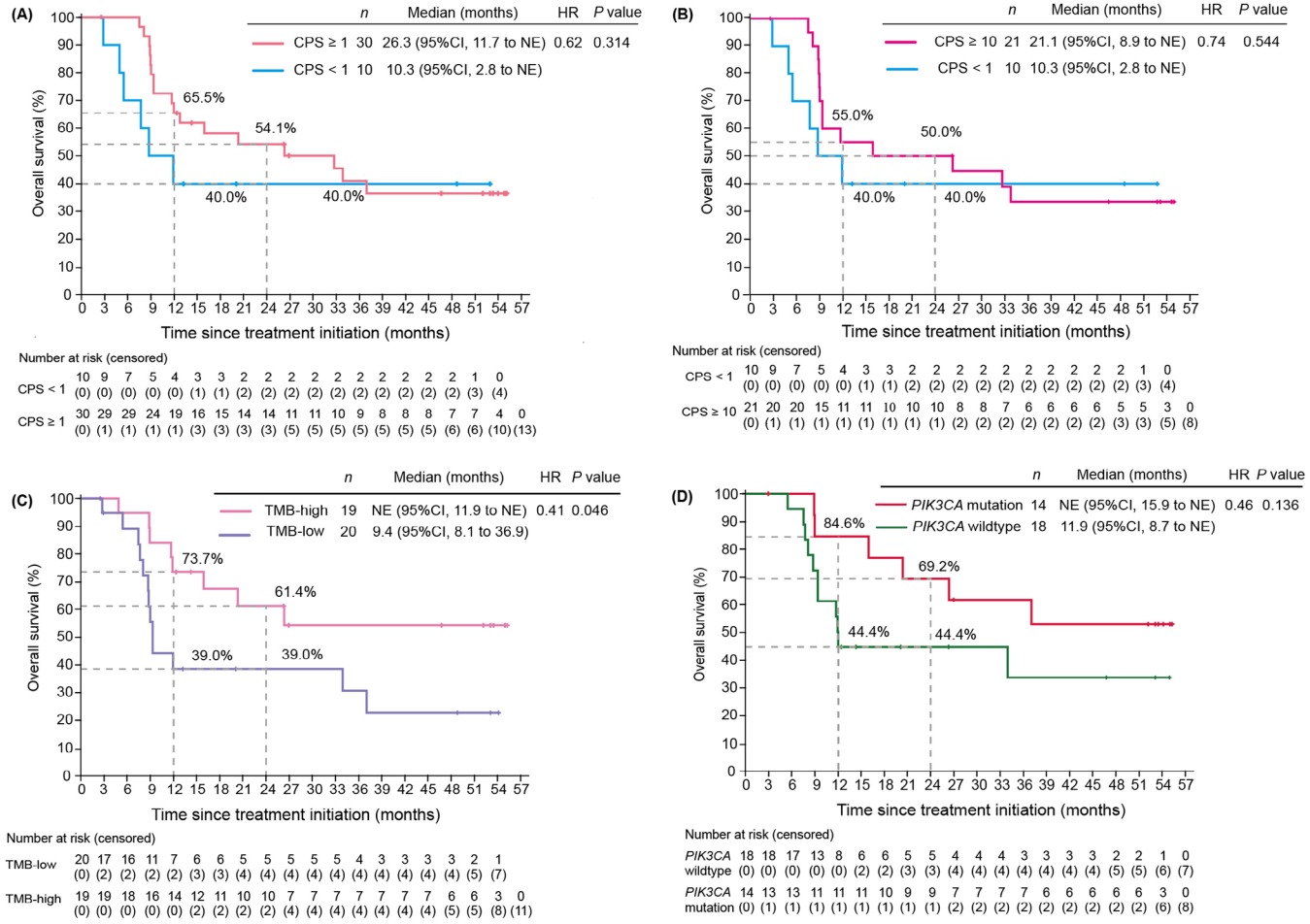

FIGURE 3 Kaplan-Meier curves of overall survival. Overall survival of patients with (A) a PD-L1 CPS ≥ 1 and a CPS < 1, (B) a CPS ≥ 10 and a CPS < 1, (C) TMB-high and TMB-low, and (D) *PIK3CA* mutation and wildtype. Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; mut/Mb, mutations per megabase; NE, not estimable; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

patients was consistent with that reported at the earlier data cutoff, with no new safety signals identified in this study.

It is noteworthy that 10 patients with PD-L1-negative tumors in our study achieved a 12-month PFS rate of 30% and a 24-month OS rate of 40%. While PD-L1 is a robust predictive biomarker of the response to PD-1/PD-L1 inhibitors, it is not the sole determinant of patient response. In some trials, patients with PD-L1-negative tumors have shown favorable responses and long-term outcomes [19–21], indicating the complicated interaction between cancer cells and the immune system [22–24]. It seems more crucial to ascertain the activation of either the PD-1 or PD-L1 pathway in tumors rather than exclusively concentrating on the expression of PD-L1.

Previously, we reported that squamous cell carcinoma, PD-L1 positive tumors, high TMB, and *PI3KCA* mutations were correlated with improved PFS [13]. In the present analysis, we found that age > 50 years, PD-L1 CPS ≥ 1 (vs. < 1), PD-L1 CPS ≥ 10 (vs. < 1), high TMB and *PI3KCA* mutations were associated with improved OS (Figure 4B). Evidence from prior studies has demonstrated a greater survival benefit in patients with a CPS ≥ 10 than in patients with a CPS ≥ 1 in terms of PD-1 inhibitor monotherapy [25–27]. Interestingly, our analysis showed comparable OS in patients with a CPS ≥ 10 or ≥ 1 tumors (Table 2, Figures 3A-B, and 4B). These findings may partially reflect a robust response to PD-1 inhibitor combination therapy that may override the influence of the CPS in patients with advanced cervical cancer. TMB has been demonstrated as a predictor of ICI response in numerous studies [28, 29]. In line with these data, a high TMB was linked to improved OS in the present analysis. It is worth mentioning that *PI3KCA* mutations were associated with a lower risk of mortality in our analysis, aligning with the findings in a study on sintilimab plus anlotinib [12], where the ORR was higher in patients with altered *PIK3CA* than in those with *PIK3CA* wildtype (91.7% vs. 46.2%, $P = 0.012$).

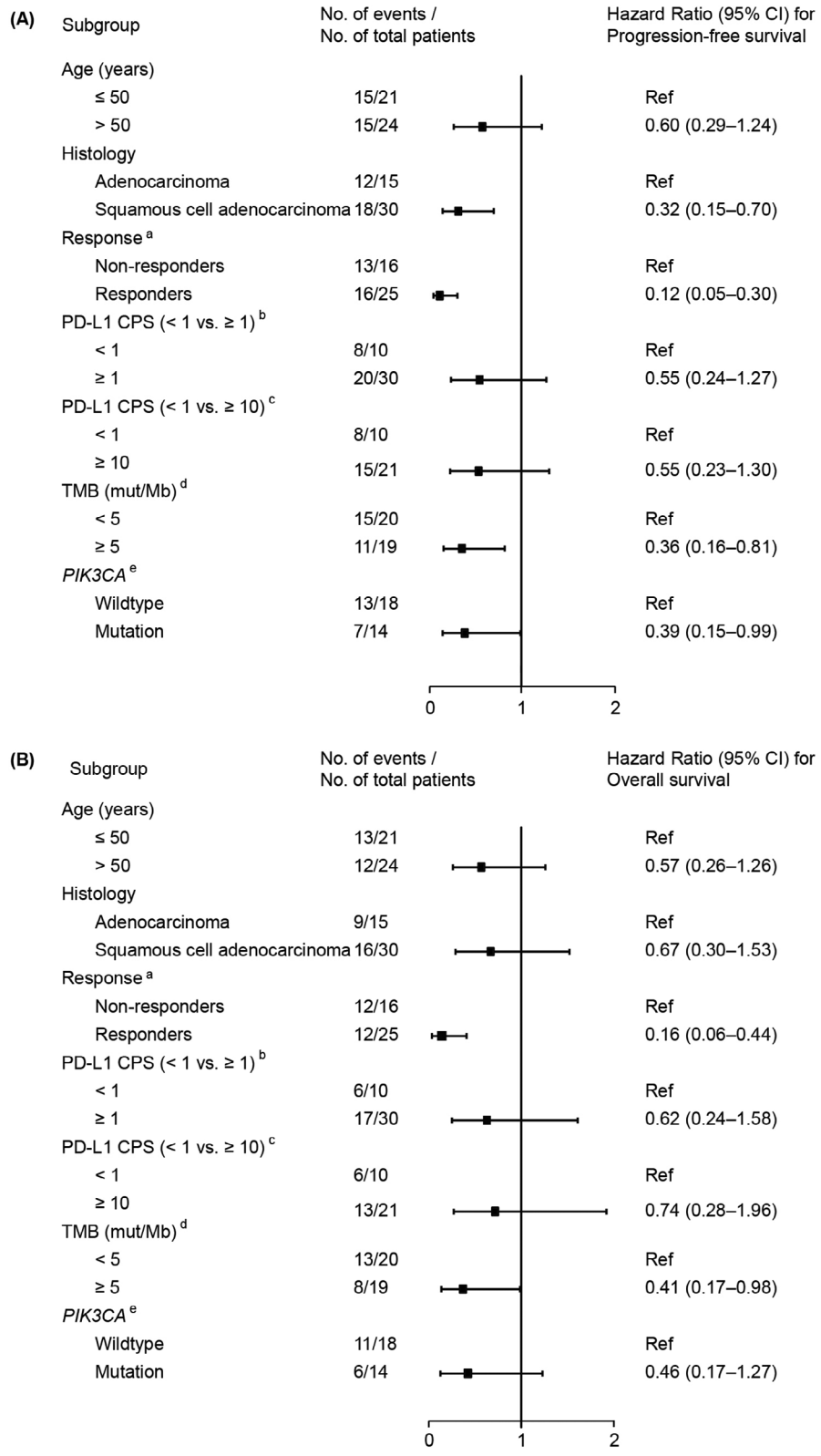

FIGURE 4 Forest plots in survival subgroup analyses. Subgroup analysis of (A) progression-free survival and (B) overall survival. (a) Forty-one patients were evaluable per Response Evaluation Criteria in Solid Tumors version 1.1. (b) A total of 40 patients had archival tumor tissue samples available for PD-L1 examination. (c) Of the patients, 10 tested negative for PD-L1, while 21 had a CPS of ≥10. (d) TMB information was available in 39 patients, with 20 having a TMB of < 5 mut/Mb and 19 having a TMB of ≥ 5 mut/Mb. (e) The *PIK3CA* mutation status was detected in 32 patients, with 14 showing *PIK3CA* mutations and 18 being *PIK3CA* wildtype. Abbreviations: CI, confidence interval; CPS, combined positive score; mut/Mb, mutations per megabase; No., number; PD-L1, programmed death-ligand 1; Ref, reference; TMB, tumor mutational burden.

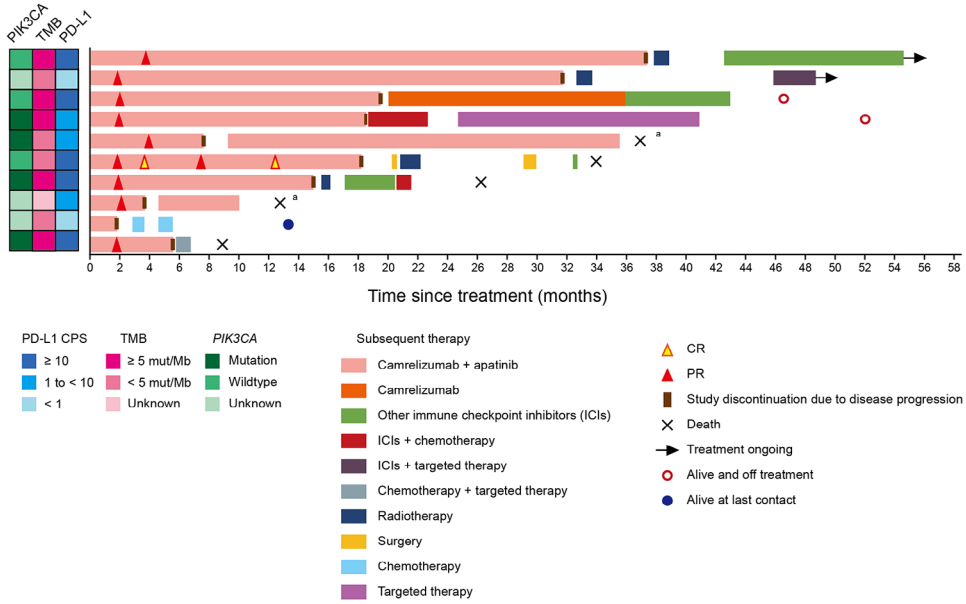

FIGURE 5 Swimmer plot for subsequent treatments. The plot shows subsequent therapies after discontinuation of the study due to disease progression ($n = 10$). Each bar represents an individual patient, and the length of each bar represents the duration of treatment for each patient. Pink bars represent the study treatment in the CLAP trial, while bars of other colors denote subsequent therapies post-trial due to disease progression. (a) The patients made the choice to continue the current treatment regimen after experiencing disease progression due to the limited alternative options. Abbreviations: CR, complete response; CPS, combined positive score; ICIs, immune checkpoint inhibitors; mut/Mb, mutations per megabase; PD-L1, programmed death-ligand 1; PR, partial response; TMB, tumor mutational burden.

Similarly, Nusrat *et al.* [30] reported that patients with colorectal cancer and *PIK3CA* mutations derived more clinical benefit from immunotherapy compared to *PIK3CA* wildtypes (50% vs. 8.6%, $P = 0.015$). Additionally, Ahn *et al.* [31] reported that *PIK3CA* mutation was significantly associated with PD-L1 expression in patients with colorectal cancer, supporting our observation that *PIK3CA* mutation correlated with a high incidence of PD-L1 expression. In their study, PD-L1 expression was found in 31.3% (15/48) of the patients with *PIK3CA* mutations and in 4.5% (8/176) of the patients without *PIK3CA* mutations [31]. Given that high PD-L1 expression is related to an increased response to PD-1 inhibitors [32], the reported correlation between *PIK3CA* mutations and PD-L1 expression may, to some extent, explain the favorable outcomes in patients with *PIK3CA* mutations. However, additional studies are needed to further understand the underlying mechanisms of these findings. It is interesting to note that older age (> 50 years) was correlated with improved OS in our study, consistent with observations in patients with melanoma [33, 34]. In a study by Perier-Muzet *et al.*, patients aged > 65 years with melanoma treated with immunotherapy had a longer PFS (4.8 vs. 3.4 months, $P = 0.04$) and OS (not reached vs. 10.1 months, $P = 0.009$) than those aged ≤ 65 years [34]. Kugel III et al. also observed a significant difference in the response to pembrolizumab by age in patients with melanoma, where the odds of progressing on pembrolizumab treatment decreased by 13% for every decade of patient age at treatment initiation [33]. However, it should be emphasized that our study was conducted with a primary interest in demonstrating the treatment effect in all patient populations, and the statistical tests in subgroup analyses were underpowered. Therefore, definitive conclusions regarding the association between these biomarkers and OS in the present study are challenging to draw.

Thus far, most clinical studies of advanced tumors are set up for two years of ICI treatment [10, 35]. However, the optimal treatment duration for patients with advanced cervical cancer who have responded to ICI therapy and have limited treatment options remains uncertain. In the present study, 8 of 9 patients were selected to continue the one-year extension treatment; 5 (62.5%) out of these 8 patients maintained their response, while 37.5% (3 out of 8) demonstrated disease progression. Given the lack of comparison, the benefit of this extended treatment period is unknown. In view of the available data from clinical trials and the recommendations of widely recognized guidelines [10, 35, 36], we argue that there is currently insufficient evidence to justify the extension of ICI treatment.

Although ICIs provide a durable response in multiple tumor types, relapse remains a common occurrence in patients with solid tumors. In our study, patients who experienced disease progression had few options for subsequent therapy. There is no recommended treatment for this setting in the existing guidelines. Evidence reveals that retreatment with ICIs has exhibited promising

TABLE 3 Subsequent immune checkpoint inhibitor after study discontinuation for disease progression.

Patient	Treatment duration in CLAP study (months)	Best response in CLAP study	The types of subsequent ICIs	Exposure to subsequent ICIs (months)	ICIs monotherapy or combination therapy in subsequent treatment	Best response to subsequent ICIs	Overall survival (months)	Status
#1	3.7	PR	Camrelizumab	5.4	Combination	SD	12.8	Death
#2	7.6	PR	Camrelizumab	26.3	Combination	SD	36.9	Death
#3	15.0	PR	ADG106, Tislelizumab	4.4	ADG106 monotherapy,† tislelizumab plus chemotherapy	SD	26.3	Death
#4	18.1	CR	Pembrolizumab	1.0	Monotherapy	PD	33.9	Death
#5	18.5	PR	Tislelizumab	4.0	Combination	SD	52.0	Alive with disease
#6	19.5	PR	Camrelizumab, Tislelizumab	23.0	Monotherapy	SD	46.6	Alive with disease
#7	31.7	PR	Zimberelimab	3.9	Combination	PR	48.7	Alive with disease
#8	37.4	PR	Cadonilimab*	13.1	Combination	PR	54.8	Alive with disease

†A new drug used in clinical trial

*A PD-1/CTLA-4 bispecific antibody

Abbreviations: ICIs, immune checkpoint inhibitors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

efficacy, particularly in melanoma [37, 38] and NSCLC [39]. However, conflicting trial results indicate limited benefits in patients with NSCLC [40, 41]. In light of the dynamic nature of the immune response and the long-term benefit of ICIs, retreatment with ICIs appears to be a suitable consideration. In our study, eight initial responders with subsequent disease progression were retreated with the same PD-1 inhibitor or different ICIs. Surprisingly, 25% of the patients achieved a BOR of PR, and four patients survived > 45 months. This study, to the best of our knowledge, is the first to report retreatment with ICIs in patients with cervical cancer. Pembrolizumab has been approved by the United States Food and Drug Administration (FDA) and recommended by the National Comprehensive Cancer Network (NCCN) guidelines in combination with chemotherapy with or without bevacizumab for patients with advanced cervical cancer whose tumors express PD-L1 as first-line therapy. Therefore, a crucial clinical question arises regarding the potential benefits of retreatment with anti-PD-1/PD-L1 therapy for those who progressed on the first-line treatment. We believe that our findings contribute significant insights into the efficacy and safety of this treatment. Despite the valuable information provided by our study, the small sample size in the current analysis posed challenges in determining robust predictive biomarkers for the efficacy of retreatment with ICIs. Nevertheless, certain biomarkers or factors have been reported to predict the efficacy of retreatment with ICIs, and the selection of appropriate candidates for retreatment with ICIs is imperative.

We acknowledge that our study has several limitations. First, as mentioned above, subgroup analyses lacked sufficient power to test the association between the biomarkers and OS due to the nature of our study design. Second, despite the promising response rate and long-term survival, the absence of a comparison prevents us from conclusively affirming that our PD-1 inhibitor combination treatment yields superior anticancer effects compared to PD-1 inhibitor monotherapy. However, we evaluated the long-term survival of patients treated with a PD-1 inhibitor combined with a VEGFR2 inhibitor in patients with advanced cervical cancer, with all patients undergoing treatment for over 48 months. To our knowledge, this is the first long-term study in this particular setting. Moreover, we are the first to report data on patients with advanced cervical cancer who underwent retreatment with ICIs. These findings could offer valuable insights into subsequent treatment for patients who progress after first-line PD-1 inhibitor combination therapy.

5 | CONCLUSION

The long-term survival follow-up data further demonstrate that camrelizumab plus apatinib provides robust, sustained, and durable efficacy in patients with advanced cervical cancer who progressed after first-line platinum-based chemotherapy. No new safety signals were noted with long-term treatment.

AUTHOR CONTRIBUTIONS

Conception and design: Chunyan Lan and Xin Huang. *Provision of study materials or patients:* Chunyan Lan, Huaiwu Lu, Lin Zhou, Kunlun Liao, Junxiu Liu, Qin Xu, Xin Huang. *Collection and assembly of data:* Chunyan Lan, Huaiwu Lu, Lin Zhou, Kunlun Liao, Junxiu Liu, Zhiwen Xie, Haixi Liang, Guorong Zou, Ting Yang, Qin Xu. *Data analysis and interpretation:* Chunyan Lan, Huaiwu Lu, Lin Zhou, Kunlun Liao, Junxiu Liu, Qin Xu, Xin Huang. *Manuscript writing:* Chunyan Lan. *Final approval of manuscript:* All authors.

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CONFLICT OF INTEREST STATEMENT

Ting Yang is an employee of Jiangsu Hengrui Medicine Co., Ltd. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The patient data in this study have been recorded at the Research Data Deposit public platform (http://www.researchdata.org.cn), with the approval RDD number RDDA2024892306. The data are available from Research Data Deposit, but restrictions apply to the availability of these data, which were used under license for the current study and thus are not publicly available. However, the data are available from the authors upon reasonable request and with permission from the Research Data Deposit public platform.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Sun Yat-sen University Cancer Center Ethics Committee (Reference Number,

B2018-169) and the ethics committee at each participating site. All patients provided written informed consent prior to enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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