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Efficacy of programmed cell death protein 1/programmed death ligand 1 inhibitors as first-line treatment for advanced cervical cancer: A multicenter retrospective study

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Abstract

The KEYNOTE-A18 trial recently demonstrated the benefits of first-line treatment with programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors for advanced cervical cancer. Herein, we investigated this using real-world data from a large Chinese cohort. From January 2020 to June 2023, 91 patients diagnosed with advanced cervical cancer receiving first-line systemic therapy incorporating PD-1/PD-L1 inhibitors were recruited as the treatment group, while 101 patients who did not receive PD-1/PD-L1 inhibitors were included as the control group. Baseline characteristics, including patient age, the International Federation of Gynecology and Obstetrics (FIGO) stage, histological subtypes, tumor diameter, PD-L1 expression, overall survival (OS), and progression-free survival (PFS), were extracted from the medical records. Survival analysis was performed utilizing the Kaplan-Meier curve and Cox regression analysis was used to compare the effects of different factors on patients' survival. The addition of PD-1/PD-L1 inhibitors significantly prolonged PFS compared to the control group (median PFS: 19 vs. 11 months, p=0.000). Stratified analysis showed that higher expression of PD-L1 (median PFS: 14 vs. 14 months, p=0.031), earlier FIGO stage (median PFS: 20 vs. 11 months, p=0.000), and tumor diameter ≤4 cm (median PFS: 47 vs. 12 months, p=0.000) were associated with a better PFS. No statistical difference was detected in OS between the two groups. In the stage IVB subgroup, PD-1/PD-L1 inhibitors showed no benefits in either OS or PFS. Moreover, Cox regression analysis showed that only the use of PD-1/PD-L1 inhibitors was associated with prolonged PFS (hazard ratio = 0.43, 95% confidence interval 0.30 – 0.61, p=0.000). The first-line treatment containing PD-1/PD-L1 inhibitors significantly delayed tumor recurrence, especially for those with positive expression of PD-L1 and relatively small tumors.

Keywords: Programmed cell death protein 1/programmed death ligand 1 inhibitors; Advanced cervical cancer; First-line treatment; The International Federation of Gynecology and Obstetrics stage; Programmed death ligand 1 status; Tumor diameter

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1. Introduction

Cervical cancer is one of the main causes of cancer-related mortality for women worldwide and has seen a recent substantial increase, particularly in China.[1] Cervical cancer emerged as the most common gynecological cancer and the fourth most common cancer among women in 2022, with approximately 661,021 new cases and 348,189 deaths.[2] In developed nations, the implementation of human papillomavirus (HPV) vaccination, screening programs, and timely intervention for precancerous lesions has led to a substantial decline in late-stage morbidity and disease-specific mortality. Conversely, a disproportionate 80% of global cervical cancer fatalities are concentrated in low- and middle-income countries, primarily due to insufficient screening initiatives and delayed diagnostic processes.[3-5] Epidemiological data indicate that the Asian region accounts for 58.3% of the global incidence of new cases, with China contributing 17% of the mortality rate.[6] These statistics underscore significant deficiencies in early detection and therapeutic interventions. Advanced cervical cancer, which is characterized by large tumors and local and distant metastasis, is typically managed with chemoradiation. The standard first-line therapeutic approach for advanced cervical cancer currently involves platinum-based chemotherapy in conjunction with bevacizumab. Nevertheless, the majority of patients with advanced disease experience recurrence following first-line treatment.[7] For advanced disease, the 5-year progression-free survival (PFS) and overall survival (OS) rates for patients are only 50 – 70%.[8] Stage IV patients exhibit a 5-year OS rate of under 20%,[9] underscoring the need for novel therapeutic agents and modalities.

In 2018, the United States Food and Drug Administration approved pembrolizumab for the treatment of programmed death-ligand 1 (PD-L1)-positive recurrent metastatic cervical cancer based on the results from the KEYNOTE-158 study, which proves that the application of immunotherapy in advanced cervical cancer is feasible.[10] In recent years, several clinical trials have provided evidence that immunotherapy is a crucial component of the treatments for cervical cancer,[11-15] and it has emerged as a transformative strategy for advanced cancers. Programmed cell death protein 1 (PD-1)/PD-L1 inhibitors, the most widely used immune checkpoint inhibitors (ICIs), attack cancer cells by reactivating and inducing the proliferation of antigen-stimulated T cells in the tumor microenvironment.[16,17] The KEYNOTE-A18 study was a prospective, international, multicenter, randomized, controlled, phase III trial targeting locally advanced cervical cancer. This study investigated the potential of immunotherapy in conjunction with concurrent radiotherapy and chemotherapy. Notably, the trial enrolled high-risk patients according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 staging system, specifically those with stages III–IVA disease, regardless of lymph node status, and patients with lymph node metastasis in stages IB2-IIB. Another highlight of the study is that compared with previous large clinical studies in Western countries, the proportion of Asian populations in the KEYNOTE-A18 study was close to 30%. Chinese patients comprised 50% of Asian patients in the study, a proportion that significantly enhances the value of therapeutic guidance for Chinese patients. Moreover, the results of the KEYNOTE-A18 trial revealed, for the 1st time, that the use of pembrolizumab + simultaneous radiotherapy in the first-line treatment regimen resulted in significant improvement in PFS and OS in locally advanced cervical cancer, with 36-month PFS and OS rates, reaching 69.3% and 82.6%, respectively. These rates were higher than those in the placebo group, indicating that the integration of ICIs into the conventional treatment protocol for locally advanced cervical cancer is justified.[18] Based on the results of that study, the National Comprehensive Cancer Network (NCCN) guideline added pembrolizumab + cisplatin/carboplatin as the preferred regimen for the treatment of cervical cancer patients with FIGO 2014 stages III–IVA.[19] This update implies the establishment of immune combination therapy as the standard of care for advanced cervical cancer. While randomized controlled trials are designed to maximize internal validity through the implementation of rigorous inclusion and exclusion criteria, the highly regulated environment may inadvertently compromise external validity. This can result in a study population that does not fully capture the heterogeneity observed in real-world clinical settings, including variations in racial and geographic distributions. To address this limitation and to assess the generalizability of the KEYNOTE-A18 trial findings within the context of routine clinical practice, we initiated a multicenter retrospective cohort study. This study, which included a substantial cohort of Chinese patients diagnosed with advanced cervical cancer (n=192), systematically evaluated the efficacy and identified the determinants of response to PD-1/PD-L1 inhibitors in a real-world setting. The primary objective was to generate evidence that more closely reflects the complexities and nuances of clinical practice scenarios.

2. Materials and methods

2.1. Participants and study design

From January 2020 to June 2023, clinical data of cervical cancer patients with FIGO 2018 stages IIIC and IV who were diagnosed and treated in the First Affiliated Hospital

of Zhengzhou University and Henan Cancer Hospital were collected. Cases within stages IB2 and IIA were not included in the study due to their low numbers. The inclusion criteria of this study are as follows: (i) pathologically confirmed primary cervical squamous carcinoma or adenocarcinoma, (ii) availability of complete case information (including age at diagnosis, histological type, FIGO 2018 stage, treatment plan, pathological results, tumor diameter, PD-L1 expression, treatment modality after recurrence/metastasis, and patient outcome), and (iii) availability of complete follow-up information. The exclusion criteria were incomplete clinical information and follow-up data. A total of 204 cases were collected, of which 12 cases were excluded due to incomplete records, and 192 cases that met the screening criteria were included in the study. All patients received conventional chemotherapy + radical hysterectomy + radiotherapy as initial treatment. There were 180 cases of squamous cervical cancer and 12 cases of adenocarcinoma in which the size of the tumor diameter was measured using magnetic resonance imaging, and subgroups were analyzed on a threshold of 4 cm. Due to factors such as patient preference, the choice of dosing regimen, and preference of the supervising physician, 91 patients received initial treatment with a PD-1/PD-L1 inhibitor as the treatment group, and the other 101 patients received therapy without a PD-1/PD-L1 inhibitor and were set up as the control group.

2.2. Follow-up

After the primary treatments, these patients were routinely followed up as recommended by the NCCN guidelines.[19] In the 1st and 2nd years, follow-up was conducted every 3 months. Subsequently, follow-ups were performed every half a year in the 3rd and 4th years. In the 5th year and onward, follow-ups were done once a year. The last follow-up was performed in May 2024. OS was defined as the interval from the diagnosis of cervical cancer to the patient's death. PFS was defined as the duration from the initial diagnosis to the onset of the first tumor progression.

2.3. Evaluation of PD-L1 expression

Immunohistochemical staining was conducted to evaluate the expression of PD-L1 in cervical cancer tissues. The primary antibody was purchased from DAKO (Germany, clone number: 22-C3). An additional pathologist validated the results. A combined positive score (CPS) was used as an indicator to evaluate PD-L1 expression during immunotherapy. It encompasses both the PD-L1 expression on tumor and tumor-associated immune cells. The CPS was determined by calculating the number of tumor cells and tumor-associated immune cells per 100 tumor cells using the formula in Equation I:

$$CPS = \frac{Number\ of\ positive\ tumor\ cells + number\ of\ positive\ immune\ cells}{Total\ number\ of\ tumor\ cells} \times 100 \quad (I)$$

The 2024 NCCN guidelines recommended immunotherapy for cervical cancer patients with a CPS ≥1. Consequently, in this study, CPS ≥1 was utilized to designate PD-L1-positive cases.

2.4. Statistical analysis

The Statistical Package for the Social Sciences statistical package (version 26.0, Chicago, United States) was used for all statistical analyses. Continuous variables with normal distribution were reported as mean ± standard deviation and independent *t*-tests were employed for comparison. Categorical variables were presented as frequencies and percentages (*n*[%]), and comparisons between groups were made using the Chi-square test or Fisher's exact test. Kaplan-Meier curves were generated to assess clinicopathologic variables and their associations with PFS and OS. Hypothesis testing for the comparison of Kaplan-Meier curves in the two groups was performed using the log-rank (Mantel-Cox) test. Screening for risk factors associated with PFS and OS was conducted using Cox regression analysis. $p \leq 0.05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics of advanced cervical cancer patients

As shown in Table 1 and Figure 1, our study examined a total of 204 patients diagnosed with advanced cervical cancer. Out of these, 12 patients were excluded from the analysis due to incomplete records. Thus, a total of 192 patients with advanced cervical cancer were evaluable for the final analysis. They were divided into the treatment group (*n*=91) and the control group (*n*=101) according to whether PD-1/PD-L1 inhibitor therapy is included in the first-line treatment.

In the treatment group, the median age was 53 (ranging from 25 to 82 years old), and 93.4% had squamous cell carcinoma (SCC). In contrast, the control group had a median age of 51 years old, with 94.1% having SCC. According to the FIGO 2018 staging criteria, 62 patients in the treatment group were classified as stage IIIC, six patients with stage IVA, and 23 patients with stage IVB. In the control group, 73, three, and 25 cases were identified as stage IIIC, stage IVA, and stage IVB, respectively. In the two groups, 51.7% (*n*=47) and 34.6% (*n*=35) of patients received the test for PD-L1 expression (Table 1). The distribution of patients between the two groups was relatively balanced,

Table 1. Baseline characteristics of 192 advanced cervical patients

Characteristics	Total (*n*=192) (%)	Treatment group (*n*=91) (%)	Control group (*n*=101) (%)	*t*-test or Chi-square test	*p*-value
Age (years)					
Median (range), years	53 (22 – 82)	53 (25 – 82)	51 (22 – 80)		
Mean±standard deviation	51.9±11.0	51.9±11.0	51.9±10.9	t=0.008	0.993
				χ^2=0.985	0.321
>50	111 (57.8)	56 (61.5)	55 (54.5)		
≤50	81 (42.2)	35 (38.5)	46 (45.5)		
Histology				χ^2=0.035	0.852
Squamous cell carcinoma	180 (93.8)	85 (93.4)	95 (94.1)		
Adenocarcinoma	12 (6.2)	6 (6.6)	6 (5.9)		
PD-L1 expression				χ^2=13.455	0.001*
CPS ≥1	71 (37.0)	45 (49.5)	26 (25.7)		
CPS <1	11 (5.7)	2 (2.2)	9 (8.9)		
Unknown	110 (57.3)	44 (48.3)	66 (65.4)		
FIGO stage					0.507
IIIC	135 (70.3)	62 (68.1)	73 (72.3)		
IVA	9 (4.7)	6 (6.6)	3 (3.0)		
IVB	48 (25.0)	23 (25.3)	25 (24.7)		
Tumor diameter				χ^2=0.030	0.862
≤4 cm	38 (28.1)	17 (27.4)	(28.8)		
>4 cm	97 (71.9)	45 (72.6)	52 (71.2)		

Notes: Data are presented as *n* (%) unless otherwise specified; *indicates statistical significance at $p<0.05$.
Abbreviations: CPS: Combined positive score; FIGO: Federation of gynecology and obstetrics; PD-L1: Programmed death-ligand 1.

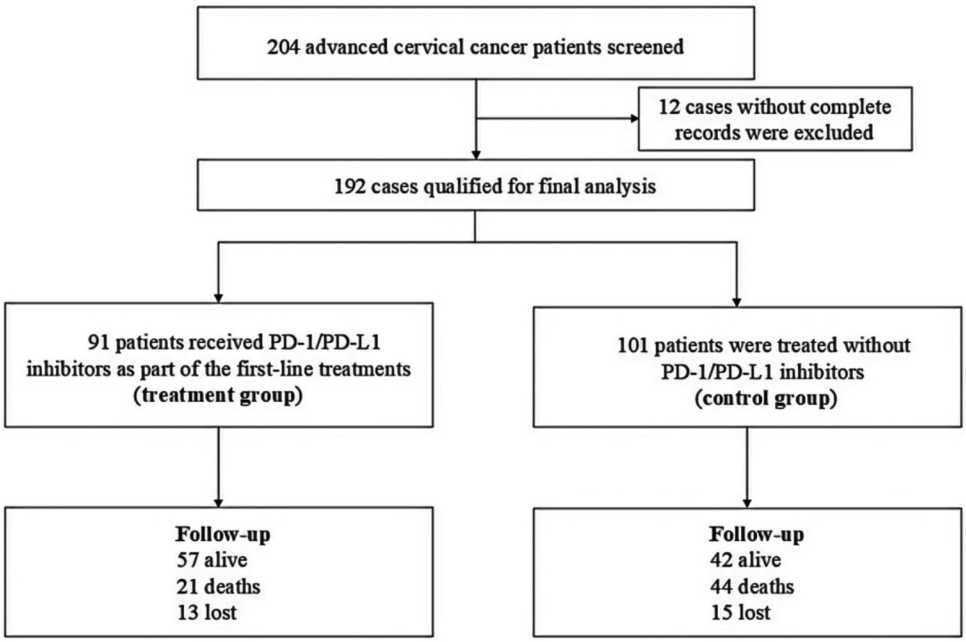


Figure 1. Flowchart of the study procedure
Abbreviations: PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1.

and no substantial disparities in clinical characteristics were observed. Confounding factors were accounted for in the subsequent analysis.

3.2. The effects of PD-1/PD-L1 inhibitors on PFS

By the end of the follow-up, there were 140 disease progression events and 65 deaths. Compared to the control group (median PFS: 11 months, 95% confidence interval [CI] 8.22 – 13.78), the median PFS of the treatment group was 19 months (95% CI 12.71 – 25.29, $p<0.001$, Figure 2A). In the subgroup analyses of the two groups, the PFS difference caused by PD-1/PD-L1 inhibitors was statistically significant in PD-L1-positive patients (median PFS: 24 vs. 14 months, $p=0.031$, Figure 2B), stage IIIC tumors (median PFS: 20 vs. 11 months, $p<0.001$, Figure 2C), and tumor diameter ≤4 cm (median PFS: 47 vs. 12 months, $p<0.001$, Figure 2D).

Due to the short follow-up period, the median OS has not been attained in either group, while the survival analysis showed no statistically significant difference in OS between the treatment and control groups. Similarly, stratification analysis indicated no benefits of immunotherapy based on PD-L1 expression, FIGO stage, or tumor diameter.

In a univariate analysis using the Cox regression model, the use of PD-1/PD-L1 inhibitors in first-line therapy was associated with better PFS (hazard ratio = 0.43, 95% CI 0.30 – 0.61, Table 2). While the other factors, including histology ($p=0.73$), patient age ($p=0.74$), surgery ($p=0.08$), PD-L1 status ($p=1.0$), FIGO stage ($p=0.21$), and tumor diameter ($p=0.29$), have no associations with PFS (Table 2). No statistically significant effect of variables on OS was observed ($p>0.05$). Based on the results of univariate analysis, we did not perform multivariate analysis.

3.3. Baseline characteristics of stage IVB patients

Given that the KEYNOTE-A18 study did not include patients with stage IVB disease, we explored this subgroup in the present study. A total of 48 stage IVB cases were analyzed ($n=23$ in the treatment group and $n=25$ in the control group). In the treatment group, the median patient age was 53 years old (ranging from 35 to 75 years old), and 95.7% ($n=22$) of cases had SCC. In the control group, the median patient's age was 54 years old (ranging from 33 to 73 years old). SCC accounts for 84.0% ($n=21$) of cases. In the two groups, 56.5% ($n=13$) and 32.0% ($n=8$) of patients received the test for PD-L1 expression. Among

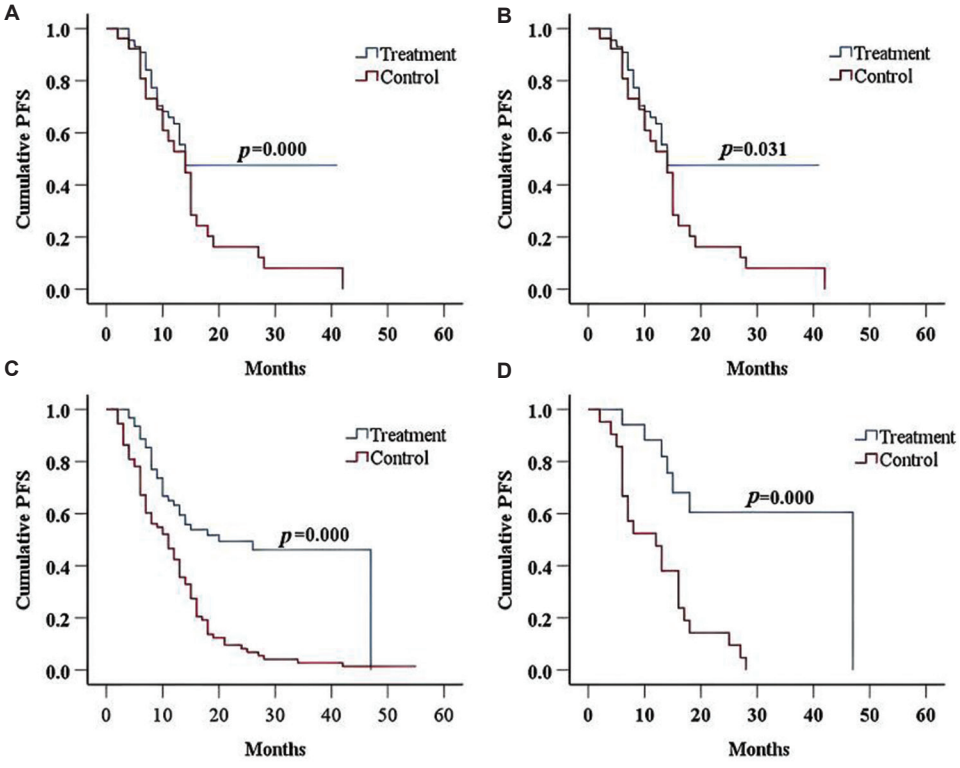


Figure 2. The Kaplan–Meier survival curves comparing PFS in different groups of 192 patients. (A) PFS was significantly prolonged in 91 cases in the treatment group compared to the control group (19 versus 11 months, $p=0.000$). (B) PFS was significantly prolonged in programmed death-ligand 1-positive patients in the treatment group than in the control group (24 versus 14 months, $p=0.031$). (C) PFS was significantly prolonged in patients with stage IIIC in the treatment group than in the control group (20 versus 11 months, $p=0.000$). (D) Patients with tumors ≤4 cm in diameter in the treatment group had significantly longer PFS than the control group (47 versus 12 months, $p=0.000$).
Abbreviation: PFS: Progression-free survival.

the patients, 52.2% tested positive in the treatment group compared with 20.0% in the control group (Table 3). Survival analysis showed that there was no significant difference in either PFS (median PFS: 17.0 vs. 15.0 months, p=0.227, Figure 3A) or OS (p=0.797, Figure 3B) between the treatment and control groups.

4. Discussion

The significant influence of immunotherapy, specifically PD-1/PD-L1 inhibitors, on the treatment of cervical cancer has been progressively substantiated by clinical trials and real-world evidence. Recent developments highlight the capacity of these agents to reshape therapeutic approaches, particularly in cases of advanced or recurrent disease.[11,15] The KEYNOTE-A18 trial marked a pivotal milestone by demonstrating that combining pembrolizumab with chemoradiotherapy significantly improved PFS in locally advanced cervical cancer, with a 36-month PFS rate of 69.3% compared to 53.6% in the placebo group.[18] This outcome represents a critical advancement, solidifying the clinical utility of immunotherapy in the treatment of cervical cancer. Conversely, the global multicenter phase III CALLA trial, which employed a similar study design, indicated that the combination of durvalumab and radiotherapy did not significantly improve PFS in patients with locally advanced cervical cancer (hazard ratio = 0.84, p=0.174) without biomarker screening despite an acceptable safety profile.[20] Unlike KEYNOTE-A18, the CALLA trial did not mandate PD-L1 testing, which may explain the differences in results. These findings collectively suggest that PD-L1 expression, as measured by the CPS, serves as a predictive biomarker for immunotherapy efficacy, underscoring the need for standardized biomarker screening protocols in clinical practice. These findings suggest that the biomarker screening strategy may modulate the clinical efficacy of immunotherapy. Within this study, our research team conducted a large-scale, real-world investigation (n=192) involving a Chinese cohort diagnosed with advanced cervical cancer, with the primary objective of assessing the clinical utility of PD-1/PD-L1 inhibitors as first-line systemic therapy. The findings demonstrated that combination immunotherapy recapitulated the PFS benefit observed in the KEYNOTE-A18 trial within a real-world clinical setting (hazard ratio = 0.43, p=0.00), although no statistically significant improvement in OS was yet evident,

Table 2. Univariate Cox regression analyses on the associations of different clinical factors with patients' progression-free survival rates

Characteristics	Hazard ratio	95% confidence interval	p-value
Histology	0.89	0.45 – 1.75	0.73
Age	0.95	0.68 – 1.32	0.74
Surgery	1.37	0.97 – 1.93	0.08
PD-L1 expression	1.00	0.77 – 1.31	1.00
FIGO stage	1.27	0.87 – 1.86	0.21
The first-line treatments containing PD-1/PD-L1 inhibitors	0.43	0.30 – 0.61	0.00*
Tumor diameter	0.90	0.75 – 1.10	0.29

Note: *Indicates statistical significance at p<0.05.
Abbreviations: FIGO: Federation of Gynecology and Obstetrics; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1.

Table 3. Baseline characteristics of patients with stage IVB cervical cancer

Characteristics	Total (n=48) (%)	Treatment group (n=23) (%)	Control group (n=25) (%)	t-test or Chi-square test	p-value
Age (years)					
Median (range), years	53 (33 – 75)	53 (35 – 75)	54 (33 – 73)		
Mean±standard deviation	51.9±11.0	53.4±9.9	54.6±9.1	t=0.411	0.683
				χ^2=0.042	0.838
>50	32 (66.7)	15 (65.2)	17 (68.0)		
≤50	16 (33.3)	8 (34.8)	8 (32.0)		
Histological features					0.350
Squamous cell carcinoma	43 (89.6)	22 (95.7)	21 (84.0)		
Adenocarcinoma	5 (10.4)	1 (4.3)	4 (16.0)		
PD-L1 expression					0.059
CPS ≥1	17 (35.4)	12 (52.2)	5 (20.0)		
CPS <1	4 (8.3)	1 (4.3)	3 (12.0)		
Unknown	27 (56.3)	10 (43.5)	17 (68.0)		

Note: Data are presented as n (%) unless otherwise specified.
Abbreviations: CPS: Combined positive score; PD-L1: Programmed death-ligand 1.

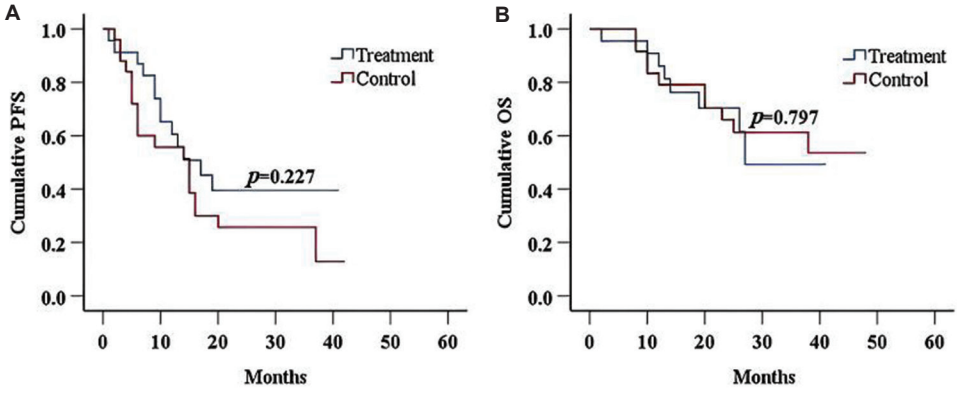


Figure 3. Kaplan-Meier curves for 23 patients in the treatment group and 25 patients in the control group at stage IVB. (A) No benefit for progression-free survival was detected in the treatment group compared to the control group (17 vs. 15 months, p=0.227). (B) No benefit for overall survival was detected in the treatment group compared to the control group (p=0.797).

likely attributable to the limited follow-up duration (p>0.05). This may be because the OS advantage tends to appear later due to the delayed effect of immune-mediated tumor control. For example, the KEYNOTE-826 trial[13] reported a delayed OS improvement in pembrolizumab-treated patients, with significant separation of survival curves after 24 months (hazard ratio = 0.64, p<0.001).

A critical strength of this study lies in its focus on the Chinese population, which addresses a longstanding gap in the evidence base. Specifically, it validates the applicability of immunotherapy in Chinese patients while also providing insights into potential disparities in treatment response between Eastern and Western populations. Ethnic and regional differences in tumor biology, genetic polymorphisms, and healthcare access may influence treatment responses. For example, Asian populations exhibit higher PD-L1 positivity rates compared to Western cohorts, potentially enhancing immunotherapy efficacy.[21] In addition, it furnishes local data to inform the refinement of biomarker screening strategies. Socioeconomic disparities in China – such as uneven HPV vaccination coverage (≤1% in rural vs. >70% in urban areas) and delayed diagnoses – contribute to advanced-stage presentations, necessitating tailored therapeutic strategies.[3] These observations offer crucial insights for the revision of cervical cancer diagnostic and therapeutic guidelines, as well as the development of precision medicine approaches within China. Our findings validate that PD-1/PD-L1 inhibitors retain efficacy in real-world settings despite these challenges, offering hope for regions with limited access to clinical trial participation.

Our stratification analysis underscores the critical interplay between tumor biology, clinical staging, and treatment response in advanced cancers. Specifically, patients with PD-L1-positive stage IIIC tumors ≤4 cm in diameter derived significant survival benefits from immunotherapy, suggesting that both molecular biomarkers and anatomical tumor characteristics synergistically influence therapeutic outcomes. This biomarker- and clinical feature-driven efficacy model aligns with emerging paradigms in precision oncology, where multidimensional stratification – incorporating immune checkpoint expression, tumor burden metrics, and disease progression patterns – is increasingly recognized as essential for optimizing therapeutic strategies.[22,23] Notably, analogous observations in gastrointestinal malignancies further validate this approach. For instance, immunotherapy has demonstrated remarkable efficacy in advanced recurrent or metastatic colorectal cancer (CRC), particularly when administered earlier in the disease course. Studies indicate that initiating ICIs before extensive chemotherapy or radiation improves PFS and OS, likely due to preserved immune function and reduced immunosuppressive effects of cytotoxic therapies.[24] These findings challenge traditional therapeutic sequences and advocate for front-line immunotherapy in biomarker-selected populations.

As an important biomarker for the prediction of immunotherapy efficacy, PD-L1 expression level shows clear predictive value in non-small cell lung cancer[25] and melanoma,[26] and its high expression status is significantly correlated with the enhanced response rate to ICI treatment. In recent years, studies have further expanded the biomarker spectrum. In a multicenter study, Shen *et al.*[27] found that in addition to PD-L1, microsatellite instability (MSI) and high tumor mutation burden could be used as a combined test to predict the response to tumor immunotherapy. Notably, in the field of CRC, Li's *et al.*[28] included a meta-analysis of 16 studies showing significant heterogeneity, in which the objective response rate (ORR) of advanced CRC patients with MSI/mismatch repair deficiency reached 37% (95% CI: 0.25 – 0.48), whereas

the ORR of patients with microsatellite stable/mismatch repair proficiency was only 11% (95% CI: 0.25 – 0.48). This difference may stem from the unique immune microenvironment characteristics of high MSI/mismatch repair deficiency tumors, which are usually accompanied by massive tumor-infiltrating lymphocyte infiltration and highly immunogenic microenvironment formation – a biological characteristic that enables patients with this subtype to achieve significant survival benefits from anti-PD-1/PD-L1 monotherapy.

Tumor size emerges as an underappreciated yet clinically actionable prognostic factor. Our analysis identified that tumors ≤4 cm serve as a favorable prognostic factor, which aligns with the cohort study by Kornprat *et al.*[29] involving 159 CRC patients. Their findings demonstrated that tumors >4.5 cm (observed in 44% of cases) were significantly associated with advanced T/N stage, higher tumor grade, and reduced cancer-specific survival. The biological rationale may involve smaller tumors maintaining a less immunosuppressive microenvironment with lower stromal desmoplasia, facilitating immune cell infiltration and drug delivery. Moreover, tumor diameter inversely correlates with surgical resectability and metastatic potential, creating a therapeutic window for neoadjuvant or adjuvant immunotherapy in locally advanced diseases. These dimensional thresholds warrant further validation across histotypes, as optimal size cut-offs may vary by organ site and tumor biology. The convergence of these findings has profound clinical implications. First, they advocated for pretreatment molecular profiling encompassing PD-L1, MSI status, and tumor mutational burden alongside conventional staging to guide first-line therapy selection. Second, they supported the integration of tumor size into risk stratification models, particularly for surgical decision-making and adjuvant therapy duration. For example, stage IIIC CRC patients with <4 cm PD-L1-positive tumors might benefit from extended adjuvant immunotherapy rather than conventional chemotherapy alone. Finally, these insights underscore the need for dynamic biomarker monitoring during treatment, as PD-L1 expression and tumor immune landscapes can evolve under therapeutic pressure.

Subgroup analyses in advanced cervical cancer have unveiled critical insights into the interplay between tumor size, molecular biomarkers, and therapeutic outcomes. Specifically, patients with stage IIIC disease and tumors <4 cm demonstrated significantly prolonged PFS, reinforcing tumor diameter as a pivotal prognostic factor. The 4 cm threshold adopted from the FIGO 2014 staging system and validated in the KEYNOTE-A18 trial, serves dual purposes: (i) it reflects anatomical tumor burden and (ii) acts as a surrogate for underlying biological and immunological heterogeneity. Smaller tumors may harbor a less immunosuppressive microenvironment, characterized by higher $CD8^+$ T-cell infiltration and reduced stromal barriers, which could enhance the efficacy of ICIs. These findings advocate for integrating PD-1/PD-L1 inhibitors into the first-line treatment for stage IIIC cervical cancer patients with limited tumor burden, potentially delaying recurrence and improving survival trajectories.

The rationale for prioritizing tumor size in therapeutic decision-making is further supported by its correlation with surgical resectability and metastatic potential. Tumors ≤4 cm are more likely to remain localized, with limited lymphatic or vascular invasion, thereby presenting a window for neoadjuvant or adjuvant immunotherapy to eradicate micrometastasis. In contrast, larger tumors often exhibit aggressive biological behavior, including hypoxia-driven immunosuppression and upregulated alternative immune checkpoints (e.g., lymphocyte activation gene 3 and T cell immunoglobulin and mucin domain 3), which may necessitate combinatorial therapeutic approaches. The KEYNOTE-A18 trial,[18] which included patients with stage IB2-IIB cervical cancer, established pembrolizumab's efficacy in this setting, particularly when combined with chemoradiotherapy.

The predictive value of PD-L1 expression as a biomarker in cervical cancer has garnered increasing research attention. In a prospective investigation of 27 stage IIA cervical SCC patients conducted by Kim *et al.*,[30] PD-L1 positivity was detected in 44.4% (12/27) of cases, with high PD-L1 expression correlating significantly with favorable clinicopathological characteristics, including lower preoperative serum SCC antigen levels and absence of parametrial invasion. These findings support the emerging hypothesis that PD-L1 upregulation in cervical malignancies may not merely represent an immune evasion mechanism but rather reflect an adaptive immune response – indicative of a pre-existing "hot" tumor microenvironment primed for engagement with ICIs. Importantly, the therapeutic benefits of anti-PD-1/PD-L1 agents appear amplified in subgroups defined by both molecular and clinical criteria. Patients with smaller, PD-L1-positive tumors may represent an "ideal" cohort for immunotherapy due to synergistic factors: (i) reduced tumor bulk lowers the threshold for immune-mediated cytotoxicity, (ii) preserved antitumor T-cell function in less advanced disease, and (iii) higher antigenicity from HPV-related neoantigens. Conversely, larger or PD-L1-negative tumors may require multimodal strategies, such as ICIs combined with vascular endothelial growth factor (VEGF) inhibitors (e.g., bevacizumab) to normalize aberrant vasculature and enhance drug delivery or radiotherapy to induce immunogenic cell death and broaden the antigen repertoire.

These findings underscore the urgency of redefining cervical cancer treatment paradigms through biomarker-driven stratification. Present guidelines, which predominantly rely on FIGO staging and histology, lack the granularity to address inter-patient variability in immune microenvironment composition. Prospective studies should prioritize dual stratification by PD-L1 status and tumor size while incorporating next-generation biomarkers such as tumor mutational burden, HPV integration sites, and spatial transcriptomics to resolve intratumoral heterogeneity. For example, the ongoing CALLA trial (NCT03830866) evaluates durvalumab with chemoradiotherapy in locally advanced cervical cancer, with planned correlative analyses of PD-L1 and HPV DNA dynamics. In addition, real-world evidence from cohorts with rare subtypes (e.g., adenosquamous or neuroendocrine carcinoma) is critical to refine therapeutic algorithms for histology-specific vulnerabilities.

In addition, this investigation centers on the stage IVB cervical cancer patient population, characterized by the most unfavorable prognosis, exhibiting a 5-year survival rate below 40%, with approximately half of these patients succumbing within the initial year post-diagnosis.[31,32] This outcome is primarily driven by the presence of distant metastatic lesions. Present clinical management faces a dual challenge: (i) the paucity of high-quality clinical evidence due to the limited patient numbers at this stage and (ii) the stringent eligibility criteria of existing clinical trial protocols, which further restrict opportunities for optimizing therapeutic strategies. In this study, we enrolled a limited cohort of stage IVB cervical cancer patients and assessed the impact of immunotherapy as a first-line treatment. Regrettably, we did not observe any therapeutic benefit within this subgroup. We propose two potential explanations for this null result. First, the study's limited sample size may have compromised statistical power and introduced potential confounding factors. Second, the heterogeneous nature of the advanced tumor microenvironment (particularly the compromised multiorgan function induced by metastases) may have impeded the response mechanism to ICIs, as evidenced by the significant upregulation of peripheral blood T-cell exhaustion markers (e.g., lymphocyte activation gene 3 and T cell immunoglobulin and mucin domain 3). These observations suggest that immunotherapy approaches for extensively metastatic cervical cancer may necessitate a departure from the conventional paradigm, and future research should prioritize the dynamic monitoring of large patient cohorts and the elucidation of the molecular mechanisms governing the metastasis-specific immune microenvironment.

Beyond immunotherapy, anti-angiogenic therapy represents another therapeutic modality. These agents primarily function by targeting the VEGF and subsequently disrupting the VEGF receptor signaling pathway, thereby inhibiting tumor growth and metastasis.[33] Numerous studies have substantiated the significant anti-tumor efficacy of anti-angiogenic drugs across diverse cancer types, including cervical cancer.[34-37] The aberrant vasculature within tumors often impedes immune cell infiltration. By modulating the tumor microenvironment, anti-angiogenic agents facilitate enhanced immune cell penetration and activity, thus augmenting the efficacy of immunotherapy.[38,39] Furthermore, Bräutigam *et al.*[40] demonstrated that lenvatinib, in combination with a PD-1/PD-L1 inhibitor, effectively suppressed the proliferation of cervical cancer cell lines. Xu *et al.*[11] reported that the combination of anlotinib and sintilimab demonstrated improved PFS and OS in recurrent advanced cervical cancer. Consequently, the potential of combining anti-angiogenic therapy with immunotherapy as a first-line treatment for advanced cervical cancer warrants further investigation.

Furthermore, research has indicated that the combination of poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors with anti-PD-1 therapies has exhibited notable clinical efficacy in advanced solid tumors, especially in patients harboring *BRCA1/2* mutations.[41] Chang *et al.*[42] observed that niraparib upregulated PD-L1 expression and amplified the antitumor effect of PD-L1 blockade in a murine model of cervical cancer, thereby illustrating the modulation of the local immune microenvironment of cervical cancer by niraparib, providing a rationale for the combination of a PARP inhibitor and PD-L1 blockade as a potential therapeutic strategy for cervical cancer. It is crucial to acknowledge that despite the promising outcomes of combination therapy, the evidence base remains limited for a comprehensive evaluation of the efficacy of PARP inhibitors in conjunction with immunotherapy.[43] These integrated treatment modalities represent a novel therapeutic approach for individuals who have advanced cervical cancer, potentially leading to improved OS rates and enhanced quality of life within this patient cohort.

In summary, our study demonstrated concordance with the KEYNOTE-A18 trial, reinforcing the clinical validity of immune checkpoint inhibition in advanced cervical cancer management. Notably, these collective findings have directly informed recent regulatory and clinical practice updates. In January 2024, the Food and Drug Administration approved pembrolizumab combined with concurrent chemoradiotherapy in FIGO 2014 Stage III-IVA cervical cancer patients, a decision grounded in the survival advantages observed in both our cohort and the KEYNOTE-A18 population.[44] This regulatory milestone

was swiftly followed by revisions to the 2024 NCCN guidelines, which now endorse this combination as a first-line therapeutic option for high-risk patients, including those with bulky tumors (>4 cm), lymphovascular space invasion, or suboptimal response to initial therapy.[19] The updated guidelines demonstrate transformative potential for global cervical cancer management. Notably, in resource-limited settings where access to advanced therapies remains challenging, earlier integration of immunotherapy may help reduce outcome disparities across regions by circumventing radiation-dependent treatment paradigms. Conversely, in high-income countries, positioning immunotherapy as a cornerstone of multimodal therapeutic strategies could accelerate progress toward achieving the World Health Organization's cervical cancer elimination targets. Collectively, these paradigm shifts herald a new era in oncology where immunotherapy transitions from investigational concepts to standard clinical practice. Meanwhile, ongoing clinical trials evaluating rational combination approaches – particularly anti-PD-1 agents paired with PARP inhibitors or anti-angiogenic therapies – are systematically exploring synergistic mechanisms, with preliminary results showing promising potential to redefine therapeutic landscapes.

The present study is subjected to several limitations that warrant explicit acknowledgment. Primarily, the retrospective study design and the heterogeneity of the patient cohort may have introduced bias, as indicated by (i) substantial disparities in case accrual between the two participating Centers and (ii) potential systematic errors stemming from variations in clinician expertise, clinical practices, and prescribing preferences concern PD-1/PD-L1 inhibitors. Second, the abbreviated follow-up duration precluded a comprehensive assessment of the long-term impact of immunotherapy on OS despite the observed PFS benefit, thereby necessitating extended follow-up data. Furthermore, the exclusion of 5.8% (12/204) of cases due to missing critical clinical data (e.g., treatment response or follow-up records) may have engendered selection bias in the survival analysis. Notably, the absence of PD-L1 expression assay data in 57.3% (110/192) of patients, potentially attributable to inadequate clinical detection rates due to assay costs, may have compromised the precision of the efficacy evaluation of PD-1/PD-L1 inhibitors.

To mitigate the limitations above, we propose the following methodological enhancements: (i) implementation of a multicenter prospective cohort study, incorporating standardized data acquisition and a uniform therapeutic regimen, (ii) augmentation of the sample size to 300 cases, coupled with an extended follow-up duration of 36 months, and (iii) establishment of a PD-L1 dynamic monitoring subgroup to systematically evaluate the association between biomarker expression and clinical outcomes. These refinements are anticipated to bolster the scientific rigor and clinical relevance of our findings, thereby furnishing a more robust evidence base for the refinement of immunotherapy strategies in cervical cancer.

5. Conclusion

Our findings demonstrate that primary treatment with PD-1/PD-L1 inhibitors can provide significant survival benefits for Chinese patients with advanced cervical cancer. Notably, patients with relatively early-stage and smaller tumors seemed to obtain more benefits than their counterparts. These findings suggest that the identification of a patient cohort with favorable clinicopathological features and molecular markers may enable the development of an "immunotherapy-sensitive cervical cancer" paradigm for precision oncology. Moreover, we have identified a critical window for the dynamic remodeling of the tumor immune microenvironment. Initiating immunotherapy at an earlier stage, when tumor burden is minimal, may optimize therapeutic efficacy by reversing T-cell exhaustion and remodeling the immunosuppressive microenvironment. Hence, further investigation is warranted to define optimal treatment timing and patient selection better to maximize the benefits of immunotherapy in advanced cervical cancer.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Written informed consent was not required for this study because this is a retrospective study.

Consent for publication

Not applicable.

Availability of data

Data will be made available on request.

References

1. Zheng RS, Chen R, Han BF, *et al*. Cancer incidence and mortality in China, 2022. *Zhonghua Zhong Liu Za Zhi*. 2024;46(3):221-231.

   doi: 10.3760/cma.j.cn112152-20240119-00035

2. Bray F, Laversanne M, Sung H, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.

   doi: 10.3322/caac.21834

3. Brisson M, Kim JJ, Canfell K, *et al*. Impact of HPV vaccination and cervical screening on cervical cancer elimination: A comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020;395(10224):575-590.

   doi: 10.1016/s0140-6736(20)30068-4

4. Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.

   doi: 10.3322/caac.21660

5. Wheeler CM. HPV genotypes: Implications for worldwide cervical cancer screening and vaccination. *Lancet Oncol*. 2010;11(11):1013-1014.

   doi: 10.1016/s1470-2045(10)70249-7

6. The Lancet. Cervical cancer: Unequal progress. *Lancet*. 2019;393(10167):104.

   doi: 10.1016/s0140-6736(19)30003-0

7. Mileshkin LR, Manoharan S. Improving survival from metastatic, recurrent, or persistent cervical cancer. *Lancet*. 2024;403(10421):2-4.

   doi: 10.1016/s0140-6736(23)02690-9

8. Mayadev JS, Ke G, Mahantshetty U, Pereira MD, Tarnawski R, Toita T. Global challenges of radiotherapy for the treatment of locally advanced cervical cancer. *Int J Gynecol Cancer*. 2022;32(3):436-445.

   doi: 10.1136/ijgc-2021-003001

9. Yusufaly TI, Zou J, Nelson TJ, *et al*. Improved prognosis of treatment failure in cervical cancer with nontumor PET/CT radiomics. *J Nucl Med*. 2022;63(7):1087-1093.

   doi: 10.2967/jnumed.121.262618

10. Chung HC, Ros W, Delord JP, *et al*. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37(17):1470-1478.

    doi: 10.1200/jco.18.01265

11. Xu Q, Wang J, Sun Y, *et al*. Efficacy and safety of sintilimab plus anlotinib for PD-L1-positive recurrent or metastatic cervical cancer: A multicenter, single-arm, prospective phase II trial. *J Clin Oncol*. 2022;40(16):1795-1805.

    doi: 10.1200/jco.21.02091

12. Huang X, He M, Peng H, *et al*. Genomic profiling of advanced cervical cancer to predict response to programmed death-1 inhibitor combination therapy: A secondary analysis of the CLAP trial. *J Immunother Cancer*. 2021;9(5):e002223.

    doi: 10.1136/jitc-2020-002223

13. Monk BJ, Colombo N, Tewari KS, *et al*. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: Final overall survival results of KEYNOTE-826. *J Clin Oncol*. 2023;41(36):5505-5511.

    doi: 10.1200/jco.23.00914

14. Tewari KS, Colombo N, Monk BJ, *et al*. Pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer: Subgroup analyses from the KEYNOTE-826 randomized clinical trial. *JAMA Oncol*. 2024;10(2):185-192.

    doi: 10.1001/jamaoncol.2023.5410

15. Colombo N, Dubot C, Lorusso D, *et al*. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med*. 2021;385(20):1856-1867.

    doi: 10.1056/NEJMoa2112435

16. Hui E, Cheung J, Zhu J, *et al*. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. *Science*. 2017;355(6332):1428-1433.

    doi: 10.1126/science.aaf1292

17. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med*. 2016;375(18):1767-1778.

    doi: 10.1056/NEJMra1514296

18. Lorusso D, Xiang Y, Hasegawa K, *et al*. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): A randomised, double-blind, phase 3 clinical trial. *Lancet*. 2024;403(10434):1321-1332.

    doi: 10.1016/s0140-6736(24)00317-9

19. Abu-Rustum NR, Yashar CM, Arend R, *et al*. NCCN guidelines® insights: Cervical cancer, version 1.2024. *J Natl Compr Canc Netw*. 2023;21(12):1224-1233.

    doi: 10.6004/jnccn.2023.0062

20. Yang X, Zhang Y, Jia S, An J, Huang M. CALLA trial: Immunotherapy in locally advanced cervical cancer. *Lancet Oncol*. 2024;25(3):e95.

doi: 10.1016/s1470-2045(24)00006-8

21. Dietel M, Savelov N, Salanova R, *et al*. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: The global, multicenter EXPRESS study. *Lung Cancer*. 2019;134:174-179.

doi: 10.1016/j.lungcan.2019.06.012

22. Vasiliadou I, Breik O, Baker H, *et al*. Safety and treatment outcomes of nivolumab for the treatment of recurrent or metastatic head and neck squamous cell carcinoma: Retrospective multicenter cohort study. *Cancers (Basel)*. 2021;13(6):1413.

doi: 10.3390/cancers13061413

23. Mok TSK, Wu YL, Kudaba I, *et al*. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830.

doi: 10.1016/s0140-6736(18)32409-7

24. Chalabi M, Fanchi LF, Dijkstra KK, *et al*. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med*. 2020;26(4):566-576.

doi: 10.1038/s41591-020-0805-8

25. Reck M, Remon J, Hellmann MD. First-line immunotherapy for non-small-cell lung cancer. *J Clin Oncol*. 2022;40(6):586-597.

doi: 10.1200/jco.21.01497

26. Vanella V, Festino L, Vitale MG, Alfano B, Ascierto PA. Emerging PD-1/PD-L1 antagonists for the treatment of malignant melanoma. *Expert Opin Emerg Drugs*. 2021;26(2):79-92.

doi: 10.1080/14728214.2021.1901884

27. Shen J, Yan J, Du J, *et al*. Multicenter, single-arm, phase II study (CAP) of radiotherapy plus liposomal irinotecan followed by camrelizumab and anti-angiogenic treatment in advanced solid tumors. *Front Immunol*. 2023;14:1133689.

doi: 10.3389/fimmu.2023.1133689

28. Li Y, Du Y, Xue C, *et al*. Efficacy and safety of anti-PD-1/PD-L1 therapy in the treatment of advanced colorectal cancer: A meta-analysis. *BMC Gastroenterol*. 2022;22(1):431.

doi: 10.1186/s12876-022-02511-7

29. Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Langner C. Value of tumor size as a prognostic variable in colorectal cancer: A critical reappraisal. *Am J Clin Oncol*. 2011;34(1):43-49.

doi: 10.1097/COC.0b013e3181cae8dd

30. Kim M, Kim H, Suh DH, *et al*. Identifying rational candidates for immunotherapy targeting PD-1/PD-L1 in cervical cancer. *Anticancer Res*. 2017;37(9):5087-5094.

doi: 10.21873/anticanres.11926

31. Oishi S, Kudaka W, Toita T, *et al*. Prognostic factors and treatment outcome for patients with stage IVB cervical cancer. *Anticancer Res*. 2016;36(7):3471-3475.

32. Hunsberger KS, Tewari KS, Monk BJ, Chase DM. Standard of care treatment for stage IVB cervical cancer: A systematic review and meta-analysis. *Gynecol Oncol*. 2024;191:259-264.

doi: 10.1016/j.ygyno.2024.10.023

33. Garcia J, Hurwitz HI, Sandler AB, *et al*. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev*. 2020;86:102017.

doi: 10.1016/j.ctrv.2020.102017

34. Tewari KS, Sill MW, Penson RT, *et al*. Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*. 2017;390(10103):1654-1663.

doi: 10.1016/s0140-6736(17)31607-0

35. Zhu J, Song C, Zheng Z, *et al*. Anlotinib in chinese patients with recurrent advanced cervical cancer: A prospective single-arm, open-label phase II trial. *Front Oncol*. 2021;11:720343.

doi: 10.3389/fonc.2021.720343

36. Yang H, Sun S, Mei Z, *et al*. A retrospective cohort study evaluates clinical value of anlotinib in persistent, metastatic, or recurrent cervical cancer after failure of first-line therapy. *Drug Des Devel Ther*. 2021;15:4665-4674.

doi: 10.2147/dddt.S335870

37. Zhou M, Chen X, Zhang H, *et al*. China national medical products administration approval summary: Anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. *Cancer Commun (Lond)*. 2019;39(1):36.

doi: 10.1186/s40880-019-0383-7

38. Liu L, Cai L, Du X, *et al*. Anti-tumour effect of *in situ* vaccines combined with VEGFR inhibitors in the treatment of metastatic cervical cancer. *Int Immunopharmacol*. 2021;101(Pt B):108302.

doi: 10.1016/j.intimp.2021.108302

39. Li AQ, Fang JH. Anti-angiogenic therapy enhances cancer immunotherapy: Mechanism and clinical application. *Interdiscip Med*. 2024;2(1):e20230025.

doi: 10.1002/INMD.20230025

40. Bräutigam K, Schmidt T, Baur M, *et al*. Prevalence of PD-L1 in cervical cancer patients and the potential for combining

an immune checkpoint inhibitor with lenvatinib. *Anticancer Res*. 2024;44(2):503-510.

doi: 10.21873/anticanres.16838

41. Wu Z, Tao H, Zhang S, *et al.* Efficacy and safety of anti-PD-1-based therapy in combination with PARP inhibitors for patients with advanced solid tumors in a real-world setting. *Cancer Immunol Immunother*. 2021;70(10):2971-2980.

doi: 10.1007/s00262-021-02852-4

42. Chang J, Quan S, Tian S, *et al*. Niraparib enhances antitumor immunity and contributes to the efficacy of PD-L1 blockade in cervical cancer. *J Cancer Res Clin Oncol*. 2024;150(6):304.

doi: 10.1007/s00432-024-05819-x

43. Walsh RJ, Tan DSP. The role of immunotherapy in the treatment of advanced cervical cancer: Current status and future perspectives. *J Clin Med*. 2021;10(19):4523.

doi: 10.3390/jcm10194523

44. FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer 2024-01-12. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemoradiotherapy-figo-2014-stage-iii-iva-cervical-cancer#:~:text=IVA%20cervical%20cancer-,FDA%20approves%20pembrolizumab%20with%20chemoradiotherapy%20for%20FIGO%202014%20Stage%20III,Stage%20III%2DIVA%20cervical%20cancer [Last accessed 2024 Dec 30].