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ORIGINAL RESEARCH

Outcomes and Safety of PD-1 Blockades Plus Anlotinib Regimen in Previously-Treated Metastatic Esophageal Squamous Cell Carcinoma: A Retrospective, Exploratory Study

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Objective: This retrospective study was to identify the outcomes and safety of anlotinib combined with PD-1 blockades in patients with metastatic esophageal squamous cell carcinoma (ESCC).

Methods: A retrospective analysis of 87 patients with histologically confirmed metastatic ESCC who received anlotinib plus PD-1 blockades as second-line or later therapy was performed. Efficacy endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS). Safety was assessed by the incidence of treatment-related adverse events (TRAEs), graded in the principle of CTCAE v5.0.

Results: Among 87 evaluable patients, no complete responses were observed, 19 subjects were partial response and 45 achieved stable disease, while 18 had disease progression and 5 were not evaluable for response. Therefore, ORR of the 87 subjects was 21.8% (95% CI: 13.7–32.0%), and DCR was 73.6% (95% CI: 63.0–82.4%). Median DoR of the 19 responders was 6.6 months [95% confidence interval (CI): 2.3–10.9 months]. Median PFS and OS for the cohort were 5.5 months (95% CI: 4.1–6.9 months) and 11.5 months (95% CI: 7.1–15.9), respectively, the 12-month and 24-month OS rates were 49.0% and 27.6%, respectively. Notably, patients with ESCC who had received prior immunotherapy showed better OS outcomes than those without prior immunotherapy exposure. Toxicity profile analysis demonstrated that the incidence of TRAEs with all grades was 92.0%. Grade ≥3 TRAEs occurred in 50.6% of the subjects. Common TRAEs included fatigue (60.9%), hypertension (52.9%), and nausea and vomiting (47.1%), most of which were grade 1–2 and manageable with supportive measures.

Discussion: PD-1 blockades plus anlotinib demonstrated encouraging effectiveness and manageable toxicity in metastatic ESCC, achieving notable disease control and survival benefits compared with historical standards. Future prospective study is needed to confirm the therapeutic benefits and identify the optimal patient selection criteria for this promising combination therapy.

Keywords: ESCC, anlotinib, PD-1 blockades, outcomes, safety

Introduction

Esophageal cancer is characterized as an aggressive malignancy with a poor prognosis. It was estimated that there were approximately 604,000 new cases and 544,000 deaths of esophageal cancer in 2020 worldwide.[1] In China alone, approximately 224,000 new esophageal cancer cases and 187,000 deaths occurred in 2022.[2] Notably, the majority of esophageal cancers in China seemed to be esophageal squamous cell carcinoma (ESCC).[3] Despite multimodal treatment approaches, the 5-year survival for metastatic ESCC remained dismal, and most patients eventually experienced disease progression after first-line therapy.[4] Historically, systemic chemotherapy was deemed to be the cornerstone of front-line therapy for ESCC, yet yielded modest outcomes with response rates around 30%-40%, median progression-free survival (PFS) of only about 4–6 months, and median overall survival (OS) of approximately <12 months.[5] Recently,

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pembrolizumab and nivolumab demonstrated improved survival in previously treated ESCC, establishing approval in second-line therapies.[6] In the KEYNOTE-181 trial, pembrolizumab significantly prolonged median OS (8.2 vs. 7.1 months) among patients with ESCC compared to chemotherapy.[7] Similarly, the ATTRACTION-3 trial also showed nivolumab improved median OS in platinum-refractory ESCC.[8] As a result, immune checkpoint inhibitors (ICIs) were increasingly integrated into earlier lines of ESCC treatment, including first-line combinations with chemotherapy (e.g. pembrolizumab in KEYNOTE-590, nivolumab in CheckMate-648, camrelizumab in ESCORT-1st, Toripalimab in JUPITER-06 and so on) for advanced disease.[9] However, considerable patients eventually progressed after ICIs-based therapy, underscoring an urgent need for effective later-line options especially previously ICIs-treated.[10]

Angiogenesis played a crucial role in ESCC progression and related with an immunosuppressive tumor microenvironment. Vascular endothelial growth factor (VEGF) overexpression in ESCC might promote tumor angiogenesis by impairing T-cell trafficking and function in the tumor bed.[11] Anlotinib demonstrated promising efficacy in different solid tumors and was approved in China for refractory NSCLC with emerging evidence of activity in ESCC. In chemotherapy-refractory ESCC (beyond first-line), anlotinib achieved disease control in a substantial proportion of patients.[12] For instance, anlotinib in ESCC after chemotherapy failure reported an objective response rate (ORR) of only 7.3% with a median PFS of 3.0 months in a Phase II trial.[13] These results indicated that while antiangiogenic monotherapy might stabilize disease in some patients, durable tumor shrinkage is uncommon. Moreover, antiangiogenic therapy in ESCC carried risks such as hemorrhage or fistula formation, especially in tumors with local invasion of vessels or mediastinal structures.[14] Thus, there had been interest in leveraging angiogenesis inhibition in combination strategies to enhance efficacy without excessive toxicity.

ICIs targeting PD-1/PD-L1 transformed the treatment landscape of multiple solid tumors, leading to durable responses and improved survival in a subset of patients. However, the overall efficacy of ICIs was constrained by primary and acquired resistance, and genetic and micro-environmental factors might limit the efficacy of anti-PD-1/PD-L1 therapy.[15] These limitations underscored the need for rational combination strategies that might enhance antitumor immunity and expand the population deriving benefit from ICIs, particularly in aggressive malignancies such as ESCC. Preclinical and clinical evidence suggested a synergistic benefit of combining ICIs with antiangiogenic agents. Anti-VEGF therapies might normalize the abnormal tumor vasculature, reduce hypoxia and interstitial pressure, thereby promoting immune cell infiltration into tumors.[16] These effects might potentially alleviate resistance to immunotherapy, and enhancing ICIs response. In support of this rationale, combining ICIs with antiangiogenic TKIs resulted in improved outcomes in multiple cancers. Emerging studies explored this approach for ESCC treatment. Several retrospective analyses and early-phase trials reported that anlotinib plus ICIs might yield a modest but notable benefit in some patients, particularly in those who progressed after prior treatments including immunotherapy.[17] Noteworthily, one recent phase II trial of 46 ESCC patients as first-line therapy with anlotinib plus PD-L1 blockade achieved potential clinical outcomes, highlighting promising prospect with chemo-free combination in ESCC.[18] In a recent Chinese retrospective study of ICIs-experienced ESCC patients, rechallenge with anlotinib plus PD-1 blockade resulted in a median OS of 11.1 months.[19] These early findings highlighted that combining anlotinib with PD-1 blockades might recapture anti-tumor activity in later-line ESCC, even after initial immunotherapy or chemotherapy failure. However, most of these studies were retrospective in nature and involved relatively small cohorts or institutions, and prospective data remained limited.

Given the growing administration of ICIs in earlier lines and the lack of established standard treatments beyond second-line treatment for ESCC, real-world evidence of novel combinations was critical. In this context, we conducted an exploratory study to evaluate the effectiveness and tolerability of anlotinib plus PD-1 blockades as later-line therapy for metastatic ESCC.

Methods

Eligibility Criteria in This Study

This study was designed as a retrospective observational cohort of consecutive patients treated in routine practice, not a prospective clinical trial, patients with advanced ESCC treated with a combination of anlotinib plus PD-1 blockades were included retrospectively. Available subjects hospitalized at the First Affiliated Hospital of Zhengzhou University between

January 2019 and December 2024 were selected consecutively. Inclusion criteria were: (1) pathologically diagnosed ESCC with metastatic disease; (2) Eastern Cooperative Oncology Group (ECOG) performance status ≤2 score; (3) age of ≥18 years; (4) had been treated with at least one systemic therapy (eg, platinum-based chemotherapy with or without prior immunotherapy) and subsequently showed disease progression or intolerance; (5) received therapy of anlotinib plus blockades after previous treatment in clinical practice; (6) adequate organ function (hematologic, hepatic, renal) as per clinical assessment. Exclusion criteria included: (1) histologically confirmed adenocarcinoma; (2) concomitant with more than one cancer or life-threatening disease; (3) presence of active brain metastases; (4) missing medical records to evaluate patients' baseline characteristics and outcomes. All eligible patients were identified using the institutional oncology database. Flowchart of this study was exhibited in Figure 1. Finally, 87 patients treated with anlotinib + PD-1 blockades participated in this study retrospectively.

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University (approved NO: 2023-KY-0910), which covered the full retrospective data collection from January 2019 to December 2024. Because this study was designed retrospectively, informed consent was waived for patients in line with the principles of the Declaration of Helsinki.

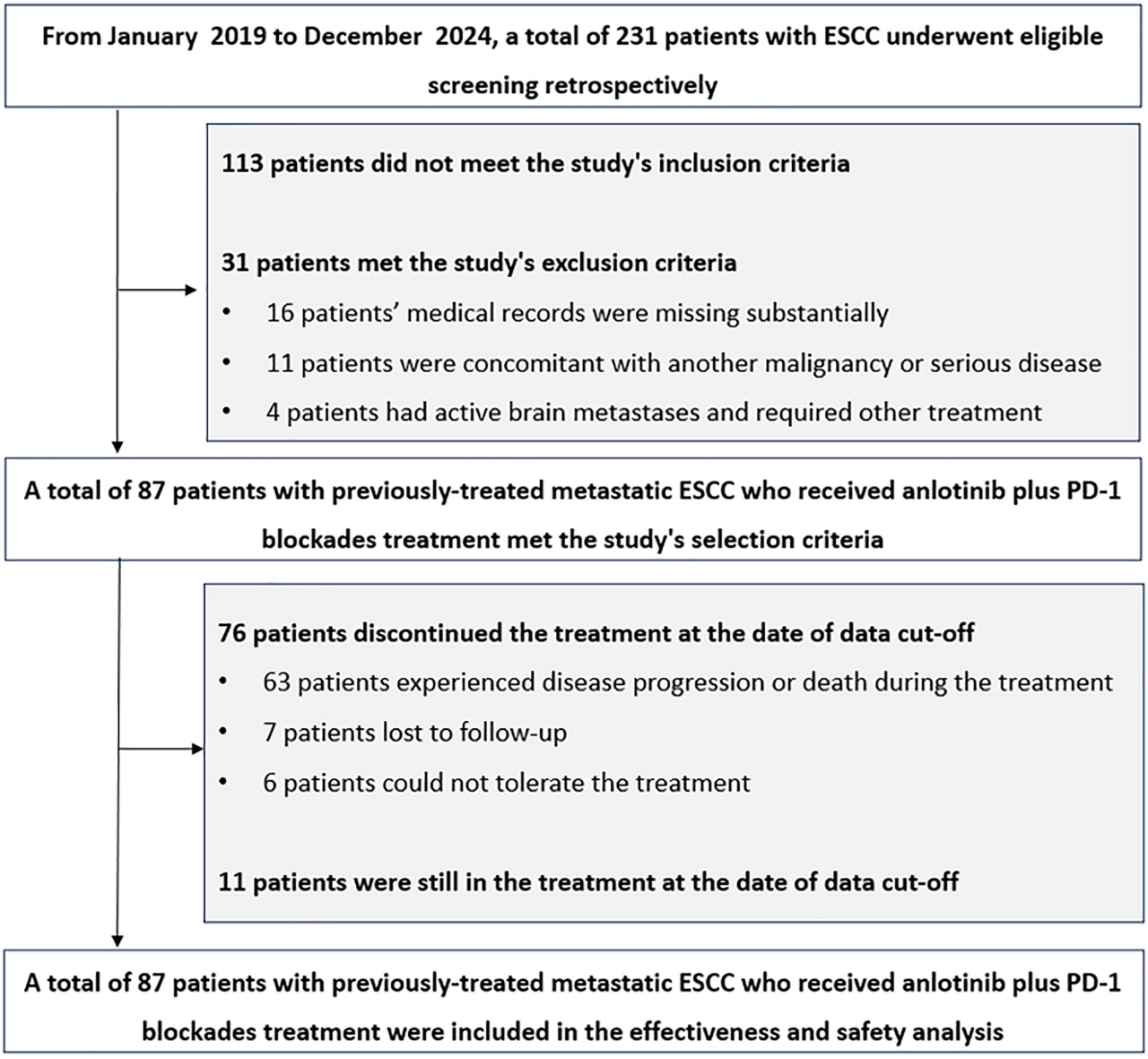

Figure 1 Study profile of this retrospective study.

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Therapeutic Regimens

Anlotinib plus PD-1 blockades therapy was administered per institutional practice guidelines with the choice of PD-1 agent guided by drug availability or prior exposure rather than arbitrary preference. Anlotinib was administered initially at 10 mg or 12 mg once daily 14 days on the drug followed by 7 days off, constituting a 21-day cycle. Dose adjustments were permitted depending on tolerance (eg, for grade ≥3 toxicity, the dose could be reduced or treatment interrupted). The PD-1 blockade was administered as an intravenous infusion at standard dosing intervals. PD-1 blockades used in this cohort included tislelizumab (administered 200 mg IV, every 3 weeks), camrelizumab (200 mg IV, every 3 weeks), and pembrolizumab (200 mg IV, every 3 weeks), which was guided by drug availability or prior exposure. For patients who had previously received ICIs, rechallenge was defined as initiation of anlotinib plus a PD-1 blockade after documented disease progression or relapse following prior ICIs–based therapy with recovery of any prior immune-related adverse events to grade ≤1. The choice of the rechallenge PD-1 blockade (same agent vs an alternative PD-1 blockade) was based on prior tolerability and drug availability, rechallenge was performed either with the same agent if the prior ICI was discontinued >3 months ago or with an alternative PD-1 blockade in some cases (physician's discretion). Among 66 rechallenged patients (75.9% of the cohort), the median treatment-free interval between the last dose of prior ICIs and the start of anlotinib plus PD-1 blockades was 6.7 months (interquartile range: 3.3–9.2 months). Both anlotinib and PD-1 blockades were continued until treatment failure or patient decision was made. Patients received supportive care (eg, proton pump inhibitors and nutritional support) as needed. The dose delays or discontinuations were recorded and collected in detail.

Assessments and Endpoints

Baseline evaluation included history, physical examination, laboratory tests, and radiological assessment (CT or MRI) of the chest, abdomen, and other disease sites. In routine clinical practice, radiologic tumor assessments were generally performed at approximately every 6–8 weeks, or earlier when clinically indicated if applicable. Treatment response and disease progression were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and the same criteria were applied consistently throughout the study. Radiological outcomes were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In this retrospective study, all radiological scans were originally read by board-certified radiologists as part of routine care, and an independent radiographic review was performed by two oncologists to confirm response categorizations per RECIST 1.1 when sufficient imaging data were available.

The primary analysis focused on OS. ORR, DCR, PFS and OS were defined in line with the previous study.[20] Additionally, we assessed the DoR in responders, measured from first documented response to progression or death.[18] Data cutoff date was July 5, 2025.

The safety analysis included the incidence of treatment-related adverse events (TRAEs) using CTCAE v5.0. Adverse event data were systematically collected from clinical notes, laboratory results, and hospitalization records. Particular attention was given to class-specific toxicities, such as hypertension, hand-foot syndrome, proteinuria (from anlotinib), and immune-related adverse events (irAEs, such as pneumonitis, hepatitis, and endocrinopathies from PD-1 blockades). An adverse event was considered treatment-related if it was documented as such in the medical assessment or if a causal link to either anlotinib or PD-1 blockades was medically reasonable and no alternate cause was evident.

Statistical Analysis

Data were analyzed using SPSS (version 25.0) and Stata (version 14.0) software. Descriptive statistics were used to summarize patients' baseline characteristics, tumor responses and safety profiles. ORR and DCR were calculated with two-sided 95% confidence intervals (CIs). PFS, OS and DOR were depicted using the Kaplan–Meier method in Stata. We performed a subgroup exploratory analysis of OS based on select factors such as ECOG performance status (0 vs ≥1 score), prior immunotherapy status (yes vs no), and number of prior lines (1 vs ≥2) to identify potential prognostic or predictive markers. Differences in PFS/OS between subgroups were examined using Log rank tests, and multivariate Cox regression was introduced. $P<0.05$ was considered suggestive.

Results

Clinical Characteristics

A total of 87 patients with metastatic ESCC met the inclusion criteria and were analyzed. Clinical characteristics of the study cohort were presented in Table 1. Median age was 63 years (range: 23–82 years) with the majority being male (70.1%), reflecting a higher incidence of ESCC in males.

At the start of treatment, all patients had ESCC with the most common primary site being the middle esophagus (43.7%). Regarding treatment line, 42.5% of patients received the study regimen as second-line therapy, whereas 57.5% received it in the third-line setting, indicating a heavily pretreated population. Interestingly, 66 patients (75.9%) previously received immunotherapy in an earlier line. Most patients had the number of metastatic sites of ≤3 (71.3%).

Table 1 Demographic and Clinical Characteristics

Characteristics	Total (N=87)	Percentage
Age (years)		
Median (range)	63 (23–82)	
Gender		
Male	61	70.1%
Female	26	29.9%
ECOG performance status score		
0	30	34.5%
1–2	57	65.5%
Primary site		
Upper	19	21.8%
Middle	38	43.7%
Lower	30	34.5%
Histology		
Esophageal squamous cell carcinoma	87	100.0%
Previous surgical treatment		
Yes	42	48.3%
No	45	51.7%
Lines of previous treatment		
First-line	37	42.5%
Second-line	28	32.2%
Third-line or further-line	22	25.3%
Previous systemic therapy exposure		
Immune checkpoint inhibitors (ICIs)	66	75.9%
Taxane	57	65.5%
Platinum-based chemotherapy	41	47.1%
Targeted drugs	22	25.3%
Number of metastatic sites		
≤3	62	71.3%
>3	25	28.7%
Combination of radiation therapy		
Yes	11	12.6%
No	76	87.4%
Initial dosage of anlotinib (mg)		
12	61	70.1%
10	26	29.9%
PD-1 blockades		
Tislelizumab	39	44.8%
Camrelizumab	31	35.6%
Pembrolizumab	17	19.5%

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Most patients received an initial dose of anlotinib (12 mg, 70.1%). Tislelizumab was administered in 39 patients (44.8%), camrelizumab in 31 patients (35.6%), and pembrolizumab in 17 patients (19.5%).

The median combination therapy treatment duration was 4.7 months (range: 0.7–22.5 months). By the cutoff date, 11 patients (12.6%) remained on treatment. Of the 76 patients who discontinued, 63 stopped treatment due to confirmed disease progression (or cancer-related death), 7 patients were out of contact, and 6 stopped due to adverse events or intolerance. No deaths were attributed directly to treatment toxicity.

Tumor Response

Radiologic evaluation of tumor response was available for 82 patients. Among the evaluable subjects, 19 patients were PR as their best response, yielding an ORR of 21.8% (95% CI: 13.7–32.0%). An additional 45 patients developed SD. DCR was 73.6% (95% CI: 63.0–82.4%). The remaining 18 patients showed a documented progression as the best response. Waterfall plot regarding therapeutic response was shown in Figure 2. A certain number of patients could benefit from anlotinib plus PD-1 blockades, and their target lesions shrank significantly. Mean shrinkage in the 82 patients was −8.07%. Interestingly, a 53-year-old male patient who progressed after previous paclitaxel and cisplatin plus camrelizumab treatment. Pembrolizumab combined with anlotinib was used after four cycles, the patient's target lesions at the esophageal site demonstrated an anticipated reduction of over 50%, and the painful symptoms associated with swallowing were greatly relieved. Radiological comparison before and after treatment was illustrated in Figure 3, indicating promising benefit of combination treatment.

Among the 19 responders (PRs), the median time to initial response was 1.6 months (approximately after 2 cycles). As shown in Figure 4, the median DoR for the 19 responders was 6.6 months (95% CI: 3.4–10.4 months). And the 12-month DoR rate was 36.8% (95% CI: 16.5–57.5%).

Survival Outcomes

By the data cutoff date (July 5, 2025), median follow-up duration was 9.5 months (range: 0.7–33.6 months). By the data cutoff, 69 progression-or-death events occurred (79.3% maturity for PFS analysis), and 59 death events occurred (67.8% maturity for OS analysis). As illustrated in Figure 5, the median PFS of the 87 subjects was 5.5 months (95% CI: 4.1–6.9 months). Additionally, the 12-month PFS rate was 28.6% (95% CI: 19.0–38.9%). Notably, approximately 19 patients (21.8%) were progression-free for 12 months, highlighting the tail of long-term PFS in some responders. Median PFS for

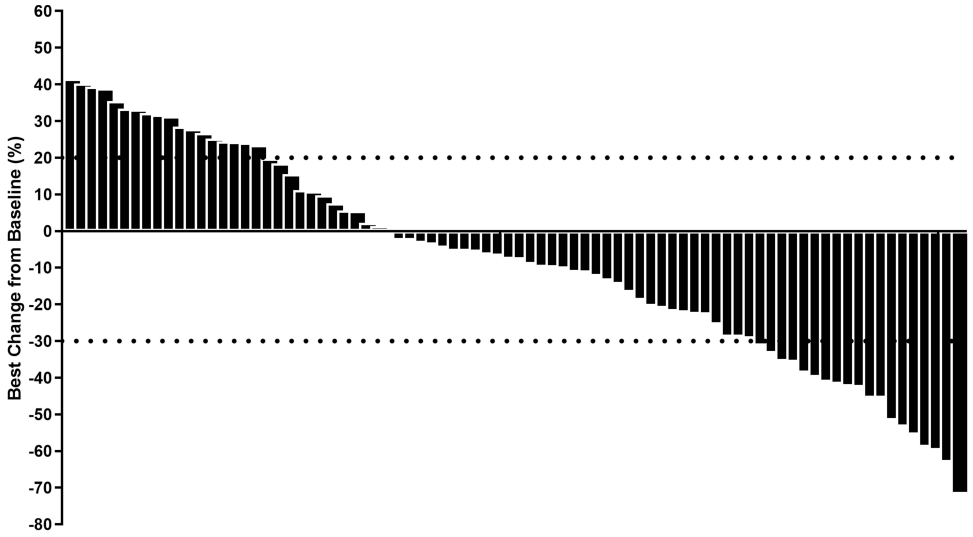

Figure 2 Waterfall plot regarding therapeutic response of 82 patients with ESCC who were treated with anlotinib plus PD-1 blockades.

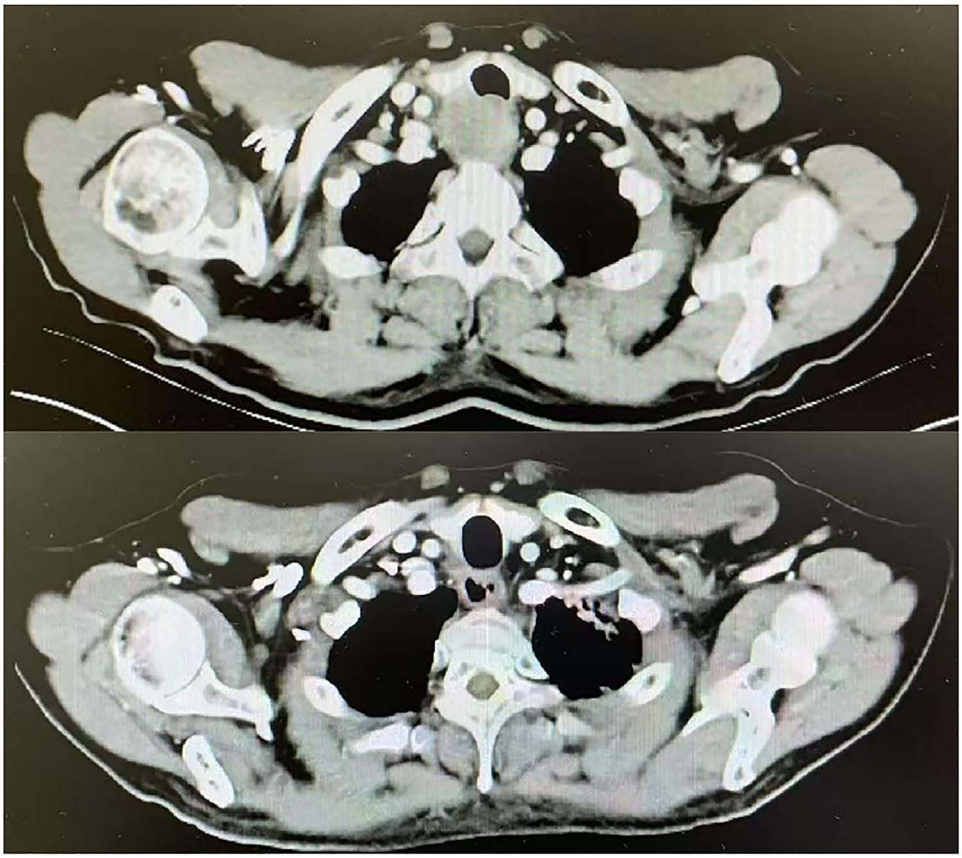

Figure 3 Radiological results of the changes for target lesions in esophagus of one subject before and after the administration of pembrolizumab combined with anlotinib.

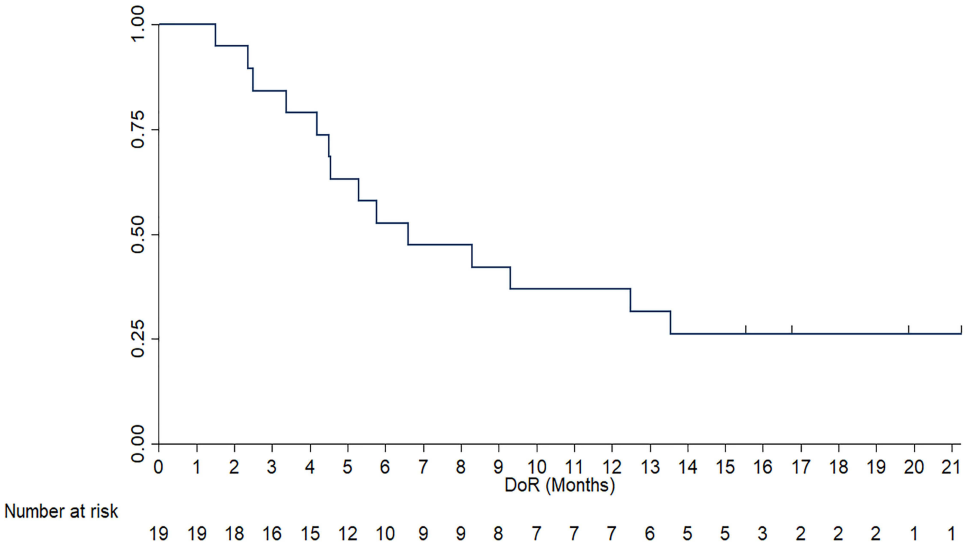

Figure 4 Duration of response survival curve of the 19 responders. Tick marks on the curve indicate censored observations. The median DoR was 6.6 months (95% CI: 3.4–10.4), and the 12-month DoR rate was 36.8% (95% CI: 16.5–57.5%). The numbers at risk at each time point are shown below the x-axis.

patients with ICIs-pretreated was 5.8 months (95% CI: 3.99–7.62) versus 4.5 months (95% CI: 2.91–6.09) for ICI-naïve patients, and the patients with ICIs-pretreatment showed a trend toward better PFS. However, no statistically significant difference was observed between the two groups (HR=0.72, *P*=0.224).

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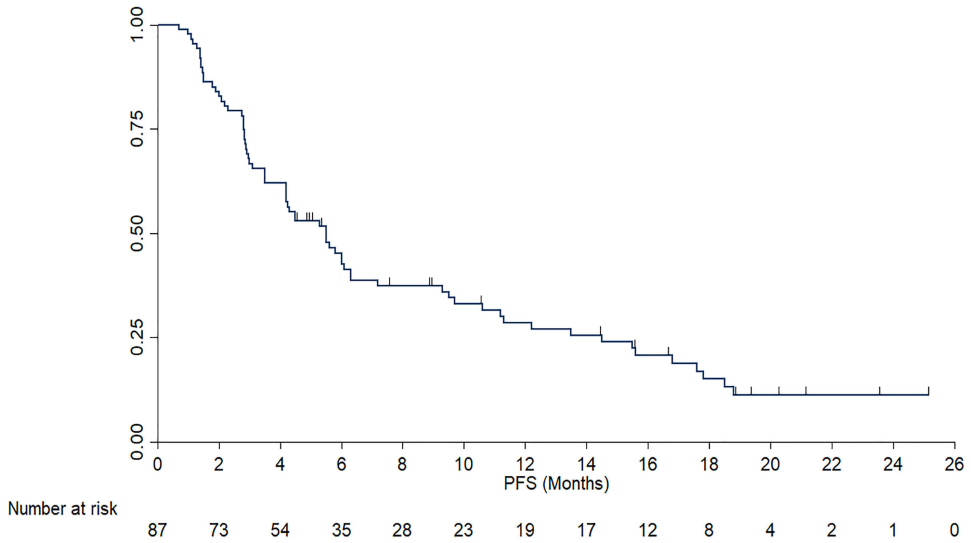

Figure 5 Progression-free survival curve of the 87 patients with ESCC who were treated with anlotinib plus PD-1 blockades. Tick marks on the curve indicate censored observations. The median PFS was 5.5 months (95% CI: 4.1–6.9). The 12-month and 24-month PFS rates were 28.6% (95% CI: 19.0–38.9%) and 11.3% (95% CI: 4.9–20.6%), respectively. The numbers at risk at each time point are shown below the x-axis.

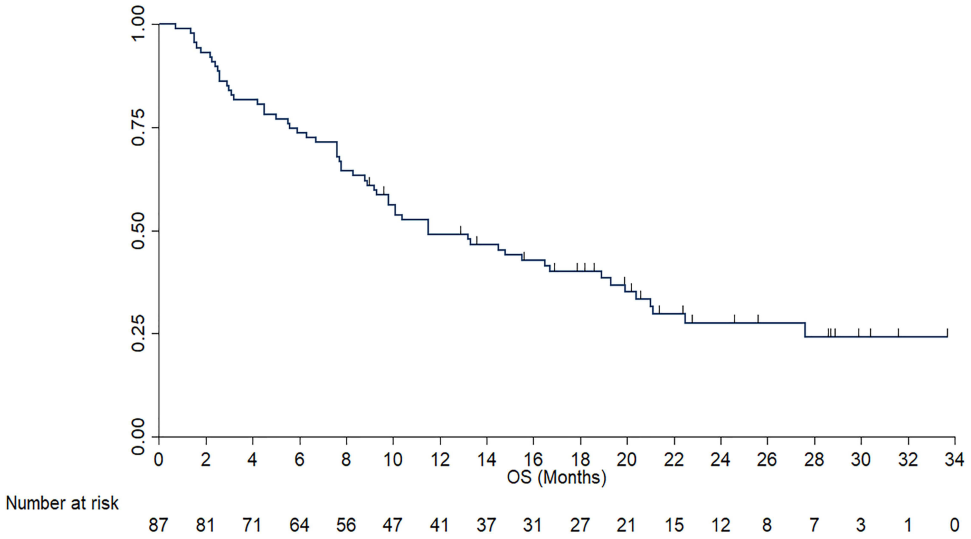

Figure 6 Overall survival curve of the 87 patients with ESCC who were treated with anlotinib plus PD-1 blockades. Tick marks on the curve indicate censored observations. The median OS was 11.5 months (95% CI: 7.1–15.9). The 12-month and 24-month OS rates were 49.0% (95% CI: 38.1–59.1%) and 27.6% (95% CI: 17.6–38.5%), respectively. The numbers at risk at each time point are shown below the x-axis.

Similarly, as exhibited in Figure 6, median OS of the 87 subjects was 11.5 months (95% CI: 7.1–15.9 months). Additionally, the 12-month OS and 24-month OS rates were 49.0% (95% CI: 38.1–59.1%) and 27.6% (95% CI: 17.6–38.5%), respectively.

Furthermore, we performed an exploratory subgroup analysis for OS in univariate and multivariate Cox analyses, which was presented in Table 2. The detailed subgroup comparison statistics, including hazard ratio (HR) and corresponding log-rank *P* values from univariate and multivariate Cox analyses, were also presented in Table 2. Noteworthily, univariate analysis suggested significant associations between OS and specific baseline characteristics: patients with ECOG performance status of 0 demonstrated significantly improved median OS (14.5 months, 95% CI: 9.7–19.3) compared with those who were 1–2 (median OS=9.3 months, HR=0.63, log-rank *P*=0.011). Additionally, patients with fewer metastatic sites (≤3) had a significantly longer median OS (13.3 months) than those with >3

Table 2 Cox Regression Between OS and Baseline Characteristics in Univariate and Multivariate Analysis

Baseline Characteristics	Median OS (95% CI)	HR (95% CI)	*P* (Univariate)	Multivariate Analysis	
				HR (95% CI)	*P*
Age (year)					
>63	10.4 (6.7–14.1)	1.09 (0.89–1.23)	0.638		
≤63	11.5 (7.5–15.5)				
Gender					
Male	10.1 (6.3–13.9)	1.11 (0.78–1.45)	0.417		
Female	13.2 (8.2–18.2)				
ECOG performance status					
0	14.5 (9.7–19.3)	0.63 (0.26–0.85)	0.011	0.65 (0.31–0.89)	0.019
1–2	9.3 (6.1–12.5)				
Primary site					
Upper	10.1 (7.2–13.0)	1.03 (0.77–1.92)	0.524		
Middle	11.5 (7.5–15.5)				
Lower	10.4 (6.9–13.9)				
Previous surgical treatment					
Yes	13.2 (7.3–19.1)	0.93 (0.55–1.47)	0.411		
No	10.4 (7.5–13.3)				
Lines of previous treatment					
First-line	13.2 (8.8–17.6)	0.91 (0.44–1.12)	0.218		
Second-line or further-line	10.1 (7.9–12.3)				
Previous exposure of immunotherapy					
Yes	13.3 (8.9–17.7)	0.68 (0.30–0.89)	0.023	0.70 (0.33–0.93)	0.031
No	9.2 (7.1–11.3)				
Number of metastatic sites					
≤3	13.3 (9.1–17.5)	0.68 (0.29–0.89)	0.019	0.69 (0.31–0.91)	0.025
>3	9.3 (7.1–11.5)				
Combination of radiation therapy					
Yes	13.2 (7.7–18.7)	0.95 (0.74–1.37)	0.432		
No	11.5 (7.4–15.6)				
Initial dosage of anlotinib (mg)					
12	13.2 (8.1–18.3)	0.98 (0.67–1.66)	0.518		
10	11.5 (7.4–15.6)				
PD-1 blockades					
Tislelizumab	11.5 (8.6–20.1)	1.03 (0.69–1.56)	0.553		
Camrelizumab	10.1 (7.8–12.4)				
Pembrolizumab	13.2 (8.9–17.5)				

metastatic sites (median OS: 9.3 months, HR=0.68, log-rank *P*=0.019). Interestingly, patients with previous exposure to immunotherapy were associated with a trend toward superior OS than those who had no exposure to immunotherapy (median OS: 13.3 vs 9.2 months, HR=0.68, log-rank *P*=0.023). As a result, these variables in univariate analysis were introduced in the multivariate Cox regression. After multivariate correction, ECOG performance status (HR=0.65, *P*=0.019), the number of metastatic sites (HR=0.69, *P*=0.025), and previous exposure to immunotherapy (HR=0.70, *P*=0.031) were still associated with OS independently. Interestingly, patients who received anlotinib plus PD-1 blockades as second-line had a median OS of 13.2 months, compared to 10.1 months for those treated in third-line or later (*P*=0.218). Median PFS was 6.1 months in second-line vs 5.0 months in ≥3rd line (*P*=0.311).

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Table 3 Toxicity Profile of the 87 Patients with Metastatic ESCC

Toxicity Profile	Total (N, %)	Grade 1–2 (N, %)	Grade ≥3 (N, %)
Treatment related adverse events	80 (92.0)		44 (50.6)
Fatigue	53 (60.9)	48 (55.2)	5 (5.7)
Hypertension	46 (52.9)	33 (38.0)	13 (14.9)
Nausea and vomiting	41 (47.1)	36 (41.4)	5 (5.7)
Anemia	38 (43.7)	35 (40.3)	3 (3.4)
Hand-foot Syndrome	33 (37.9)	27 (31.0)	6 (6.9)
Liver function abnormality	29 (33.3)	22 (25.3)	7 (8.0)
Hypothyroidism	25 (28.7)	23 (26.4)	2 (2.3)
Proteinuria	19 (21.8)	16 (18.4)	3 (3.4)
Pneumonia	18 (20.7)	14 (16.1)	4 (4.6)
Mucositis oral	12 (13.8)	11 (12.6)	1 (1.2)
Rash	9 (10.3)	9 (10.3)	0 (0.0)
Hemorrhage	5 (5.7)	5 (5.7)	0 (0.0)

Safety and Tolerability

All the 87 patients were included in the safety analysis. A summary of treatment-related adverse events (TRAEs) was exhibited in Table 3. Generally, TRAEs of any grade were observed in 80 patients (92.0%) and grade ≥3 TRAEs were recorded in 44 patients (50.6%).

Common TRAEs manifested as fatigue (60.9%), hypertension (52.9%), nausea and vomiting (47.1%), anemia (43.7%), hand-foot syndrome (37.9%), liver function abnormalities (33.3%), hypothyroidism (28.7%), proteinuria (21.8%), pneumonia (20.7%), oral mucositis (13.8%), rash (10.3%), and hemorrhage (5.7%). The most common grade ≥3 TRAEs were hypertension (14.9%), liver function abnormalities (8.0%), hand-foot syndrome (6.9%), fatigue (5.7%), nausea and vomiting (5.7%), pneumonia (4.6%), anemia (3.4%), proteinuria (3.4%), and mucositis (1.2%).

In this real-world setting, clinicians proactively managed toxicities with dose adjustments. Dose reductions of anlotinib were required in 14 patients (16.1%) due to toxicity (commonly hand-foot syndrome, hypertension or fatigue). The majority (83.9%) remained on the initial anlotinib dose throughout. The median duration of therapy was 4.7 months, which corresponded to approximately 6 cycles of treatment. The relative dose intensity of anlotinib was 90% on average across the cohort. PD-1 blockades dosing was generally maintained at full schedule: only 3 patients (3.4%) required any dose delay or hold due to immune-related adverse events, and no PD-1 dose reductions (fixed dosing) were necessary. From a safety perspective, no unexpected toxicities emerged from combination therapy. The profile was essentially the additive effect of each agent, with some overlapping toxicities, such as fatigue, possibly being enhanced. In the clinical notes, many patients reported that they maintained their performance status during disease control. Several patients with an initial symptomatic tumor burden (dysphagia and pain) showed improvement in symptoms, correlating with tumor response or stabilization.

Discussion

Effectiveness and tolerability of combining anlotinib with PD-1 blockades in subjects with metastatic ESCC that had progressed with prior therapies was explored in this study. Our results demonstrated that this chemo-free combination therapy showed clinical activity in this difficult-to-treat population in a later-line setting, consistent with emerging evidence from independent cohorts and early trials. Interestingly, ECOG performance status, previous exposure to immunotherapy and metastatic sites might act as independent variates for OS. Mechanistically, vascular normalization and relief of VEGF-driven immunosuppression might enhance T-cell trafficking and restore sensitivity to PD-1 blockade, providing a biologic rationale for the observed activity. Furthermore, the safety profile (hypertension, hand–foot syndrome, hypothyroidism and immune-related events, largely manageable) was in line with prior anlotinib monotherapy and anlotinib plus PD-1 blockades, reinforcing feasibility of this regimen in routine practice.

In this retrospective study, we found combination of anlotinib plus PD-1 blockade yielded encouraging efficacy outcomes in metastatic ESCC who had undergone previous treatment. These outcomes were quite noteworthy given the refractory nature of the population.[21] This study seemed to be one of the most comprehensive real-world analysis regarding anlotinib plus PD-1 blockades in ESCC with a sample size of 87 comparable to or larger than most published series.[10,19,22] The findings suggested a growing body of evidence that combining angiogenesis inhibition with immunotherapy might recapture tumor control in ESCC after progression on standard treatments.[23] Our efficacy results aligned with and reinforced data from recent studies in this domain. For instance, Hong et al (2025) reported a multicenter retrospective study of 110 previously ICI-treated ESCC administered with anlotinib plus PD-1 blockades and observed an ORR of 19.1% with a median OS of 11.1 months.[19] Our ORR (21.8%) and DCR (73.6%) were slightly higher but on the same order of magnitude. This consistency across independent cohorts, despite some differences in patient characteristics, provided credibility for the robustness of the efficacy signal. Another retrospective by Zhu et al (2025) specifically looked at 29 ESCC progressed on prior ICIs and were given anlotinib plus PD-1 blockades; notably, they found a higher ORR of 31.0% and DCR 86.2%, with a median OS of 10.37 months.[17] The higher response rate in that study might be due to the smaller sample and possibly inclusion of patients with less bulky disease (79% had prior surgery) or shorter interval from prior therapy.[24] Nonetheless, their median survival was around 10 months, in line with ours. Meanwhile, CAP 02 trial examined camrelizumab plus apatinib in 49 ESCC previously treated with ICIs: this trial reported a confirmed ORR of 10.2%, DCR of 69.4%, and the median PFS was 4.6 months, median OS was 7.5 months.[10] The ORR was relatively modest (only 10%), which the authors noted did not meet their predefined threshold for clinically potential improvement. Several factors might explain the lower ORR in CAP 02: (1) apatinib at 250 mg might have a different potency/toxicity balance compared to anlotinib; (2) nearly two-thirds of the patients had received ICIs with chemotherapy as the first-line treatment (ESCORT-1st regimen) and were then rechallenged with the same PD-1 (camrelizumab) plus apatinib, which might lower responsiveness;[25] (3) strict RECIST confirmation of response was required. In our real-world cohort, those who had not received prior immunotherapy also had a response of 24.1% or had a longer break from prior immunotherapy, potentially boosting ORR. The observed DCR of 73.6% was comparable to that of 69.4%, suggesting that disease stabilization was the main benefit of the combination. Notably, even in CAP 02, the median PFS of 4.6 months was superior to the expected PFS with single-agent PD-1 blockade (approximately 2–3 months for primary refractory patients) or single-agent apatinib (3.8 months),[14,26] reinforcing that the combination yielded additive disease control. Additionally, a 2022 retrospective study by Liu et al compared anlotinib combined with ICIs and anlotinib monotherapy: ORR was 23.9% vs 10.4% (P=0.082), median PFS was 5.4 vs 3.0 months (P<0.001).[27] Our study lacked a monotherapy control, mirrored the combination arm outcomes of Liu et al, which indirectly suggested that anlotinib combined with ICIs was more efficacious than anlotinib alone in a similar setting.

Considering the historical controls, these combination outcomes were favorable. Prior to immunotherapy, salvage options for ESCC were still limited.[22] Single-agent chemotherapy (paclitaxel and irinotecan) in the third line yielded ORRs <10% with a disappointing OS by 5–6 months. For example, patients receiving salvage irinotecan or paclitaxel after failing platinum/5-FU resulted in ORRs around 5–10% in small studies.[28] Advent of PD-1 blockades improved second-line OS (nivolumab's 3-month OS benefit over chemotherapy).[29] Unfortunately, considerable patients still failed to respond to PD-1 blockades monotherapy (primary resistance rates was 50–60%).[30] Our combination strategy attempted to convert some of these non-responders into responders by modulating the tumor microenvironment.[31] The efficacy we observed (median OS of 11.5 months from time of salvage therapy) indicated that some patients achieved substantial survival extension, potentially beyond what sequential monotherapies might offer. The median OS was encouraging but must be interpreted cautiously given the retrospective nature and lack of randomization. Indeed, in a retrospective analysis of patients who did not receive combination therapy and continued chemotherapy after immunotherapy, the median OS was only 6–7 months.[22] While acknowledging differences in patient populations, the consistency of 10–11 month OS across our study and others using anlotinib plus PD-1 blockades was encouraging.[19] Furthermore, approximately 18% of our patients were progression-free at 1 year and 46.5% were alive at 1 year, indicating a subset with long-term benefit. For comparison, in PD-L1 positive ESCC patients receiving second-line pembrolizumab (KEYNOTE-181), the 12-month OS rate was 43%,[7,32] which was similar to our 12-month OS rate (although our patients were later line). This suggested that the addition of anlotinib might allow heavily pretreated

patients to achieve survival outcomes approaching those of earlier line immunotherapy in selected cases. Although most patients ultimately experienced disease progression or death, this was expected in heavily pre-treated metastatic ESCC.[33] The observed ORR, DCR and median OS with anlotinib plus PD-1 blockades compared favorably with published later-line regimens, suggesting that the combination offered clinically relevant benefit for a subset of patients, while remaining clearly non-curative. One possible explanation for the observed activity, especially in patients previously exposed to immunotherapy, was that anlotinib's antiangiogenic and immunomodulatory effects might help restore sensitivity to PD-1 blockades. Preclinical studies suggested that normalizing the tumor vasculature and reducing VEGF-driven immunosuppression might improve T-cell infiltration, thereby potentiating the effect of PD-1 blockades.[34] However, we acknowledged that we did not directly investigate mechanism in this study; thus, this hypothesis remained speculative.

Additionally, we performed exploratory subgroup analyses of OS and found that subjects with lower ECOG performance status conferred a better OS (14.5 months) compared to those with an ECOG 1–2 (9.3 months, P=0.011 by Log rank test). This aligned with performance status as an expected prognostic factor.[35] Interestingly, previous exposure to immunotherapy did not markedly reduce PFS in our preliminary analysis (P>0.05, data not shown in results section). However, patients who had previous exposure of immunotherapy tended to confer longer OS when received anlotinib plus PD-1 blockades, implying that rechallenging immunotherapy in combination with anlotinib was particularly efficacious for patients who underwent ICIs previously.[36] We speculated that the reason might be anlotinib's antiangiogenic and immunomodulatory actions likely restored sensitivity to PD-1 blockades: by normalizing abnormal tumor vasculature, improving perfusion and reducing VEGF-driven immunosuppression (dampening Tregs/MDSCs and enhancing T-cell trafficking), anlotinib might convert "cold" to "hot" tumor microenvironments and potentiate PD-1 activity.[37] Clinically, several real-world series showed potential activity regarding anlotinib plus PD-1 in previously-treated ESCC—including after prior ICIs—consistent with our observation.[38] Additionally, we also observed that patients who had fewer metastatic sites (≤3) had slightly longer median OS than those with metastatic sites of >3, indicating that lower metastatic burden conferred a survival advantage with this chemo-free regimen. This pattern was consistent with esophageal cancer literature showing that tumor burden was a strong prognostic factor for survival with outcomes deteriorating as metastatic burden increases.[39] It also fit the broader oligometastatic paradigm in esophagogastric cancer, where limited metastatic disease (often defined as ≤3 lesions across ≤2 sites) was biologically less aggressive and associated with superior survival under multimodal therapy.[40] Additionally, outcomes did not significantly differ between second-line and later-line subgroups, which suggested the regimen might provide benefit even in very advanced settings (though patient numbers were limited).

The positive results observed regarding anlotinib plus PD-1 blockades regimen could be understood by the synergistic mechanisms between angiogenesis inhibition and immune checkpoint blockade. Chronic VEGF-driven angiogenesis in tumors such as ESCC created abnormal, leaky blood vessels that both promoted metastasis and hindered immune cell infiltration.[41] Anlotinib's blockade of VEGFR2/3 and other angiogenic pathways likely normalized tumor vasculature, improving perfusion.[16] By reducing tumor hypoxia and lowering interstitial pressure, anlotinib might transform the tumor microenvironment from immunosuppressive to immune-permissive.[42] Preclinical studies demonstrated that antiangiogenic TKIs decreased immunosuppressive cells (Tregs, myeloid suppressor cells) and increased cytotoxic T-lymphocytes within tumors.[43] This effect might sensitize or re-sensitize tumors to immune attack, especially in cases where initial ICI therapy failed, perhaps due to an immunosuppressive microenvironment. Clinically, this rationale was supported by successes in other cancers; eg, in hepatocellular carcinoma, the combination of an anti-VEGF antibody (bevacizumab) with PD-L1 blockade (atezolizumab) significantly improved survival over sorafenib, transforming the standard of care.[44] In ESCC, while anti-VEGF antibodies (like ramucirumab) or TKIs were not standard historically, our results along with other study suggested that targeting angiogenesis might potentiate immunotherapy efficacy. In fact, a Phase I trial by Ning et al (2024) combining a PD-L1 inhibitor with a novel TKI (AL2846) in immunotherapy-refractory ESCC reported that the median PFS was 5.55 months and DCR was 66.7%, echoing the benefit of such combinations.[45]

Toxicity profile observed with anlotinib plus PD-1 blockades regimen was acceptable and comparable to previous reports.[18] We did not find any synergistic increase in severe toxicity; rather, patients experienced the expected class effects (hypertension, hand-foot syndrome from anlotinib; immune effects like hypothyroidism from PD-1 blockades) mostly at mild grades.[46] Grade ≥3 TRAEs was 50.6%, similar with Wang et al's 41% and clearly lower than what was

typically seen with cytotoxic chemotherapy in second-line (for example, in ATTRACTION-3 trial, grade ≥3 TRAEs with nivolumab were 18% vs 63% with chemotherapy).[8,47] This suggested the combination was more tolerable than traditional chemotherapy in a late-line setting where maintaining performance status was critical. One area of caution was the risk of bleeding or fistula: while we did not encounter any grade 3–5 bleeding events, we mitigated risk by excluding patients with active tumoral erosions.[13] The apatinib monotherapy trial reported 2 fatal bleeds and 2 fistulas in patients with uncontrolled primary tumors, underscoring that proper patient selection was needed when using anti-VEGF agents in ESCC.[14] In our practice, we performed baseline endoscopy and imaging to ensure no looming fistula and monitor closely; dose adjustments of anlotinib might manage bleeding risk.[48] Immune-related toxicities were manageable: notably, only 20.7% pneumonitis (all low grade) was observed, which was reassuring since the re-administration of PD-1 blockades in those who had heavy prior treatment might raise concern for toxicity. It seemed that anlotinib did not significantly exacerbate immune-related adverse events; a similar observation was made in combination studies in lung cancer.[47] On the contrary, some studies highlighted that antiangiogenic therapy might mitigate some immune toxicities by affecting inflammatory cytokines, although this was not well established. Regardless, combination of anlotinib plus ICIs might be delivered safely with routine monitoring and was suitable for a palliative setting.

Looking ahead, our findings support advancing anlotinib plus PD-1 blockades from real-world use into prospective trials with appropriate controls (vs anlotinib or PD-1 alone) to validate the survival signal and define the true effect size in previously treated ESCC. Parallel biomarker programs should be embedded—PD-L1 expression (CPS), angiogenic signatures (eg, VEGF-A/VEGFR2), immune-inflammation composites, and ctDNA dynamics/TCR clonality—to refine patient selection and to test the mechanistic hypothesis that vascular normalization alleviates VEGF-driven immunosuppression and restores sensitivity to PD-1 therapy. Given the encouraging activity of anti-VEGF/IO combinations in ICI-experienced ESCC, a multicenter phase II/III focused on ICIs-pretreated patients is warranted with co-primary endpoints of PFS and OS and prespecifies bleeding/fistula safety monitoring. Two translational extensions merit testing: (i) earlier-line, chemo-free strategies in biomarker-enriched subsets (building on first-line anlotinib plus anti–PD-L1 signals) and (ii) triplet approaches (anlotinib plus PD-1 ± short-course chemotherapy or radiotherapy) designed to exploit transient vascular normalization to enhance drug/t-cell delivery. At the same time, cross-disease experience reminds us that not all IO–TKI pairings translate across histology (eg, pembrolizumab plus lenvatinib with chemotherapy failed to improve OS in gastro-esophageal adenocarcinoma), underscoring the need for histology-specific development and robust safety oversight in ESCC, where local invasion raises hemorrhage/fistula risk. Finally, future studies should incorporate patient-reported outcomes and functional status endpoints, given the manageable toxicity profile observed to date, and benchmark results against contemporary first-line standards (KEYNOTE-590, CheckMate-648) to clarify where chemo-free anti-angiogenic/IO regimens may fit in evolving treatment algorithms. We acknowledge that OS and patient-center clinical benefit are the most important outcomes. Therefore, in our study, radiologic response is interpreted as a supportive endpoint that complemented, but did not replace, the survival data.

Despite these interesting findings, our study had some limitations that must be acknowledged. Firstly, owing to its retrospective observational design, the analysis was subject to inherent selection bias, information bias and residual confounding despite predefined eligibility criteria and standardized outcome assessment. Secondly, this was a single-center real-world study, which might limit the generalizability of the findings to other populations and practice settings. Thirdly, the study lacked a concurrent control arm, precluding direct comparative inference regarding the relative efficacy and safety of this chemotherapy-free regimen. Subjects who were fit enough to receive later-line anlotinib plus PD-1 blockades likely had better performance status and organ function than the broader population of metastatic ESCC, which might partly account for the favorable survival we observed. Fourthly, prior systemic therapies and lines of treatment were heterogeneous, and although we performed subgroup and sensitivity analyses, residual confounding by treatment sequence remained possible. Fifthly, tumor response and progression were assessed by routine clinical imaging rather than centralized blinded review, which might influence PFS estimates. PD-L1 expression and other biomarkers were not consistently available, limiting our ability to identify predictive subgroups. Another limitation was the relatively heterogeneous nature of prior treatments in the cohort. While most patients had prior chemotherapy and PD-1 blockade, a small minority did not receive prior PD-1 treatment, and some had one prior line vs others 2–3 prior lines. We combined these data to reflect the real-world usage of these regimens. This heterogeneity might have introduced

variability. Therefore, our findings should be considered hypothesis-generating. Nonetheless, these real-world data provided clinically relevant preliminary evidence and might support the design of future prospective, multicenter, controlled trials to further evaluate this combination strategy in previously treated ESCC. And our outcomes were similar to those of multicenter studies from other regions in China, suggesting broader applicability, at least in populations of Asian ethnicity where ESCC was predominant.

Conclusions

In conclusion, this retrospective cohort suggested that anlotinib plus PD-1 blockades demonstrated encouraging antitumor activity and a manageable safety profile in previously treated metastatic ESCC, including patients with prior immunotherapy exposure. Therapeutic outcomes appeared favorable in context but could partly reflect patient selection. Nonetheless, most patients ultimately experienced disease progression or death, and the non-randomized design and reliance on historical comparisons meant that a survival benefit could not be firmly established. These results should therefore be interpreted cautiously and viewed as hypothesis-generating. Prospective, multicenter randomized trials were required to validate the clinical benefit of this combination and to define the patients most likely to benefit. It would also be valuable to explore a combination of PD-L1 blockades and triplet chemotherapy regimens. Another future direction was to investigate this combination in earlier lines for patients who could not tolerate chemotherapy. If a chemotherapy-sparing regimen achieved a high response and long survival, it might benefit frail patients. In summary, as the landscape of ESCC treatment evolved, integrating antiangiogenic therapy with immunotherapy might further improve patient outcomes.

Ethics and Consent Statements

Despite the informed consent was waived by the ethics committee of the First Affiliated Hospital of Zhengzhou University, we confirmed that the data of the patients included in this study was anonymized or maintained with confidentiality.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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