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ORIGINAL ARTICLE

Phase II clinical trial using camrelizumab combined with apatinib and chemotherapy as the first-line treatment of advanced esophageal squamous cell carcinoma

Bo Zhang[1,*] | **Ling Qi**[1,*] | **Xi Wang**[1] | **Jianping Xu**[1] | **Yun Liu**[1] | **Lan Mu**[1] | **Xingyuan Wang**[1] | **Lidan Bai**[2] | **Jing Huang**[1]

[1] Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, P. R. China

[2] Jiangsu Hengrui Medicine Co. Ltd., Lianyungang, Jiangsu 222047, P. R. China

Correspondence
Dr. Jing Huang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan Nanli, Beijing, 100021, P. R. China.
Email: huangjing@cicams.ac.cn.com

[*] BZ and LQ contributed equally to this work.

Abstract

Background: Effective therapeutic options are limited for patients with advanced esophageal squamous cell carcinoma (ESCC). The incorporation of an immune checkpoint inhibitor and a molecular anti-angiogenic agent into the commonly adopted chemotherapy may produce synergistic effects. Therefore, we aimed to investigate the efficacy and safety of camrelizumab plus apatinib combined with chemotherapy as the first-line treatment of advanced ESCC.

Methods: In this single-arm prospective phase II trial, patients with unresectable locally advanced or recurrent/metastatic ESCC received camrelizumab 200 mg, liposomal paclitaxel 150 mg/m^2, and nedaplatin 50 mg/m^2 on day 1, and apatinib 250 mg on days 1-14. The treatments were repeated every 14 days for up to 9 cycles, followed by maintenance therapy with camrelizumab and apatinib. The primary endpoint was objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (version 1.1). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: We enrolled 30 patients between August 7, 2018 and February 23, 2019. The median follow-up was 24.98 months (95% confidence interval [CI]: 23.05-26.16 months). The centrally assessed ORR was 80.0% (95% CI: 61.4%-92.3%), with a median duration of response of 9.77 months (range: 1.54 to 24.82+ months). The DCR reached 96.7% (95% CI: 82.8%-99.9%). The median PFS was 6.85 months (95% CI: 4.46-14.20 months), and the median OS was 19.43 months (95% CI: 9.93 months – not reached). The most common grade 3-4 treatment-related adverse events (AEs) were leukopenia (83.3%), neutropenia (60.0%), and

Abbreviations: AE, adverse event; CPS, combined positive score; CR, complete response; DCR, disease control rate; DoR, duration of response; ESCC, esophageal squamous cell carcinoma; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

increased aspartate aminotransferase level (26.7%). Treatment-related serious AEs included febrile neutropenia, leukopenia, and anorexia in one patient (3.3%), and single cases of increased blood bilirubin level (3.3%) and toxic epidermal necrolysis (3.3%). No treatment-related deaths occurred.

Conclusions: Camrelizumab plus apatinib combined with liposomal paclitaxel and nedaplatin as first-line treatment demonstrated feasible anti-tumor activity and manageable safety in patients with advanced ESCC. Randomized trials to evaluate this new combination strategy are warranted.

Trial registration: This trial was registered on July 27, 2018, at ClinicalTrials.gov (identifier: NCT03603756).

KEYWORDS

anti-angiogenesis, apatinib, camrelizumab, chemotherapy, esophageal squamous cell carcinoma, first-line, immunotherapy, liposomal paclitaxel, nedaplatin, objective response rate

1 | BACKGROUND

Esophageal cancer remains a common malignancy worldwide, with an estimated 572,034 new cases and 508,585 deaths in 2018 [1]. Esophageal squamous cell carcinoma (ESCC) is the predominant histologic subtype globally, and the incidence of ESCC is the highest in East and Southeast Asia [2]. Nearly half of esophageal cancer patients present with metastatic disease at the time of diagnosis [3]. However, the standard of care for patients with metastatic ESCC in the front-line setting has not yet been established. Currently, 5-fluorouracil and platinum are the therapeutic combination recommended in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines [4] and the Pan-Asian adapted European Society of Medical Oncology (ESMO) Clinical Practice Guidelines [5] as the first-line treatment for patients with metastatic ESCC, while newer agents including paclitaxel, docetaxel, and irinotecan are also acceptable options although lack of solid evidence from phase III clinical trials. The response rates ranged between 35%-56.5% with doublet chemotherapy [6–11] and 43.9%-72.7% with triplet regimens [12–14]. The survival outcomes of patients treated with these combinations have been unsatisfactory, as the median progression-free survival (PFS) ranged between 4.5 and 7 months, and the median overall survival (OS) was typically around 1 year [6–15]. Hence, there is an unmet need for novel anti-tumor agents to treat patients with advanced ESCC.

Improved understanding of the tumor immune escape and angiogenesis mechanisms has revealed new possibilities for anti-cancer treatments. Specifically, several immune checkpoint inhibitors (ICIs) have demonstrated promising efficacy on advanced ESCC; response rates to different anti-program death-1 (anti-PD-1) antibodies in patients with previously treated ESCC were reported to be 14.3%-33.3% [16–18]. Recently, two randomized phase III trials (ATTRACTION-3 [19] and ESCORT [20]) showed that PD-1 blockade, compared with chemotherapy, could significantly prolong the OS of advanced ESCC patients as the second-line treatment. Regarding anti-angiogenesis treatment, a few tyrosine kinase inhibitors (TKIs) that target vascular endothelial growth factor receptor (VEGFR) have shown modest activity during the management of ESCC patients [21–23]. In a Chinese prospective phase II trial, the response rate with anlotinib was 7% in advanced ESCC patients whose disease had progressed after platinum- or taxane-containing chemotherapy [].

Although the efficacy of both PD-1 blockade and VEGFR inhibition as monotherapy has been limited in the management of patients with metastatic ESCC, it is possible that the combination of these agents with chemotherapy may have synergistic effects. This may be because of the potential role of chemotherapy to overcome immunosuppression [24, 25], facilitate tumor antigen presentation [26, 27], and modulate activities of anti-angiogenesis [28, 29]. The phase III study of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) plus chemotherapy in non-small cell lung cancer has demonstrated improved survival outcomes, providing evidence supporting this combination strategy [30]. However, to date, there are no reports on the efficacy of ICIs and molecular anti-angiogenic agents in combination with chemotherapy in patients with ESCC. Based on the promising anti-tumor activity of camrelizumab in pretreated advanced ESCC patients observed in our previous study [18] and its potential synergy with anti-angiogenesis and chemotherapy, we conducted this prospective trial to investigate the efficacy

and safety of camrelizumab (anti-PD-1 antibody) plus apatinib (VEGFR TKI) and chemotherapy as the front-line treatment for patients with unresectable locally advanced or recurrent/metastatic ESCC.

2 | PATIENTS AND METHODS

2.1 | Study design and participants

This prospective, open-labeled, phase II clinical trial was conducted in a single center in China. We recruited patients aged 18-70 years old who had histologically/cytologically-proven unresectable, locally advanced or recurrent/metastatic ESCC and had not received prior systemic therapies. Additional eligibility requirements included having at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group performance status of 0-1; an expected life expectancy of at least 3 months; and adequate organ functions assessed by complete blood count and blood chemistry tests.

Patients were excluded if they presented with central nervous system metastases; had active or history of autoimmune disease; had previously been treated with any ICIs; had uncontrolled hypertension or clinically significant heart disease; or presented with active infection or an unexplained fever > 38.5°C before 4 weeks of enrollment. Patients who had previously received neoadjuvant or adjuvant chemotherapy were eligible if the last treatment was at least 6 months prior to enrollment.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The research protocol was reviewed and approved by the institutional review board of the Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China). All patients provided written informed consent before the study treatment.

2.2 | Procedures

Eligible patients received intravenous administration of 200 mg camrelizumab (Jiangsu Hengrui Medicine Co. Ltd., Lianyungang, Jiangsu, China), 150 mg/m^2 liposomal paclitaxel (Nanjing Luye Pharmaceutical Co. Ltd., Nanjing, Jiangsu, China), and 50 mg/m^2 nedaplatin (Jiangsu Aosaikang Pharmaceutical Co. Ltd., Nanjing, Jiangsu, China, or Qilu Pharmaceutical Co. Ltd., Jinan, Shandong, China) on day 1, and oral administration of 250 mg apatinib (Jiangsu Hengrui Medicine Co. Ltd.) on days 1-14. All treatments were repeated every 14 days for up to 9 cycles, followed by maintenance therapy with camrelizumab and apatinib until either disease progression or unacceptable toxicity.

Dose reductions were not permitted for camrelizumab. Patients could, at the discretion of the treating physician, temporarily suspend or permanently discontinue treatment with camrelizumab if they experienced an adverse event (AE) suspected to be immune-related. Dose adjustments for the cytotoxic agents and dose interruptions for apatinib were allowed and conducted according to the treating physician's judgment and local standard practice.

Baseline computed tomography (CT) or magnetic resonance imaging (MRI) was performed within 28 days before the initiation of the study treatment. Subsequent imaging studies were conducted every 6 weeks during the first 6 months and every 12 weeks thereafter until disease progression. Evaluation of response was performed by an independent reviewer using the RECIST criteria. Laboratory tests, including standard complete blood counts and chemistry panel, were monitored every 2 weeks. Electrocardiograms, urine and fecal routine tests, and coagulation function and thyroid function tests were repeated every 4 weeks.

Program death-ligand 1 (PD-L1) expression in archived or newly obtained tumor samples was assessed at a central laboratory using a human PD-L1 immunohistochemistry kit and the 6E8 antibody (Shuwen Biotech Co. Ltd., Huzhou, Zhejiang, China) and then reported using the combined positive score (CPS): CPS = the number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) / the total number of tumor cells × 100.

AEs were recorded throughout the study treatment and for 3 months after treatment discontinuation. Patients were followed up via telephone every 4 weeks after the discontinuation of the study treatment until death.

2.3 | Endpoints and assessment

The primary endpoint of the study was the objective response rate (ORR), defined as the percentage of patients achieving a best response of complete response (CR) or partial response (PR) as per the RECIST version 1.1. Secondary endpoints included disease control rate (DCR), PFS, OS, duration of response (DoR), and safety. DCR was defined as the percentage of patients achieving a best response of CR, PR, or stable disease (SD). PFS was defined as the time period between treatment initiation and the first documented disease progression or death of any cause, whereas OS was defined as the time period between treatment initiation and death of any cause. DoR was defined as the time period between the first objective response and the first documented disease progression or death of any cause. The exploratory endpoint was the

association between the PD-L1 CPS in tumor samples and response to the study treatment. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. A serious AE was defined as any AE that was fatal, life-threatening, required prolonged hospitalization, resulted in persistent or significant disability/incapacity, or resulted in congenial anomaly/birth defect in a neonate/infant born to a mother exposed to the study treatment.

2.4 | Statistical analysis

With the planned sample size of 30 patients, the study had at least 90% power to detect an improvement in the response rate from 40% to 70%, with an α level of 0.025 one-sided. Therefore, the null hypothesis was rejected if 18 or more responses were observed in the enrolled patients. The null hypothesis of 40% was based on the presumed efficacy of the paclitaxel plus nedaplatin regimen in this patient population demonstrated in previous studies [7, 8]. The efficacy analysis was performed in the intention-to-treat population; the safety analysis was assessed in all patients who received at least one dose of any of the study drugs.

The 95% confidence intervals (CIs) for the ORR and DCR were calculated based on the Clopper-Pearson method. The Kaplan-Meier method was used to estimate time-to-event variables. We used SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) for statistical analyses.

3 | RESULTS

3.1 | Patient characteristics

Thirty eligible patients were enrolled between August 7, 2018, and February 23, 2019 (Table 1). The median age was 61.5 years (range: 43-70 years), and 23 (76.7%) of the patients were male. Most patients presented with distant metastatic disease (24/30, 80.0%). Prior treatment before the onset of the recurrent disease included surgical resection in 9 patients and radiotherapy in 4 patients. The median follow-up duration was 24.98 months (95% CI: 23.05-26.16 months) as of the data cut-off date (November 20, 2020), and all patients had discontinued the study treatment. The reasons for treatment discontinuation were adverse events ($n = 12$), disease progression ($n = 10$), patient withdrawal ($n = 5$), and the impact of the coronavirus disease 2019 (COVID-19) pandemic ($n = 3$). The reasons for consent withdrawal in the 5 patients are as follows: 2 patients achieved PR but requested discontinuation of maintenance therapy; 1 underwent surgical resection after radiographical PR, and pathological CR was subsequently

TABLE 1 Baseline characteristics of the 30 enrolled patients with unresectable locally advanced or recurrent/metastatic ESCC

Characteristic	Number of patients [cases (%)]
Age (years)	
≤50	4 (13.3)
51-60	9 (30.0)
61-70	17 (56.7)
Gender	
Male	23 (76.7)
Female	7 (23.3)
ECOG PS score	
0	25 (83.3)
1	5 (16.7)
Histologic grade	
G1	2 (6.7)
G2	13 (43.3)
G3	15 (50.0)
Site of metastases	
Lymph node	29 (96.7)
Lung	9 (30.0)
Liver	6 (20.0)
Bone	2 (6.7)
History of heavy alcohol use[†]	
Yes	14 (46.7)
No	16 (53.3)
PD-L1 CPS score[‡]	
< 1	5 (16.7)
≥1	23 (76.7)
< 5	9 (30.0)
≥5	19 (63.3)
< 10	12 (40.0)
≥10	16 (53.3)
Previous treatment	
Surgery	9 (30.0)
Radiotherapy	4 (13.3)
Extent of disease	
Unresectable locally advanced	5 (16.7)
Recurrent	1 (3.3)
Metastatic	24 (80.0)

[†]Heavy alcohol use was defined as more than 40 g of pure alcohol per day for men or more than 20 g of pure alcohol per day for women, lasting over 5 years.
[‡]PD-L1 CPS score was defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) as a proportion of the total number of tumor cells multiplied by 100. PD-L1 CPS score was not calculated for 2 patients due to inadequate tissue samples for the staining of PD-L1 expression.
Abbreviations: CPS, combined positive score.; ECOG, Eastern Cooperative Oncology Group;ESCC, esophageal squamous cell carcinoma; PD-L1, program death-ligand 1; PS, performance status.

TABLE 2 Activity of camrelizumab and apatinib plus chemotherapy in the first-line treatment of patients with advanced ESCC

Efficacy variable	Number of patients [cases (%)]
Best overall response	
Complete response	5 (16.7)
Partial response	19 (63.3)
Stable disease	5 (16.7)
Progressive disease	1 (3.3)
Objective response	24 (80.0)
Disease control	29 (96.7)

Abbreviation: ESCC, esophageal squamous cell carcinoma.

confirmed; 1 with distant metastases underwent palliative resection of the esophagus after radiographical PR; and 1 withdrew from the study due to unsatisfactory treatment outcomes (radiographical SD) and received radiotherapy.

3.2 | Efficacy

All 30 patients were included in the efficacy analysis. On the basis of a central review, the ORR was 80.0% (24/30, 95% CI: 61.4%-92.3%), and the DCR was 96.7% (29/30, 95% CI: 82.8%-99.9%) (Table 2). The median PFS was 6.85 months (95% CI: 4.46 – 14.20 months). Eighteen patients died, and the median OS was 19.43 months (95% CI: 9.93 months - not reached) at the time of data cut-off. Specifically, the median PFS and OS of the 24 patients with distant metastatic disease were 6.46 months (95% CI: 4.16-11.31 months) and 17.39 months (95% CI: 8.56 months -not reached), respectively.

Among the 24 responders, 5 (16.7%) had a confirmed CR, and 19 (63.3%) achieved a confirmed PR. Twenty-nine (96.7%) patients experienced a reduction in target lesion burden from the baseline (Figure 1A), which was maintained in most patients over several subsequent assessments (Figure 1B). The median time to initial response was 1.38 months (range: 1.18-3.05 months) in the 24 patients with an objective response, and the median duration of response (DoR) was 9.77 months (range: 1.54-24.82+ months) (Figure 1C). Nine of the responders remained progression-free 6 months after discontinuation of the study treatment.

3.3 | Safety

Safety analyses were based on the 30 eligible patients. The median duration of treatment with camrelizumab was 3.28 months (range, 0-16.03 months), with a median of 8 doses (range, 1-33 doses). The median duration of treatment with chemotherapy was 2.77 months (range, 0-4.03 months), with a median of 7 cycles (range, 1-9 cycles). Treatment-related AEs occurred in all patients, and the rate of grade 3-4 treatment-related AEs was 90.0%. The most common grade 3-4 treatment-related AEs were neutropenia in 25 patients (83.3%), leukopenia in 18 patients (60.0%), and increased AST level in 8 patients (26.7%) (Table 3).

Treatment-related AEs led to dose reductions of chemotherapy in 24 patients (80.0%), discontinuation of camrelizumab in 10 patients (33.3%), and discontinuation of apatinib in 8 patients (26.7%). Twenty-nine (96.7%) patients had dose interruptions of apatinib due to treatment-related AEs, and the most common reason was myelosuppression caused by chemotherapy.

Treatment-related serious AEs were reported in 3 patients (10.0%), including 1 case of grade 3 febrile neutropenia along with grade 4 leukopenia and grade 3 anorexia, 1 case of grade 4 blood bilirubin level increase, and 1 case of toxic epidermal necrolysis. All treatment-related serious AEs were managed with appropriate medical care. There were no treatment-related deaths.

AEs that were potentially immune-related, determined by the investigator, occurred in 22 patients (73.3%) (Table 4). Grade 3-4 immune-related AEs were noticed in 6 patients (20.0%), namely, hepatitis in 3 patients (10.0%), rash in 2 patients (6.7%), myocarditis in 1 patient (3.3%), and toxic epidermal necrolysis in 1 patient (3.3%) (1 patient developed both rash and toxic epidermal necrolysis). All grade 3-4 immune-related AEs were resolved with the administration of corticosteroids in addition to supportive care, or the discontinuation of the study treatment.

3.4 | PD-L1 expression

Evaluable tissue samples were collected from 28 patients for the assessment of baseline PD-L1 expression. Among them, 23 (82.1%) had a PD-L1 CPS of ≥1, and 16 (57.1%) had a PD-L1 CPS of ≥10 (Table 1). In the patients with a PD-L1 CPS of ≥1, the ORR was 78.3% (18/23), and the DCR was 95.6% (22/23). The ORR and DCR were 75.0% (12/16) and 93.8% (15/16) in the patients with a PD-L1 CPS of ≥10. The median PFS and OS for patients with a PD-L1 CPS of ≥10 were 9.93 months (95% CI: 4.16 months - not reached) and 20.31 months (95% CI: 8.56 months - not reached), respectively, whereas the median PFS and OS for those with a PD-L1 CPS of < 10 were 8.59 months (95% CI: 2.72 – 21.77 months) and 20.39 (95% CI: 6.30 months - not reached), respectively. Notably, the PD-L1 CPS of the 5 patients achieving a best response of CR were above 10 (range: 25-80).

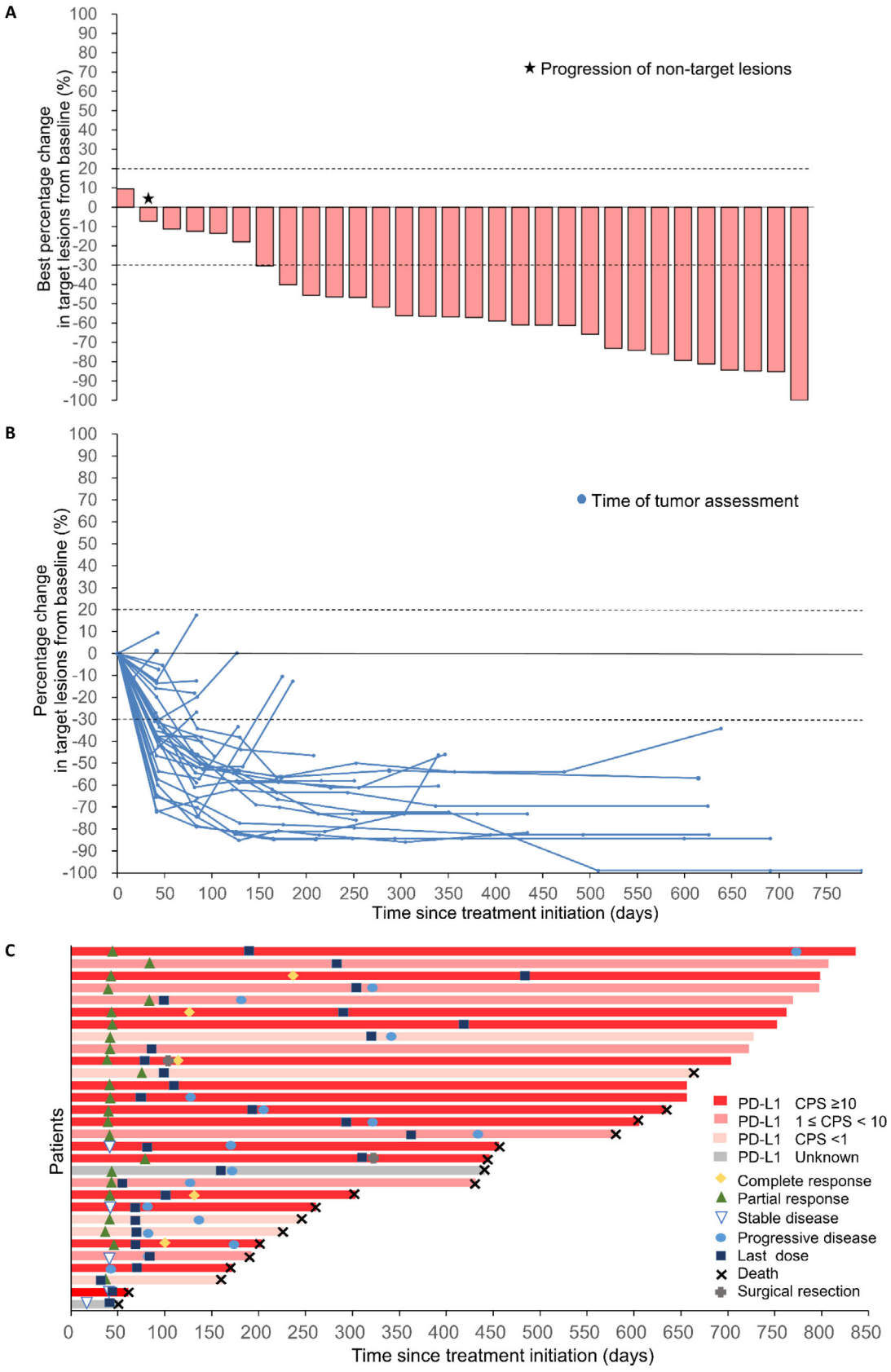

FIGURE 1 Responses to camrelizumab and apatinib plus chemotherapy in the first-line treatment of patients with advanced ESCC. (A) Best change of target lesions from baseline by independent central review. Each bar represents an individual patient. The asterisk indicates the progression of non-target lesions. (B) Longitudinal change of target lesions from baseline by independent central review. (C) Records of responses during treatment. The length of each bar represents the time from treatment initiation to the last follow-up. Abbreviations: ESCC, esophageal squamous cell carcinoma; PD-L1, program death-ligand 1; CPS, combined positive score

TABLE 3 Treatment-related adverse events observed with camrelizumab and apatinib plus chemotherapy

Event	Number of patients [cases (%)]			
	Grade 1	Grade 2	Grade 3	Grade 4
Reactive capillary hemangiomas	18 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	17 (56.7)	2 (6.7)	0 (0.0)	0 (0.0)
Increased ALT level	15 (50.0)	1 (3.3)	4 (13.3)	0 (0.0)
Thrombocytopenia	12 (40.0)	8 (26.7)	3 (10.0)	0 (0.0)
Anemia	12 (40.0)	6 (20.0)	2 (6.7)	0 (0.0)
Anorexia	7 (23.3)	3 (10.0)	1 (3.3)	0 (0.0)
Fatigue	6 (20.0)	4 (13.3)	0 (0.0)	0 (0.0)
Increased AST level	6 (20.0)	1 (3.3)	8 (26.7)	0 (0.0)
Hypothyroidism	5 (16.7)	2 (6.7)	0 (0.0)	0 (0.0)
Blood bilirubin level increase	5 (16.7)	1 (3.3)	3 (10.0)	1 (3.3)
Epistaxis	4 (13.3)	1 (3.3)	0 (0.0)	0 (0.0)
Gum bleeding	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	3 (10.0)	9 (30.0)	12 (40.0)	6 (20.0)
Laryngeal hemorrhage	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	2 (6.7)	7 (23.3)	0 (0.0)	0 (0.0)
Pruritus	2 (6.7)	3 (10.0)	0 (0.0)	0 (0.0)
Vomiting	2 (6.7)	1 (3.3)	0 (0.0)	0 (0.0)
Hypertension	1 (3.3)	3 (10.0)	2 (6.7)	0 (0.0)
Diarrhea	1 (3.3)	3 (10.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	4 (13.3)	12 (40.0)	13 (43.3)
Rash	0 (0.0)	1 (3.3)	2 (6.7)	0 (0.0)
Urticaria	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	3 (10.0)	0 (0.0)
Myocarditis	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)
Toxic epidermal necrolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)

Treatment-related adverse events observed in ≥10% of the patients and all grade 3-4 adverse events are listed. No grade 5 adverse events were recorded.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 4 Immune-related adverse events observed with camrelizumab and apatinib plus chemotherapy

Event	Number of patients [cases (%)]			
	Grade 1	Grade 2	Grade 3	Grade 4
Reactive capillary hemangiomas	18 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	5 (16.7)	2 (6.7)	0 (0.0)	0 (0.0)
Hyperthyroidism	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	1 (3.3)	2 (6.7)	0 (0.0)
Adrenal insufficiency	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)
Diabetes mellitus	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)
Hepatitis	0 (0.0)	0 (0.0)	2 (6.7)	1 (3.3)
Myocarditis	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)
Toxic epidermal necrolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)

There were no grade 5 immune-related adverse events.

4 | DISCUSSION

The management of patients with advanced ESCC is challenging given the aggressive nature of the disease and the limited choice of effective anti-tumor drugs. This single-arm, phase II study met its prespecified primary endpoint, with 80.0% of patients achieving an objective response based on an independent central review. Furthermore, 16.7% of the patients achieved a best response of CR. In contrast, the ORR reported in previous phase II studies evaluating the efficacy of paclitaxel plus platinum in the upfront treatment of advanced ESCC patients ranged from 41.7% to 56.5%, with a median PFS between 5.6 and 6.1 months [8–10]. As the regimens of these trials were similar to the chemotherapy backbone in the present study, the notable contrast in ORR, reflecting a remarkable tumor regression in the present trial, strongly supports the hypothesis of synergy between immunotherapy, anti-angiogenesis, and chemotherapy. The encouraging response outcomes also suggest the potential future application of this regimen not only in patients with recurrent/metastatic ESCC, but also in those with unresectable disease potentially convertible to a resectable status. Regarding the survival outcomes in the present trial, the improvement in PFS was modest compared with the results from previous studies using doublet chemotherapy [8–10]. However, the DoR observed in the present trial was impressive, with a median DoR of 9.77 months. In contrast, in a previous phase II study of paclitaxel and nedaplatin as first-line chemotherapy for patients with advanced esophageal cancer, the reported DoR was 5.6 months [10]. Notably, 9 patients remained progression-free 6 months after discontinuation of the study treatment. This was probably due to the high response rate achieved in the present study and the durable anti-tumor host immunity restored by the PD-1 blockade. Our findings in an unselected cohort highlight the importance to distinguish patients that would most likely to benefit from this new combination strategy through certain biomarkers.

PD-L1 expression is associated with the therapeutic effect of PD-1 blockade in many cancers [31]. However, the predictive role of PD-L1 expression for the treatment responses with a single-agent PD-1 inhibitor in esophageal cancer patients remains controversial. In the ATTRACTION-3 [19] and ESCORT trials [20], the OS benefit with nivolumab or camrelizumab compared with chemotherapy in the second-line treatment of ESCC patients occurred regardless of tumor cell PD-L1 expression. Nevertheless, in the KEYNOTE-181 trial, pembrolizumab significantly prolonged OS compared with chemotherapy in the subgroup of patients with a PD-L1 CPS $\geq$ 10, while in the intent-to-treat population, the OS was similar [32]. In the present study, we failed to observe a tendency of higher response rates in patients with higher PD-L1 CPS. We also noted that the median PFS for patients with PD-L1 CPS of $\geq$10 was longer than those with PD-L1 CPS $<$ 10. However, the median OS for the two subgroups was similar. Besides, all patients achieving a best response of CR had CPS $>$ 10. The interpretation of these findings is difficult due to the relatively small sample size of the present study and the complexity of the tumor-immune microenvironment interaction. When PD-1 inhibition is performed in combination with other treatment approaches, the predictive value of PD-L1 expression for response or survival in ESCC patients becomes even more complicated and requires further exploration.

The majority of the AEs observed with the addition of camrelizumab and apatinib to chemotherapy were consistent with the safety profiles of the individual drugs [9, 10, 18, 22]. However, grade 3-4 myelosuppression and hepatic toxicity were more frequently reported in our combination therapy. One possible explanation could be that the chemotherapy was delivered every 2 weeks in the present trial, resulting in a higher dose intensity of paclitaxel compared with those in previous studies (175 mg/m^2 every 3 weeks) [9,10]. The median duration of treatment with chemotherapy was also longer than those in previous reports (2.77 months vs. 1.5-2.25 months) [9, 10]. Additionally, we have noted that 14 patients (46.7%) in the present study had a history of heavy alcohol consumption, which might have increased their risk of developing myelosuppression and liver injury. The rates of most potentially immune-related AEs were comparable to those reported for single-agent camrelizumab in a phase 1 trial [33], except that the rate of grade 3-4 hepatitis (n = 3, 10.0%) seemed higher in the present trial. The 3 patients developing grade 3-4 hepatitis in the present study were successfully managed with corticosteroid administration, suggesting that an immune-related mechanism was likely involved in the pathogenesis of these events. However, acknowledging the limited number of patients in the present trial, there remains no concrete evidence that chemotherapy and apatinib may intensify the toxicities of camrelizumab or vice versa. Based on the safety data in the present study, full doses of camrelizumab and the two cytotoxic drugs could be administered in combination. We recommend a shortened course of apatinib administration (5-7 days per cycle) to avoid deteriorating the preexisting myelosuppression, which was the most common reason for dose interruption with apatinib and typically occurred at the end of the first week after chemotherapy administration.

Limitations of the present study included the single-center, single-arm design, and the relatively small sample size. Therefore, we are unable to compare our findings

directly with the treatment outcomes of chemotherapy alone.

5 | CONCLUSIONS

Camrelizumab plus apatinib and chemotherapy showed encouraging anti-tumor activity and manageable safety in the first-line treatment of patients with unresectable locally advanced or recurrent/metastatic ESCC, providing a feasible and well-tolerated treatment option for this patient population. Evaluation of this new combination approach in a randomized phase III trial is warranted in the near future.

AUTHORS' CONTRIBUTIONS

JH and LB conceived and designed the study. All authors contributed to data acquisition and data analysis. BZ and JH drafted the manuscript. All authors participated in the review and final approval of the submitted report.

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CONFLICT OF INTEREST

LB is an employee of Jiangsu Hengrui Medicine Co. Ltd; other authors declare no potential conflict of interest.

ORCID

Jing Huang https://orcid.org/0000-0002-2167-8385

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