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ORIGINAL ARTICLE

Perioperative toripalimab plus neoadjuvant chemotherapy might improve outcomes in resectable esophageal cancer: an interim analysis of a phase III randomized clinical trial

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Abstract

Background: In the era of immunotherapy, neoadjuvant immunochemotherapy (NAIC) for the treatment of locally advanced esophageal squamous cell carcinoma (ESCC) is used clinically but lacks of high-level clinical evidence. This study aimed to compare the safety and long-term efficacy of NAIC

List of abbreviations: AE, adverse event; CPS, combined positive score; CT, computed tomography; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; ESCC, esophageal squamous cell carcinoma; irAE, immune-related adverse event; ITT, intent-to-treat; MIE, minimally invasive esophagectomy; MPR, major pathological response; N/A, not available; NAC, neoadjuvant chemotherapy; NACR, neoadjuvant chemoradiotherapy; NAIC, neoadjuvant immunochemotherapy; NRS-2002, nutritional risk screening 2002; OS, overall survival; pCR, pathological complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q, quaque; R, random; RCT, randomized controlled trial; TP, paclitaxel and cisplatin; TRAE, treatment-related adverse event; W, week.

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followed by minimally invasive esophagectomy (MIE) with those of neoadjuvant chemotherapy (NAC) followed by MIE.

Methods: A prospective, single-center, open-label, randomized phase III clinical trial was conducted at Henan Cancer Hospital, Zhengzhou, China. Patients were randomly assigned to receive either neoadjuvant toripalimab (240 mg) plus paclitaxel (175 mg/m^2) + cisplatin (75 mg/m^2) (toripalimab group) or paclitaxel + cisplatin alone (chemotherapy group) every 3 weeks for 2 cycles. After surgery, the toripalimab group received toripalimab (240 mg every 3 weeks for up to 6 months). The primary endpoint was event-free survival (EFS). The pathological complete response (pCR) and overall survival (OS) were key secondary endpoints. Adverse events (AEs) and quality of life were also assessed.

Results: Between May 15, 2020 and August 13, 2021, 252 ESCC patients ranging from T1N1-3M0 to T2-3N0-3M0 were enrolled for interim analysis, with 127 in the toripalimab group and 125 in the chemotherapy group. The 1-year EFS rate was 77.9% in the toripalimab group compared to 64.3% in the chemotherapy group (hazard ratio [HR] = 0.62; 95% confidence interval [CI] = 0.39 to 1.00; $P = 0.05$). The 1-year OS rates were 94.1% and 83.0% in the toripalimab and chemotherapy groups, respectively (HR = 0.48; 95% CI = 0.24 to 0.97; $P = 0.037$). The patients in the toripalimab group had a higher pCR rate (18.6% vs. 4.6%; $P = 0.001$). The rates of postoperative Clavien-Dindo grade IIIb or higher morbidity were 9.8% in the toripalimab group and 6.8% in the chemotherapy group, with no significant difference observed ($P = 0.460$). The rates of grade 3 or 4 treatment-related AEs did not differ between the two groups (12.5% versus 12.4%).

Conclusions: The interim results of this ongoing trial showed that in resectable ESCC, the addition of perioperative toripalimab to NAC is safe, may improve OS and might change the standard treatment in the future.

KEYWORDS
esophageal squamous cell carcinoma, minimally invasive esophagectomy, neoadjuvant chemotherapy, neoadjuvant immunochemotherapy, survival

1 | BACKGROUND

Surgery is the most effective treatment for localized esophageal squamous cell carcinoma (ESCC). Neoadjuvant chemotherapy (NAC) and neoadjuvant chemoradiotherapy (NACR) are currently utilized as adjuncts for surgery [1]. However, even following R0 resection and neoadjuvant treatment, approximately 30% of these patients experience distant recurrence within 2 years [2, 3], and 53% die of cancer within 5 years [3, 4]. Moreover, a limited number of patients treated with NAC achieve a pathological complete response (pCR) (median, 6.85%; range, 2.00% to 17.00%) [5]. Although the pCR rate of NACR was 43.2%, the relationship between the pCR and overall survival (OS) of patients receiving NACR was unclear [6].

Recent advances have been made in understanding programmed cell death protein 1 (PD-1) antibodies as systematic adjuvant therapies for resectable ESCC [7]. Checkmate 577 was a milestone in resectable ESCC treatment [7]. However, the median disease-free survival (DFS) with adjuvant PD-1 antibody treatment was still only 22 months [8]. Compared with that in the adjuvant stage, Anti-PD-1 therapy in the neoadjuvant stage might be more effective [9]. The promising results was shown in precedence neoadjuvant-adjuvant melanoma trials for neoadjuvant PD-1 antibodies [10, 11]. Therefore, an effective systemic treatment modality is still needed for localized resectable disease in the perioperative stage.

Among agents targeting the PD-1 pathway, toripalimab is a human anti-PD-1 immunoglobulin G 4K (IgG4K) monoclonal antibody [12]. Toripalimab-based immunotherapy

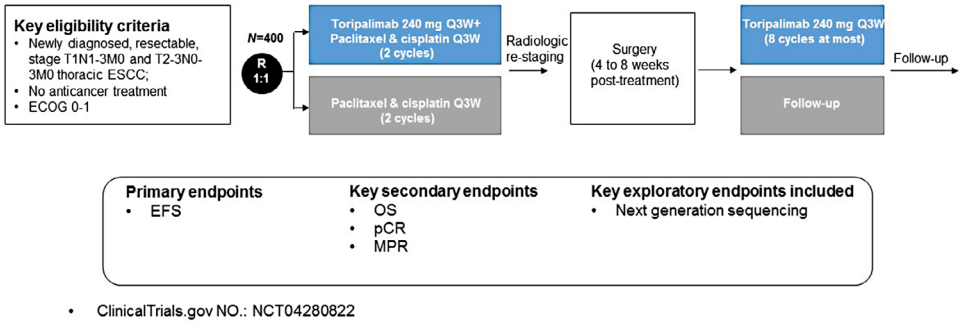

FIGURE 1 Study design. Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; EFS, event-free survival; MPR, major pathological response; N, node; OS, overall survival; pCR, pathological complete response; Q, quaque; R, random; T, tumor; W, week.

regimens have been proven to prolong survival in patients with stage IV ESCC and were approved as first-line treatments for metastatic ESCC by the National Medical Product Administration in China [13]. Therefore, the combination of toripalimab with chemotherapy might be more effectively activate the antitumor activity of the immune system than NAC alone.

In prior phase II studies of resectable ESCC, 36% of patients who received neoadjuvant toripalimab on day 3 plus paclitaxel and cisplatin (TP) chemotherapy on day 1 achieved a promising pCR with manageable safety profiles, with 2 patients experiencing grade ≥ 3 adverse events (AEs) [14, 15]. Based on previous promising phase II clinical results, we conducted this single-center, randomized, open, controlled phase III trial (HCHTOG1909) to test if addition of perioperative toripalimab to NAC might improve OS of ESCC (the trial design was reported [16]).

2 | MATERIALS AND METHODS

2.1 | Trial design and treatment arms

This single-center, open-label, phase III trial focus on patients with resectable ESCC. Patients were randomly assigned to two arms at a 1:1 ratio: toripalimab group or chemotherapy group. In toripalimab group, TopAlliance, Shanghai, China (240 mg, intravenous drip, 1 hour for first time and 30 min for the other times, on day 3, 3 weeks for 2 cycles) combined with cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2 (TP) chemotherapy on day 1, 3 weeks for 2 cycles. In chemotherapy group, the same dose of TP chemotherapy alone (every 3 weeks for 2 cycles) before definitive surgery. After surgery, patients in the toripalimab group received up to 8 cycles of adjuvant toripalimab (240 mg every 3 weeks) (Figure 1). The CONSORT guidelines were adhered to throughout the study. The study started on April 21, 2020, and the first patient was recruited on May 15, 2020. The single center was the Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital (Zhengzhou, Henan, China). The stratified section randomization method was adopted by using the LinkLab Clinical Research- Electronic Data Capture (LinkDoc, Beijing, China). Stratification factors included clinical lymph node status (±) and programmed death-ligand 1 (PD-L1) combined positive score (<5%/≥5%). PD-L1 expression was assessed with a 22C3 pharmDx (Dako, Santa Clara, CA, USA).

2.2 | Patient eligibility criteria

The inclusion criteria were as follows: 18-75 years of age, resectable thoracic ESCC staged as T1N1-3M0 or T2-3N0-3M0 based on the 8th Union for International Cancer Control -TNM system, expected to undergo R0 resection; an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, absence of other cancer diagnoses, and no history of previous anticancer treatment. The detailed eligibility criteria have been previously reported [16].

2.3 | Surgical approach

MIE was performed 4-8 weeks after the completion of neoadjuvant therapy. Total 2-field lymphadenectomy was strictly performed, and 3-field lymphadenectomy was performed for patients with cervical lymph node metastasis.

2.4 | Endpoints and assessments

The primary endpoint was event-free survival (EFS), defined as the time from randomization to the first record of unresectable disease, local recurrence, distant metastasis, or death from any cause. The secondary endpoints

included the pCR rate (0% residual viable tumor cells in the primary tumor and sampled lymph nodes), R0 resection rate, major pathological response (MPR) rate (residual tumor ≤10%), OS (defined as the time from start of randomization until the patient's death or last contact), DFS (defined as the time from start of randomization until the recurrence of disease or death (from any cause), and AEs (assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 [CTC AE5]). AEs were evaluated up to 3 months after the last cycle of neoadjuvant treatment. Patients' quality of life and nutritional risk screening 2002 (NRS-2002) score were also evaluated. Postoperative complications, except for pneumonia, were defined as previously reported [17]. In this study, we defined pneumonia as a patchy appearance of the lungs on chest computed tomography (CT) scans. Death and recurrence data were collected during the follow-up process. To collect further information, patients were followed up by telephone or re-examination. The patients were followed up every 3 months in the first two years post-surgery. The latest follow-up evaluation was performed in August 13,2022. Recurrence events were assessed by the combination of postoperative CT scans, magnetic resonance imaging (MRI), and other clinical examinations. The exploratory endpoints included gene sequencing by next generation sequencing.

2.5 | Trial oversight

The trial was approved by the Institutional Review Board of Henan Cancer Hospital. Ethical approval was obtained from the independent Ethics Committee of Henan Cancer Hospital (ID: 2019092702). The data were gathered by the investigators. All the authors vouch for the accuracy and integrity of the data. The Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines were strictly followed. Written informed consent was obtained from all patients before entering the research trial. The efficacy and safety of the trial were monitored by the independent data and safety monitoring committee.

2.6 | Statistical analysis

The sample size was determined based on the primary endpoint, EFS, with a type I error allocation (two-sided) of 0.05, a power of 90% and a 10% drop-out rate in the first 5 years. It was assumed that hazard ratio (HR) of experimental group and control group was 0.68, and the median EFS of control group was 20 months. We planned 3 interim analyses, with the primary efficacy endpoint, EFS, to be analyzed during the first interim analysis. This was a planned first interim analysis. The significance boundaries (0.000,02 for EFS at the first interim analysis) were adjusted with the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary that accounted for the actual number of events. $P < 0.05$ indicated statistical significance.

Data was collected for efficacy analyses from patients who were randomly assigned to either the toripalimab group or the chemotherapy group. The stratified log-rank test was used to compare EFS and OS (database lock, August 13, 2022). Patients who undergo surgery were included for the pCR analysis. The stratified Cochran-Mantel-Haenszel test was used to compare the pCRs between the 2 groups.

3 | RESULTS

3.1 | Patients and treatments

From May 15, 2020, to August 13, 2021, a total of 329 patients were screened; 252 patients were recruited successfully. They were randomized to either the toripalimab group ($n = 127$, 50.4%) or chemotherapy group ($n = 125$, 49.6%) (Figure 2). Among the 252 patients (194 [77.0%] men; median age [range], 67 [41-75] years), baseline characteristics of the 2 groups were well balanced (Table 1). Overall, 115 (93.5%) patients in the toripalimab group and 108 (90.0%) of patients in the chemotherapy group completed the prespecified neoadjuvant treatment (Figure 2). The summary of the exposures was presented in Supplementary Tables S1-S3.

3.2 | Surgical summary

The addition of toripalimab did not impair surgical treatment. Among the randomized patients, 102 (80.3%) patients in the toripalimab group and 88 (70.4%) patients in the chemotherapy group underwent definitive surgery (Table 2). The reasons for cancellations of surgery included disease progression (4 [16.7%] in the toripalimab group and 4 [11.4%] in the chemotherapy group), AEs (1 [4.2%] in the toripalimab group and 1 [2.9%] in the chemotherapy group), and other factors (19 [79.2%] in the toripalimab group and 30 [85.7%] in the chemotherapy group), such as patient refusal, unresectability, and poor lung function. The details are showed in Figure 2. The rates of delayed surgery did not significantly differ between the 2 groups (4 [3.9%] in the toripalimab group and 3 [3.4%] in the chemotherapy group, $P > 0.999$). Only 1 (1.1%) patient in the chemotherapy group underwent explorative surgery.

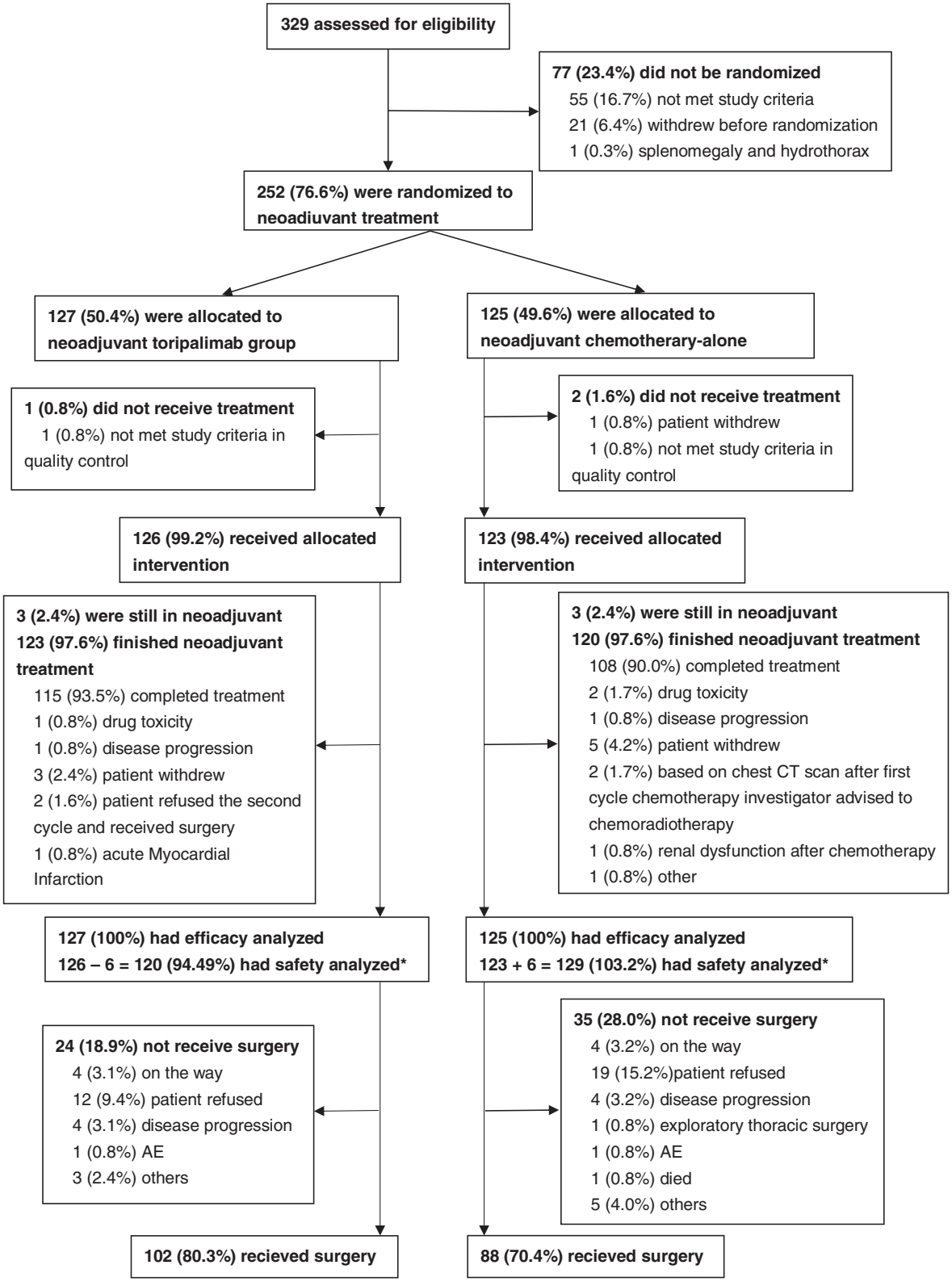

FIGURE 2 CONSORT flow chart of patient enrollment. *Six patients in the toripalimab group refused toripalimab, and they were excluded from the safety analysis. The patients were added to the chemotherapy group for safety analysis. Abbreviations: AE, adverse event; CT, computed tomography.

TABLE 1 Baseline characteristics of 252 patients with ESCC.

Characteristic	Treatment group		Test statistic χ^2	*P* value
	Toripalimab ($n = 127$)	Chemotherapy ($n = 125$)		
Age, years, median (range)	66 (41-75)	68 (45-75)	1.468	0.142[a]
Age distribution, *n* (%)			0.469	0.493[b]
< 60 years	31 (24.41)	26 (20.80)		
≥ 60 years	96 (75.59)	99 (79.20)		
Sex, *n* (%)			0.053	0.818[b]
Male	97 (76.38)	97 (77.60)		
Female	30 (23.62)	28 (22.40)		
Ethnicity, *n* (%)			0.496	0.496[c]
Han population	127 (100.00)	124 (99.20)		
Others	0 (0)	1 (0.80)		
Marital status, *n* (%)			1.000	1.000[c]
Married	124 (97.64)	123 (98.40)		
Unmarried	1 (0.79)	1 (0.80)		
Divorced	1 (0.79)	0 (0)		
Unknown	1 (0.79)	1 (0.80)		
BMI (kg/m^2)			0.025	0.9799[d]
Mean ± SD	23.49 ± 2.79	23.48 ± 3.42		
Median (interquartile range)	23.31 (21.80-25.04)	23.63 (21.09-25.34)		
Range	16.02-32.65	16.41-35.42		
Clinical T stage, *n* (%)			0.617	0.617[c]
T1b	1 (0.79)	0 (0)		
T2	10 (7.87)	7 (5.60)		
T3	116 (91.34)	118 (94.40)		
Clinical N stage, *n* (%)			0.009	0.923[b]
N0	47 (37.01)	47 (37.60)		
N+	80 (62.99)	78 (62.40)		
Clinical TNM stage, *n* (%)			0.974	0.974[c]
I	1 (0.79)	0 (0)		
II	55 (43.31)	56 (44.80)		
III	70 (55.12)	68 (54.40)		
IVA	1 (0.79)	1 (0.80)		
Classification of tissue differentiation, *n* (%)			0.345	0.345[c]
Well differentiated	72 (56.69)	62 (49.60)		
Moderately differentiated	30 (23.62)	35 (28.00)		
Poorly differentiated	23 (18.11)	28 (22.40)		
Undifferentiated	2 (1.57)	0 (0.00)		
CPS score for PD-L1, *n* (%)			0.078	0.780[b]
<5%	53 (41.73)	50 (40.00)		
≥5%	74 (58.27)	75 (60.00)		
ECOG performance status score, *n* (%)			0.200	0.200[c]
0	98 (77.17)	105 (84.00)		
1	27 (21.26)	20 (16.00)		
2	2 (1.57)	0 (0)		

(Continues)

TABLE 1 (Continued)

Characteristic	Treatment group		Test statistic χ^2	*P* value
	Toripalimab ($n = 127$)	Chemotherapy ($n = 125$)		
History of gastroesophageal disease, *n* (%)	8 (6.30)	11 (8.80)	0.565	0.452[b]
Reflux esophagitis	0 (0)	4 (3.20)		
Gastritis	6 (4.72)	7 (5.60)		
Esophageal ulcer	0 (0)	1 (0.80)		
Gastric ulcer	3 (2.36)	2 (1.60)		
Medical history, *n* (%)	97 (76.38)	80 (64.00)	4.617	0.032[b]
Diabetes	11 (8.66)	12 (9.60)		
Hepatitis B	2 (1.57)	0 (0.00)		
Coronary heart disease	9 (7.09)	7 (5.60)		
Arrhythmia	1 (0.79)	1 (0.80)		
Hypertension	41 (32.28)	35 (28.00)		
Cerebrovascular disease	12 (9.45)	13 (10.40)		
Chroniccardiac dysfunction	0 (0)	1 (0.80)		
Peripheral vascular disease	1 (0.79)	0 (0)		
Other diseases	69 (54.33)	54 (43.20)		
Smoking status, *n* (%)			0.784	0.376[b]
Smoking	86 (67.72)	78 (62.40)		
None	41 (32.28)	47 (37.60)		
Alcohol status, *n* (%)			0.023	0.879[b]
Alcohol abuse	75 (59.06)	75 (60.00)		
None	52 (40.94)	50 (40.00)		
Follow-up time[e], months, median (range)	14.0 (0-24.6)	11.4 (0.1-26.3)	−1.688	0.091[a]

Abbreviations: BMI, body mass index; CPS, combined positive score; PD-L1, programmed death-ligand 1; ECOG, eastern cooperative oncology group; SD, standard deviation; TNM, tumor node metastasis.

[a]Wilcoxon rank-sum test.

[b]chi-square test.

[c]Fisher's exact test.

[d]t test.

[e]Follow-up time = last visit date - randomization date + 1.

The median time from the completion of neoadjuvant treatment to surgery was 4.6 weeks in the toripalimab group and 4.0 weeks in the chemotherapy group, and a high percentage of patients in both groups were able to undergo surgery via minimally invasive approaches (91 [89.2%] in the toripalimab group and 76 [86.4%] in the chemotherapy group). One (1.1%) patient in the chemotherapy group died due to electrolyte disturbance.

3.3 | Primary endpoint (EFS) and key secondary endpoints (OS, pCR, and MPR)

The median follow-up time was 14.0 months in the toripalimab group and 11.4 months in the chemotherapy group. The minimum follow-up time of all patients recruited in this study was 0 (range, 0 to 26.3 months), and the median EFS was not reached in toripalimab and chemotherapy group. In the ITT population, the 1-year EFS rate was 77.9% (95% CI, 68.6 to 84.8) in the toripalimab group and 64.3% (95% CI, 54.1 to 72.8) in the chemotherapy group (hazard ratio [HR], 0.62; 95% CI, 0.39 to 1.00; $P = 0.050$) (Figure 3). The 1-year OS rate was 94.1% (95% CI, 87.2 to 97.3) in the toripalimab group and 83.0% (95% CI, 73.6 to 89.2) in the chemotherapy group (HR, 0.48; 95% CI, 0.24 to 0.97; $P = 0.037$) (Figure 4).

Among surgical patients, 18.6% of patients in the toripalimab group attained pCR, versus 4.6% in the chemotherapy group (odds ratio [OR], 14.85; 95% CI, 6.84 to 22.87; $P = 0.001$) (Supplementary Table S4).

The percentage of patients achieving MPR was higher in the toripalimab group 30 (29.4%) compared to the chemotherapy group 6 (6.8%) (Supplementary Table S5). The rates of MPR were higher among those with lymph node involvement at baseline in toripalimab and chemotherapy group (Supplementary Table S6).

TABLE 2 Surgical outcome of 190 patients with ESCC.

Surgical outcome[a]	Treatment group		*P* value
	Toripalimab (*n* = 102)	Chemotherapy (*n* = 88)	
Time from last neoadjuvant dose to definitive surgery, weeks, median (IQR)	4.6 (3.6, 5.3)	4.0 (1.4, 4.9)	0.065
Duration of surgery, min, median (IQR)	300.0 (270.0, 340.0)	300.0 (256.5, 345.0)	0.651
Surgical approach, *n* (%)			0.654
McKeown minimally invasive surgery	91 (89.22)	76 (86.36)	
Right thoracotomy	2 (1.96)	1 (1.14)	
Others[b]	9 (8.82)	11 (12.50)	
Intraoperative blood loss[c], mL			0.490
Mean ± SD	136.8 ± 94.46	144.3 ± 97.50	
Median (Q1, Q3)	100 (100, 200)	100 (100, 200)	
Range	0-800	0-750	
Number of resected lymph nodes[d], *n*			0.303
Mean (SD)	25.40 (7.92)	24.70 (10.06)	
Median (Q1, Q3)	25 (20, 30)	23 (17, 30)	
Min, Max	9, 55	9, 58	
Placement time of a postoperative drainage tube, min			0.886
Mean ± SD	12.70 ± 6.07	12.70 ± 6.19	
Median (interquartile range)	12.0 (9.0-15.0)	12.0 (9.0-15.0)	
Range	6-54	7-52	
Postoperative complication, *n* (%)			0.918
Yes	91 (89.11)	78 (88.64)	
No	11 (10.89)	10 (11.36)	
Length of postoperative hospital stay, days, median (IQR)	12 (10, 15)	12 (10, 15)	0.949
30-day mortality after surgery, *n* (%)	2 (1.96)	0 (0)	0.500
90-day mortality after surgery, *n* (%)	3 (2.94)	3 (3.41)	> 0.999
Patients receiving a second operation within 90 days after surgery, *n* (%)	1 (0.98)	0 (0)	> 0.999
Delayed surgery, days, Mean ± SD	4 ± 3.92	3 ± 3.41	> 0.999
Pathological N stage, *n* (%)			< 0.001
N0	76 (74.51)	54 (61.36)	
N1	19 (18.63)	19 (21.59)	
N2	7 (6.86)	11 (12.50)	
N3	0 (0)	3 (3.41)	
Unknown	0 (0)	1 (1.14)	
Pathological TNM stage, *n* (%)			< 0.001
I	56 (54.90)	29 (32.95)	
II	21 (20.59)	25 (28.41)	
IIIa	8 (7.84)	7 (7.95)	
IIIb	17 (16.67)	23 (26.14)	
IVa	0 (0)	3 (3.41)	
Unknown	0 (0)	1 (1.14)	

(Continues)

TABLE 2 (Continued)

Surgical outcome[a]	Treatment group: Toripalimab ($n = 102$)	Treatment group: Chemotherapy ($n = 88$)	*P* value
TRG, *n* (%)			< 0.001
TRG0	31 (30.39)	6 (6.82)	
TRG1	14 (13.73)	7 (7.95)	
TRG2	35 (34.31)	50 (56.82)	
TRG3	17 (16.67)	22 (25.00)	
Unknown	5 (4.90)	3 (3.41)	
R0 resection rate, *n* (%)	102 (100)	88 (100)	> 0.999

Abbreviations: IQR, interquartile range; N, node; Q, quartile; SD, standard deviation; TNM, tumor node metastasis; TRG, tumor regression grade.

[a]Denominator based on the number of patients included in the intent-to-treat cohort.

[b]Included robot-assisted laparoscopic surgery and hybrid minimally invasive surgery.

[c]One patient in toripalimab group and one patient in chemotherapy group had missing information on intraoperative blood loss.

[d]One patient in toripalimab group and one patient in chemotherapy group had missing information on the number of resected lymph nodes.

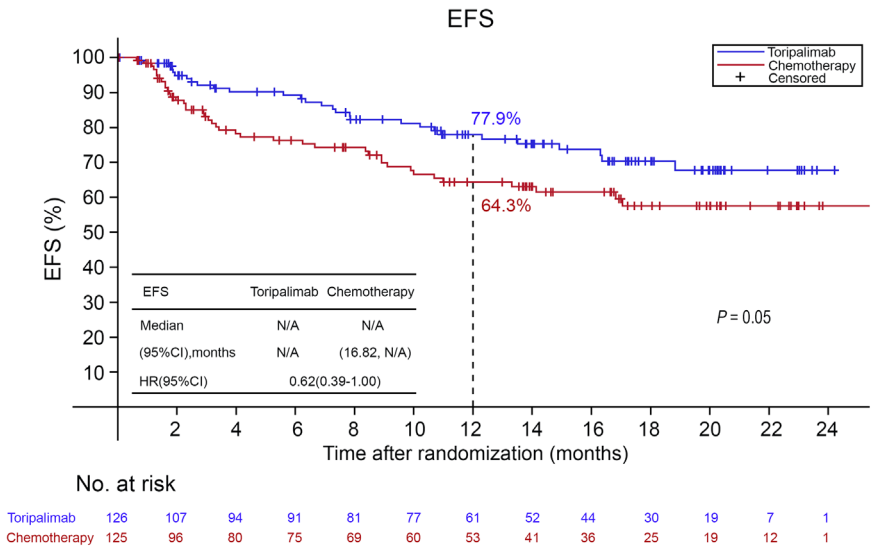

FIGURE 3 The EFS in this study. The 95% CI of the HR for EFS was 0.39 to 1.00. At this first prespecified interim analysis, the *P* value for OS did not cross the boundary for statistical significance. Abbreviations: CI, confidence interval; EFS, event free survival; HR, hazard ratio; NAIC, immunochemotherapy; N/A, not available; NAC, neoadjuvant chemotherapy; OS, overall survival.

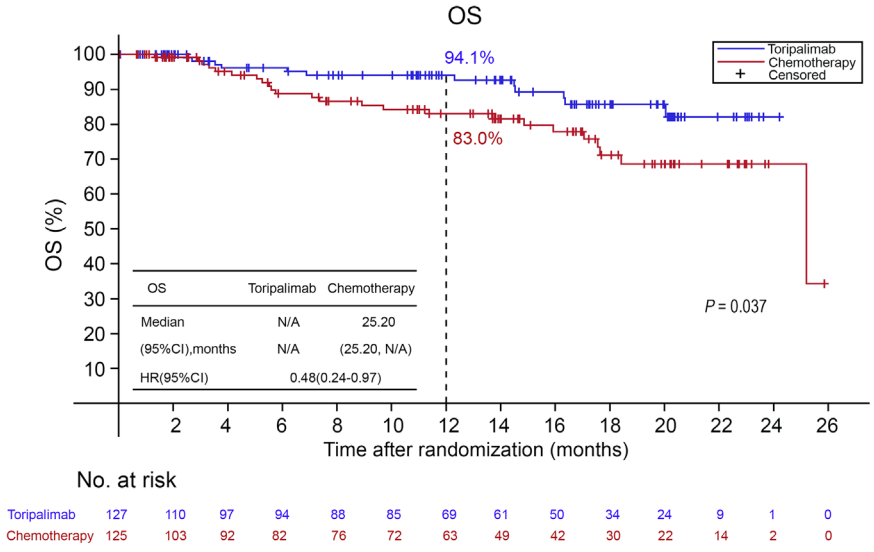

FIGURE 4 The OS in this study. The 95% CI of the HR for OS was 0.24 to 0.97. At this first prespecified interim analysis, the *P* value for OS was statistical significance. Abbreviations: CI, confidence interval; HR, hazard ratio; N/A, not available; NAIC, immunochemotherapy; NAC, neoadjuvant chemotherapy; OS, overall survival.

TABLE 3 Most frequent TRAEs in toripalimab group and chemotherapy group (≥15% of patients in any treatment group).

Event	Treatment group				Test statistic χ^2	*P* value
	Toripalimab ($n = 120$)		Chemotherapy ($n = 129$)			
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4		
TRAE, *n* (%)	120 (100.00)	15 (12.50)	129 (100.00)	16 (12.40)	N/A	N/A
Metabolic and nutritional disease, *n* (%)	118 (98.33)	3 (2.50)	125 (96.90)	2 (1.55)	0.105	0.746
Hypoalbuminemia	44 (36.67)	0 (0)	41 (31.78)	0 (0)	0.659	0.417
Hypocalcemia	17 (14.17)	0 (0)	20 (15.50)	0 (0)	0.088	0.767
Hypokalemia	18 (15.00)	0 (0)	17 (13.18)	0 (0)	0.171	0.679
Hyponatremia	51 (42.50)	2 (1.67)	35 (27.13)	1 (0.78)	6.494	0.011
Hyperglycemia	22 (18.33)	0 (0)	24 (18.60)	0 (0)	0.003	0.956
Loss of appetite	117 (97.50)	0 (0)	116 (89.92)	1 (0.78)	5.937	0.015
Hyperkalemia	5 (4.17)	1 (0.83)	5 (3.88)	0 (0)	N/A	1.000
Musculoskeletal and connective tissue disease, *n* (%)	19 (15.83)	0 (0)	19 (14.73)	2 (1.55)	0.059	0.809
Skin and subcutaneous tissue disease, *n* (%)	111 (92.50)	0 (0)	120 (93.02)	1 (0.78)	0.025	0.873
Rash	18 (15.00)	0 (0)	5 (3.88)	1 (0.78)	9.176	0.002
Loss of hair	107 (89.17)	0 (0)	114 (88.37)	0 (0)	0.039	0.843
Itching	35 (29.17)	0 (0)	23 (17.83)	1 (0.78)	4.472	0.034
Systemic disease, *n* (%)	117 (97.50)	11 (9.17)	120 (93.02)	7 (5.43)	2.716	0.099
Fever	23 (19.17)	1 (0.83)	18 (13.95)	1 (0.78)	1.228	0.268
Fatigue	115 (95.83)	9 (7.50)	116 (89.92)	4 (3.10)	3.239	0.072
Pain	78 (65.00)	8 (6.67)	63 (48.84)	2 (1.55)	N/A	0.011[a]
Gastrointestinal disease, *n* (%)	115 (95.83)	1 (0.83)	125 (96.90)	3 (2.33)	0.012	0.912
Constipation	56 (46.67)	0 (0)	62 (48.06)	0 (0)	0.049	0.826
Nausea	101 (84.17)	1 (0.83)	108 (83.72)	0 (0)	0.009	0.924
Diarrhea	58 (48.33)	0 (0)	62 (48.06)	1 (0.78)	0.002	0.966
Abdominal distention	27 (22.50)	0 (0)	26 (20.16)	0 (0)	0.204	0.651
Dry mouth	31 (25.83)	0 (0)	27 (20.93)	0 (0)	0.836	0.360
Abdominal pain	3 (2.50)	0 (0.00)	6 (4.65)	1 (0.78)	N/A	0.502[a]
Vomiting	42 (35.00)	1 (0.83)	39 (30.23)	1 (0.78)	N/A	0.499[a]

[a]Fisher's exact test.

Abbreviations: N/A, not available; TRAE, treatment-related adverse event.

3.4 | Safety and surgical complications

Treatment-related AEs (TRAEs) of any grade occurred in 100% of patients in toripalimab and chemotherapy group, with the most common grade 1 or 2 TRAEs were lymphopenia and leukopenia (60.0% and 64.3%, respectively) (Table 3). The incidences of grade 3 or 4 TRAEs were 12.5% and 12.4%, respectively (Supplementary Table S7). The most common grade 3 or 4 TRAEs were hyponatremia (1.7%) in the toripalimab group and leukopenia (3.9%) in the chemotherapy group. The incidence of any grade AEs leading to surgical delay and/or cancellation was 0.8% in the toripalimab group and 1.6% in the chemotherapy group (Supplementary Table S7). Overall, immune-related AEs (irAEs) were infrequent, with grade 1 or 2 events being the most frequent. The incidences of grade 3-4 irAEs were 2.5% (toripalimab group) and 0.8% (chemotherapy group). Hypothyroidism (23.3% of patients) was the most common irAE of any grade, four patients (3.3%) had grade 1 or 2 pneumonitis in the toripalimab group. There were also irAE occurred in the chemotherapy group, one patient (0.8%) had grade 3 skin rash (Supplementary Table S8). No treatment-related deaths were reported. None of the patients experienced fatal AEs unrelated to

surgery; 3 patients in each group died within 90 days after surgery.

The surgical delay rates were 3.9% in the toripalimab group and 3.4% in the chemotherapy group. The rates of grade 3 or 4 surgery- related AEs alone were 13.1% in the toripalimab group and 29.7% in the chemotherapy group (Supplementary Table S7). Details regarding surgical complications were presented in Table 4.

4 | DISCUSSION

This phase III study evaluated the efficacy and safety of PD-1 inhibitor combined with chemotherapy in neoadjuvant and adjuvant setting compared with NAC in patients with resectable ESCC. This interim analysis of EFS ($P = 0.050$) and OS ($P = 0.037$) demonstrated a potential survival trend in favor of immunochemotherapy. Although the EFS did not achieve statistical significance, which may attribute to the very early midterm analysis, the noteworthy trends were observed. In the era of PD-1 inhibitor, it was soon demonstrated to be effective in melanoma [18]. Then it was moving from late stage to early stage carcinoma, from adjuvant to neoadjuvant setting in melanoma [11], lung cancer [9], and so on. An increasing amount of data also has shown that immunochemotherapy was more effective than single PD-1 antibodies or chemotherapy alone [19]. Our study also supports this theory and previous findings [19]. The other secondary endpoints, pCR rate, R0 resection rate and MPR rate, also favored the toripalimab group. The safety of this treatment was quite consistent with that in previous studies [14, 15]. The final analysis was still needed to draw a convincing conclusion.

The addition of toripalimab to NAC resulted in a higher percentage of patients who achieved a pCR (18.6% vs. 4.6%), suggesting potential improvements in survival outcomes [5]. Notably, the pCR rate in the toripalimab group (18.6%) was lower than that in the other neoadjuvant immunochemotherapy group, as shown in our previous phase II study (36%) [14, 15] and the NICE study (39.2%) [20]. The sample size of this study was much larger than that of the phase II study, which might make the results of this study more convincing. According to the KEYNOTE-671 trial, the pCR rate of lung cancer patients receiving neoadjuvant immunochemotherapy was 18.1% [21], which was consistent with our data. Although there was a lock of prospective clinical trial evidence regarding the correlation between pCR and survival outcomes in patients with ESCC undergoing immunotherapy. This study demonstrated a correlation between pCR and OS. The rate of pCR may serve as an early predictor of treatment effectiveness in surgically resectable ESCC patients. Further investigation is needed to assess the potential survival benefits associated with a pathological response in ongoing trials of immunochemotherapy for ESCC.

This study showed that neither the incidence nor severity of AEs increased with the addition of toripalimab to NAC. Consequently, there was no significant difference in the postoperative complication rate, mortality or reduced feasibility of surgery; moreover, the safety of these methods was consistent with that in previous studies [14, 15, 20, 22].

The incidence of grade 3-4 leukopenia was lower in this study than in the NACR group within the NEOCRTEC5010 trial (17%) [23] and in our previous phase II study (13.33%) [14]. In our present study, the incidence of grade 3-4 irAEs was 2.5% in the toripalimab group, similar to that in the CheckMate 816 trial (1.7%) [9], slightly higher than that in the CheckMate 577 trial (<1%) [8], and lower than that reported for toripalimab as advanced first-line therapy (7%) [13]. The most common irAE in our study was hypothyroidism (23.3%), and grade 1-2 irAEs are most observed [24]. Therefore, perioperative treatment with toripalimab combined with NAC for ESCC does not increase AEs in the perioperative setting.

The surgical data demonstrated that neoadjuvant immunochemotherapy maintained a high R0 resection rate comparable to that of NACR and did not increase the difficulty of resection of the primary tumor or lymph nodes [3, 23]. Moreover, the median number of harvested lymph nodes in this study (25) was much higher than that in previous randomized controlled trials (RCTs) (20.0 in NEOCRTEC 5010 [23] and unknown in CheckMate 577 [8]). The anastomotic leakage rate was 4.0% in the toripalimab group, which was much lower than 8.6% in the NACR group in NEOCRTEC 5010 [24] and 7% in the NAC group in OEO2 [25]. Overall, the surgical outcomes were favorable in the toripalimab group, characterized by fewer surgical cancellations (including for disease progression) and fewer cases of blood loss. MIE was an approach for improving the recovery of physical function and reducing serious AEs. In this study, 89.2% patients in toripalimab group were able to undergo surgery via MIE compared to 86.4% in the chemotherapy group. Although the reasons for this difference have yet to be determined, the higher rate of radiographic downstaging, higher response rate and greater pathological regression than that in the NAC group may have contributed to the seemingly improved surgical outcomes.

This study has several limitations that should be acknowledged. First, because this study was an interim analysis, the number of enrolled patients was relatively small, and the follow-up period was not long enough to draw a clear conclusion. Consequently, the survival data should be carefully interpreted to avoid potential confounders. Second, as a single-center randomized phase

TABLE 4 Surgical complications in toripalimab group and chemotherapy group.

Morbidity type	Treatment group, *n* (%)		Between-group difference, RD (95%CI)[a]	*P* value
	Toripalimab (*n* = 102)	Chemotherapy (*n* = 88)		
All complications	99 (97.06)	87 (98.86)	−1.8 (−7.24 to 3.58)	0.721
Metabolic and nutritional diseases	4 (3.92)	1 (1.14)	2.79 (−2.78 to 8.59)	0.458
Hyponatremia	1 (0.98)	1 (1.14)		
Hyperkalemia	1 (0.98)	1 (1.14)		
Anorexia	2 (1.96)	0 (0)		
Hypoproteinemia	0 (0)	1 (1.14)		
Hypokalemia	1 (0.98)	0 (0)		
Infection and inflammation	79 (77.45)	58 (65.91)	11.54 (−1.24 to 24.08)	0.077
Pneumonia[b]	78 (76.47)	58 (65.91)		
Septic shock	1 (0.98)	1 (1.14)		
Incision infection	1 (0.98)	1 (1.14)		
Injuries and operative complications	9 (8.82)	10 (11.36)	−2.54 (−11.81 to 6.19)	0.561
Anastomotic fistula	6 (5.88)	6 (6.82)		
Anastomotic stricture	2 (1.96)	4 (4.55)		
Incision swelling	1 (0.98)	0 (0)		
Respiratory, chest and mediastinal diseases	96 (94.12)	82 (93.18)	0.94 (−6.4 to 8.86)	0.791
Cough	27 (26.47)	16 (18.18)		
Respiratory failure	5 (4.90)	5 (5.68)		
Tracheal fistula	0 (0)	2 (2.27)		
Chest hemorrhage	1 (0.98)	0 (0)		
Pleural effusion	60 (58.82)	60 (68.18)		
dysphonia	54 (52.94)	53 (60.23)		
Atelectasis	56 (54.90)	45 (51.14)		
pneumothorax	22 (21.57)	25 (28.41)		
Gastrointestinal diseases	17 (16.67)	4 (4.55)	12.12 (3.23 to 20.98)	0.008
Diarrhea	8 (7.84)	0 (0)		
Abdominal hemorrhage	2 (1.96)	0 (0)		
Flatulence	1 (0.98)	0 (0)		
Gastric emptying disorder	1 (0.98)	0 (0)		
Gastric fistula	1 (0.98)	0 (0)		
Others	4 (3.92)	4 (4.55)		
Heart disease	46 (45.10)	46 (52.27)	−7.17 (−20.92 to 6.95)	0.324
Arrhythmia	36 (35.29)	34 (38.64)		
Sinus arrhythmia	5 (4.90)	10 (11.36)		
Atrial fibrillation	5 (4.90)	0 (0)		
Sinus tachycardia	3 (2.94)	2 (2.27)		
Clavien–Dindo grade				
I-II	78 (76.47)	61 (69.32)	7.15 (−5.41 to 19.69)	0.267
III-IV	19 (18.63)	26 (29.55)	−10.92 (−22.96 to 1.21)	0.078
V	2 (1.96)	0 (0)	1.96 (−2.46 to 6.87)	0.500
Clavien-Dindo grade IIIb or higher	10 (9.80)	6 (6.82)	2.99 (−5.51 to 11.16)	0.460
90-day postoperative mortality	3 (2.94)	3 (3.41)	−0.47 (−6.91 to 5.33)	>0.999

[a]Calculated using the Newcombe method.
[b]Any patchy on chest CT scan.
Abbreviations: RD, rate difference; CI, confidence interval.

III study, center bias could not be avoided. Our center is located in the area with the highest incidence of ESCC in the world; the number of esophagectomy procedures for ESCC is approximately 1,000 to 1,500 per year. This rich experience might have impacted the survival data.

5 | CONCLUSIONS

Overall, this phase III RCT provided robust evidence supporting the efficacy of neoadjuvant toripalimab in combination with NAC-TP and adjuvant toripalimab for resectable ESCC. Our findings in this study support further insights into potential new immunotherapy algorithms for resectable ESCC, such as the duration and dosage of adjuvant treatment, as well as the possibility of reducing the amount of combined chemotherapy and other chemotherapeutic regimens.

AUTHOR CONTRIBUTIONS

Conception and design: Yan Zheng. Supervision of study: Jiangong Zhang, Wenqun Xing, Peng Zhang, and Wenjie Ma. Provision of study materials or patients: Guanghui Liang, Dongfeng Yuan, Xianben Liu, Yufeng Ba, Zimin Qin, Sining Shen, Zhenxuan Li, Haibo Sun, Baoxing Liu, Peng Li, Zongfei Wang, Shilei Liu, Jianping Zhu, Haoran Wang, Haibo Ma, Ming Yan, Yongkui Yu, Zhenzhen Liu, Fei Zhao, Jun Zhang, He Zhang, Daoyuan Wu, Jinrong Qu, and Jie Ma. Collection and assembly of data: Qing Li, Yan Zheng, Guanghui Liang, Dongfeng Yuan and Quanli Gao. Data analysis and interpretation: Qing Li, Yan Zheng, Guanghui Liang, and Dongfeng Yuan. Manuscript writing: all authors. Final approval of manuscript: all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data and data sets generated in current work are available from corresponding authors on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the independent Ethics Committee of Henan Cancer Hospital (ID: 2019092702). The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The written informed consent was obtained from every participate.

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REFERENCES

1. Demarest CT, Chang AC. The Landmark Series: Multimodal Therapy for Esophageal Cancer. Ann Surg Oncol. 2021;28(6):3375-82.
2. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19(1):68-74.
3. van Heijl M, van Lanschot JJ, Koppert LB, van Berge Henegouwen MI, Muller K, Steyerberg EW, et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). BMC Surg. 2008;8:21.
4. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062-7.
5. Zheng Y, Li Y, Liu X, Sun H, Wang Z, Zhang R. Reevaluation of Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma: A Meta-Analysis of Randomized Controlled Trials Over the Past 20 Years. Medicine (Baltimore). 2015;94(27):e1102.
6. Klevebro F, Alexandersson von Dobeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660-7.
7. Zhao JJ, Yap DWT, Chan YH, Tan BKJ, Teo CB, Syn NL, et al. Low Programmed Death-Ligand 1-Expressing Subgroup Outcomes of First-Line Immune Checkpoint Inhibitors in Gastric or Esophageal Adenocarcinoma. J Clin Oncol. 2022;40(4):392-402.
8. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021;384(13):1191-203.

9. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022;386(21):1973-85.
10. Long GV, Menzies AM, Scolyer RA. Neoadjuvant Checkpoint Immunotherapy and Melanoma: The Time Is Now. J Clin Oncol. 2023;41(17):3236-48.
11. Patel SP, Othus M, Chen Y, Wright GP, Jr., Yost KJ, Hyngstrom JR, et al. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. N Engl J Med. 2023;388(9):813-23.
12. Zhang L, Hao B, Geng Z, Geng Q. Toripalimab: the First Domestic Anti-Tumor PD-1 Antibody in China. Front Immunol. 2021;12:730666.
13. Wang ZX, Cui C, Yao J, Zhang Y, Li M, Feng J, et al. Toripalimab plus chemotherapy in treatment-naive, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. Cancer Cell. 2022;40(3):277-88 e3.
14. Xing W, Zhao L, Zheng Y, Liu B, Liu X, Li T, et al. The Sequence of Chemotherapy and Toripalimab Might Influence the Efficacy of Neoadjuvant Chemoimmunotherapy in Locally Advanced Esophageal Squamous Cell Cancer-A Phase II Study. Front Immunol. 2021;12:772450.
15. Xing W, Zhao L, Fu X, Liang G, Zhang Y, Yuan D, et al. A phase II, single-centre trial of neoadjuvant toripalimab plus chemotherapy in locally advanced esophageal squamous cell carcinoma. J Thorac Dis. 2020;12(11):6861-7.
16. Zheng Y, Liu XB, Sun HB, Xu J, Shen S, Ba YF, et al. A phase III study on neoadjuvant chemotherapy versus neoadjuvant toripalimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: Henan Cancer Hospital Thoracic Oncology Group 1909 (HCHTOG1909). Ann Transl Med. 2021;9(1):73.
17. Sun HB, Li Y, Liu XB, Zhang RX, Wang ZF, Lerut T, et al. Early Oral Feeding Following McKeown Minimally Invasive Esophagectomy: An Open-label, Randomized, Controlled, Non-inferiority Trial. Ann Surg. 2018;267(3):435-42.
18. Breakthrough of the year 2013. Notable developments. Science. 2013;342(6165):1435-41.
19. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol. 2015;33(17):1974-82.
20. Liu J, Yang Y, Liu Z, Fu X, Cai X, Li H, et al. Multicenter, single-arm, phase II trial of camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma. J Immunother Cancer. 2022;10(3):e004291.
21. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med. 2023;389(6):491-503.
22. Yan X, Duan H, Ni Y, Zhou Y, Wang X, Qi H, et al. Tislelizumab combined with chemotherapy as neoadjuvant therapy for surgically resectable esophageal cancer: A prospective, single-arm, phase II study (TD-NICE). Int J Surg. 2022;103:106680.
23. Yang H, Liu H, Chen Y, Zhu C, Fang W, Yu Z, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol. 2018;36(27):2796-803.
24. Yoon JH, Hong AR, Kim HK, Kang HC. Characteristics of Immune-Related Thyroid Adverse Events in Patients Treated with PD-1/PD-L1 Inhibitors. Endocrinol Metab (Seoul). 2021;36(2):413-23.
25. Medical Research Council Oesophageal Cancer Working G. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727-33.

SUPPORTING INFORMATION

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

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