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Title page

Neoadjuvant camrelizumab plus chemotherapy for resectable, locally advanced esophageal squamous cell carcinoma (NIC-ESCC2019): a multicenter, phase 2 study

Short Title: Neoadjuvant camrelizumab plus chemotherapy for ESCC

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ijc.33976

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Keywords: neoadjuvant chemoimmunotherapy; camrelizumab; resectable; locally advanced; esophageal squamous cell carcinoma.

Abbreviations:

AE, adverse event; AJCC, American Joint Committee on Cancer; CPR, complete pathologic response; CPS, combined positive score; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; IPR, incomplete pathologic response; mIHC, multiplex immunohistochemistry; MPR, major pathologic response; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy;

NIC, neoadjuvant chemoimmunotherapy; ORR, objective response rate; OS, overall survival; PD, progressive disease; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TIL, tumor-infiltrating lymphocyte; TRAE, treatment-related adverse event; TRG, tumor regression grade.

Article category: Research Article

Novelty and Impact:

This is the first comprehensive report of neoadjuvant chemoimmunotherapy for esophageal squamous cell carcinoma (ESCC). Neoadjuvant camrelizumab plus chemotherapy shows promising complete pathologic response in primary tumor, complete tumor resection, high downstaging rate, manageable safety profile, and low postoperative comorbidity in patients with resectable, locally advanced ESCC. Additionally, lymphatic metastases seem to have better response compared with primary lesions.

Word count: 2488

Figures: 2

Tables: 4

Supplemental material: 1

Abstract

Optimal treatment for resectable esophageal squamous cell carcinoma (ESCC) is controversial, especially in the context of potential benefit of combining PD-1 blockade with neoadjuvant therapy. This phase 2 study aimed to assess neoadjuvant camrelizumab plus chemotherapy in this population. Patients (clinical stage II-IVA) received two cycles of neoadjuvant chemoimmunotherapy (NIC) with camrelizumab (200 mg on day 1) plus nab-paclitaxel (260 mg/m² in total on day 1 and day 8) and cisplatin (75 mg/m² in total on days 1 to 3) of each 21-day cycle. Surgery was performed approximately six weeks after completion of NIC. Primary endpoint was complete pathologic response (CPR) rate in primary tumor. Secondary endpoints were objective response rate (ORR) per RECIST v1.1, two-year progression-free survival (PFS) rate after surgery, PFS, overall survival (OS), and safety during NIC and perioperative period. Between Jan 17, 2020 and Dec 8, 2020, 56 patients were enrolled, and 51 received esophagectomy. Data cutoff date was Aug 25, 2021. The CPR rate was 35.3% (95% CI, 21.7%-48.9%). NIC had an ORR of 66.7% (95% CI, 40.0%-70.4%) and treatment-related adverse events (TRAEs) of low severity (grade 1-2, 75.0%; grade 3, 10.7%; grade 4-5, no). No perioperative mortality occurred. Three (5.9%) patients had tumor recurrence and one (2.0%) patient died. The two-year PFS rate, median PFS, and median OS had not been reached yet. Camrelizumab plus neoadjuvant chemotherapy in resectable ESCC demonstrates promising efficacy with acceptable toxicity, providing a feasible and effective option. Study is ongoing for long-term survival analyses.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related deaths worldwide [1]. Esophageal squamous cell carcinoma (ESCC) remains the predominant histologic subtype, especially in Asia [2]. For patients with resectable, locally advanced ESCC, neoadjuvant chemoradiotherapy (nCRT) followed by surgery is recommended as the first choice [3-6]. However, many patients fail to complete the whole treatment cycle in clinical practices due to adverse events (AEs). Although nCRT resulted in a higher complete pathologic response (CPR) rate in the primary tumor over neoadjuvant chemotherapy (nCT), no survival benefits were reported [7, 8], and the AEs during neoadjuvant treatment [8] or postoperative complications were more severe with nCRT [7]. In addition, 33.7% to 48.3% of patients eventually experienced recurrences after nCRT [9-11]. Resectable, locally advanced ESCC patients still lack effective systemic therapies.

Immune checkpoint blockade has changed the treatment paradigm of multiple advanced cancers. Compared with esophageal adenocarcinoma, ESCC exhibited a relatively higher prevalence of immune-related biomarkers (such as TMB-high and PD-L1 overexpression; especially in primary tumors than metastatic tumors) and earlier lymphatic spread (mainly lymphatic vessel invasion) [12, 13], demonstrating the potential sensitivity of ESCC to immune checkpoint inhibitors. Combination of nCRT with pembrolizumab increased the CPR rate, but the incidence of grade 3 or worse AEs was high and deaths during neoadjuvant therapy were reported [14, 15]. Hence, there is still an unmet need for the development of alternative therapies without radiation.

Camrelizumab (SHR-1210, an anti-PD-1 antibody) monotherapy was approved as the second-line therapy [16] and its combination with chemotherapy was approved as the first-line therapy [17] for patients with advanced or metastatic ESCC in China. Addition of camrelizumab to chemotherapy showed clinical and statistical survival benefits in the first-line setting [17], suggesting the synergistic or additive effect of camrelizumab on a chemotherapy regimen. We

designed this study to assess the feasibility, safety, and efficacy of neoadjuvant camrelizumab plus chemotherapy in patients with resectable ESCC.

Methods

Study design and participants

NIC-ESCC2019 is a multicenter, open-label, single-arm, phase 2 study conducted in China (ClinicalTrials.gov, number NCT04225364; Supplementary Figure S1). Eligible patients were 18 to 70 years of age and had histologically or cytologically confirmed resectable thoracic ESCC with clinical stages of T2N1-3M0/T3N0-3M0/T4N0-3M0 (stage II-IVA) according to American Joint Committee on Cancer (AJCC) staging manual 8th edition [18]. Prior systemic or topical treatment for ESCC was not allowed. Full inclusion and exclusion criteria are listed in Supplemental Method.

Pre-treatment staging

All patients underwent pre-treatment tumor staging centrally according to AJCC criteria (8th edition), by means of esophagogastroduodenoscopy diagnostic biopsy with endoscopic ultrasound (EUS), magnetic resonance imaging of brain and cervical-abdominal contrast-enhanced CT or chest-abdominal contrast-enhanced CT and cervical ultrasonography. Either positron emission tomography computed tomography or radionuclide bone imaging were also performed.

Neoadjuvant treatment and outcome measurements

Eligible patients were given two cycles of NIC with intravenous camrelizumab at 200 mg on day 1, nab-paclitaxel at 260 mg/m² in total on day 1 and day 8 (i.e. 130 mg/m² per day), and cisplatin at 75 mg/m² in total on days 1-3 (i.e. 25 mg/m² per day) of each 21-day cycle. Treatment interruptions as well as dose reductions of nab-paclitaxel to 220 and then 180 mg/m²

and reductions of cisplatin to 50 and then 25 mg/m² were allowed.

After completion of NIC, patients underwent clinical restaging by means of esophagogastroduodenoscopy with ultrasound endoscopy, chest-abdominal contrast-enhanced CT and cervical ultrasonography or cervical-abdominal contrast-enhanced CT, as well as physical examination, standard laboratory tests, and pulmonary function tests.

Radiologic responses were assessed one week before surgery and every three months after surgery by an independent central expert radiologist based on RECIST v1.1.

Any AEs occurring during the period from the signing of the informed consent form to surgery were recorded and graded according to NCI-CTCAE v5.0.

Surgical procedure and outcome measurements

Minimally invasive McKeown esophagectomy including extensive two-field lymphadenectomy [19] was performed approximately six weeks after completion of NIC. The dissection of left and right recurrent laryngeal nerve nodes was requested. Adjuvant treatment was permitted but not mandatory. The decision was made by patients and his or her relatives depending on the recommendation of multi-disciplinary team.

Objective pathologic response was assessed by local pathologists and confirmed by two independent central pathologists. CPR was defined as no evidence of residual tumor cells, major pathologic response (MPR) was defined as 10% or fewer residue, and incomplete pathologic response (IPR) was defined as more than 10% residue.

Surgical outcomes including intraoperative findings as well as morbidity, mortality, and complications during the first 30 days after surgery were monitored.

Procedures for biomarker assessments

PD-L1 expression was assessed by a central laboratory on pre-treatment FFPE tumor tissue sections using an automated immunohistochemistry (IHC) assay (PD-L1 IHC 22C3 pharmDx; Dako, Santa Clara, CA). PD-L1 positivity was defined as combined positive score (CPS) ≥1.

Paired resection specimens (pre-treatment and post-treatment) were subjected to fluorescence multiplex immunohistochemistry (mIHC) staining to assess tumor-infiltrating lymphocytes (TILs) density and dynamic changes.

Outcomes

The primary endpoint was CPR rate in the primary tumor, and secondary endpoints were objective response rate (ORR) per RECIST version 1.1, two-year progression-free survival (PFS) rate after surgery, PFS, overall survival (OS), and safety during NIC and perioperative period. Prespecified exploratory endpoints included investigating whether immune cell populations in the tumor microenvironment could identify response biomarkers.

Statistical analysis

The reported CPR rate of primary esophagus after nCT was approximately 16% [20]. Assuming that neoadjuvant camrelizumab plus nab-paclitaxel-cisplatin regimen would achieve a CPR rate of 30%, a sample size of 49 was required to provide 80% power, calculated using the one-proportion Z-test with a one-sided type I error of 5%. Considering a dropout rate of 15%, we planned to enroll 58 patients.

Comparisons among three groups (CPR, MPR, *vs.* IPR) were done using Fisher's exact test for categorical variables and Kruskal-Wallis H test for continuous variables. Comparisons between patients with pathologic/radiologic response and non-response were performed using Pearson's Chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. In addition, changes in TILs before and after NIC were analyzed by using Wilcoxon signed-rank test. $P < 0.05$ was considered to indicate a statistically significant difference. The data cutoff for the present analysis here was Aug 25, 2021. Stata software was used for all statistical analyses (version 15.0).

Results

Patients characteristics and disposition

From Jan 17, 2020 through Dec 8, 2020, 80 patients were assessed for eligibility, of whom 24 were excluded due to occult metastasis (n=12), withdrawal by patients (n=6), unresectable disease (n=4), or compromised general condition (n=2; Figure 1). As a result, 56 patients were enrolled. The median age was 61 years (range, 40 to 70), and majority of patients had tumors located in the middle or lower esophagus (98.2%; Table 1).

All 56 patients received at least once study NIC treatment, and 51 (91.1%) of them completed the preplanned two cycles of NIC and underwent surgery (Figure 1). Twenty-three (45.1%) patients received adjuvant therapy (chemotherapy plus PD-1, 14 [27.5%]; chemotherapy, five [9.8%]; PD-1 inhibitor, four [7.8%]). The median cycle of adjuvant therapy was 4 (range, 1 to 6).

Pathologic and radiologic outcomes

Pathologic profile of the 51 patients after tumor resection are summarized in Supplementary Table S1 and S2. Eighteen (35.3%; 95% CI, 21.7% to 48.9%, power = 0.942) patients achieved a CPR in the primary tumor (ypT0), 12 (23.5%) had an MPR, and 21 (41.2%) had an IPR. Of note, 16 (31.4%; 95% CI, 18.2% to 44.6%) patients achieved a CPR in the primary tumor and lymph nodes (ypT0N0). All patients achieved R0 resection (51/51, 100%). The pathologic downstaging occurred in 39 (76.5%) patients.

In a post-hoc analysis, no significant associations were observed between baseline characteristics and pathologic response, but chemotherapy dose reduction during the second cycle of NIC was related to a poor pathologic response ($p = 0.006$; Table 2).

According to RECIST v1.1, seven (13.7%) of the 51 patients achieved complete response (CR), 27 (52.9%) achieved partial response (PR), and 17 (33.3%) had stable disease (SD). The ORR was 66.7% (95% CI, 40.0% to 70.4%). No significant association between radiologic

response to NIC and pathologic response after surgery was observed (Table 2).

As of data cutoff, only three (5.9%) patients experienced tumor recurrence (recurrence-free survival time after surgery, 1.1, 5.6, and 6.8 months). Their pathologic and radiologic responses before surgery were relatively poor (all IPR; one PR and two SD). The two-year PFS rate and median PFS had not been reached yet (Supplementary Figure S2). One (2.0%) patient died (survival time after surgery, 11.4 months), and the median OS had not been reached yet (Supplementary Figure S2).

Safety following NIC and surgical profiles

In total, 48 (85.7%) of the 56 patients had treatment-related AEs (TRAEs) of any grade following neoadjuvant treatment, and only six (10.7%) patients had TRAEs of grade 3 (Table 3). The grade 3 TRAEs included diarrhea (two [3.6%]), decreased white blood cell, decreased neutrophil count, decreased platelet count, vomiting, rash maculo-papular, hyperthyroidism, and enterocolitis (one [1.8%] for each). No grade 4 or 5 TRAEs were reported. Five (8.9%) patients had serious TRAEs, including diarrhea (two [3.6%]), vomiting (two [3.6%]), enterocolitis, pyrexia, hyperthyroidism, myocarditis, and rash maculo-papular (one [1.8%] for each). None of the TRAEs led to treatment discontinuation or death. Eleven (19.6%) patients had TRAEs leading to treatment delay. Six (10.7%) patients had TRAEs leading to dose reduction.

The surgical findings are summarized in Table 4. All 51 patients underwent minimally invasive thoracoscopic and laparoscopic esophagectomy, except one patient was convert to open thoracotomy due to intraoperative detecting of tumor invaded into inferior pulmonary vein. No perioperative mortality occurred. Postoperative complications were observed in 14 (27.5%) patients.

Biomarker analyses

Among the 28 patients whose tumor cells were considered adequate for PD-L1 CPS testing, 13 were PD-L1-positive (including seven CPR, two MPR, and four IPR). Baseline PD-L1 CPS did not have obvious correlation with neither pathologic response (CPR, MPR, *vs.* IPR Table 2) nor pathologic/radiologic response (Supplementary Figure S3).

mIHC was successfully performed on 23 paired samples (10 CPR, four MPR, and nine IPR). The number of most immune populations analyzed increased in post-neoadjuvant surgical specimens than pre-neoadjuvant samples and the degree of increase was more obvious in the tumor area than in the stroma area (Figure 2A; Supplementary Figure S4). Among the immune populations, CD8+, CD8+PD-1+, and CD8+PD-L1+ T cells increased significantly after two doses of NIC ($p = 0.002$, < 0.001, and $= 0.007$, respectively), especially CD8+ and CD8+PD-1+ in the patients who achieved CPR or MPR ($p = 0.013$ and < 0.001, respectively) (Figure 2B-G).

Discussion

To our knowledge, this is the first comprehensive phase 2 study designed to assess NIC in patients with resectable ESCC. The addition of camrelizumab to nCT in patients with resectable, locally advanced ESCC (stage II to IVA) achieved a considerable CPR rate in the primary tumor (35.3%, which was above the 30% reference cutoff value), a high ORR of 66.7%, a well-tolerated safety profile during NIC, no perioperative mortality, and a low incidence of postoperative complications.

The sample size of this study was calculated based on the CPR rate of nCT in the SCC subset of the esophagus or gastro-esophageal junction (16%, 3/19) [20], as there was no data from a large-scale study in ESCC patients at study design. Recently, two studies reported that the CPR rate was as low as 3.8% (4/104) and 4% (20/483) after nCT in resectable ESCC patients

(Supplementary Table S3) [8, 21]. Although cross-trial comparisons should be made with caution, our study indicated a promising activity of adding camrelizumab to nCT in patients with resectable ESCC, which was worthy of further verification.

All patients in our study had T1-4 primary tumor and 83.9% had presumed lymphatic metastases at baseline, but after NIC followed by tumor resection, 64.7% had residual tumor in the esophagus (ypT+) and only 23.5% of patients had residual tumor in the lymph nodes (ypN+). It seems that lymphatic metastases showed better response to NIC compared with primary lesions, which possibly could be explained by enriched lymphocytes in lymph nodes.

31.4% of patients who underwent NIC followed by surgery in this study achieved CPR in the primary tumor and lymph nodes (ypT0N0), which was similar to that with nCRT followed by surgery (33.3%, 43.2%, and 49% in the FFCD 9901, NEOCRTEC5010, and CROSS studies, respectively; Supplementary Table S3) [3, 5, 6]. Additionally, 23.5% of patients achieved an MPR. The acceptable safety profile and TRAEs of low severity with NIC make it possible to translate the competitive CPR rate into survival benefit.

Per protocol, if the patient had high risks of recurrence after surgery, the investigator could propose personalized adjuvant therapy. In the CROSS and NEOCRTEC5010 study [9, 10], the main recurrence pattern after nCRT and surgery was distant recurrence (82.6% and 70.1%, respectively). In addition, the CheckMate 577 study recently proved that compared with placebo, adjuvant treatment with nivolumab had significantly longer median disease-free survival, regardless of pathological lymph node status and pathological tumor status [22]. In our study, 23 patients received adjuvant treatment mainly due to ypN+ and poor pathologic response after NIC. Differences in long-term survival outcomes between patients with and without adjuvant therapy as well as between patients with different adjuvant regimens worthy of further exploration.

In this study, AEs with NIC treatment were observed until surgery which was scheduled

approximately six weeks after completion of NIC. The half-life of 200 mg camrelizumab was 5.6 days [23], indicating that camrelizumab could be metabolized before surgery and thus the immune-related AEs was fully accessed. The reason accounted for the relatively low incidence of immune-related AEs may lay in the regimen and administration of chemotherapy. First, reactive cutaneous capillary endothelial proliferation, the most common AE with camrelizumab monotherapy (67% to 77% reported in previous studies) [23-25], occurred in only 8.9% of patients when combined with nab-paclitaxel and cisplatin in this study. Second, we chose a two-week per cycle chemotherapy instead of general one-week per cycle, as full dosage nab-paclitaxel (260 mg/m^2) in one day would significantly increase the possibility of peripheral neuropathy in our practice. This two-week pattern might also be part of the reason for higher CPR rates compared with neoadjuvant therapy with toripalimab plus chemotherapy [26, 27]. Multiple administration of low-dose chemotherapy strategies could repeatedly stimulate the release of tumor antigens, thereby enhancing the effect of immunotherapy. Therefore, addition of radiotherapy or increasing the cycles of NIC may further improve the CPR rate, but may result in more and severe AEs. In the new era of immunotherapy, it is of critical importance to further explore the optimal neoadjuvant treatment strategy to balance toxicity and efficacy.

Our trial has some limitations, including lack of control and long-term outcomes. Besides, the number of samples for biomarker analyses was small. Associations between PD-L1 CPS and TILs dynamic changes with treatment outcomes need to be verified in further studies.

Overall, this study suggests that preoperative camrelizumab plus nab-paclitaxel-cisplatin in patients with resectable, locally advanced ESCC has an encouraging pathologic response and a manageable safety profile, providing a feasible and effective neoadjuvant option for these patients. Furthermore, lymphatic metastases seem to have better response to NIC compared with primary lesions.

Declarations

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was approved by the institutional review board or independent ethics committee of each study site. All patients provided written informed consent. This study is registered with ClinicalTrials.gov (NCT04225364).

Conflict of Interest

Jun Liu reported receipt of research support from Jiangsu Hengrui Pharmaceuticals Co., Ltd and BGI Genomics. Di Shao, Wenxi Jiang, and Kui Wu reported being employed at BGI Genomics. For the remaining authors, none were declared.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files. Further information is available from the corresponding author upon request.

Funding

This study was funded by Jiangsu Hengrui Pharmaceuticals Co., Ltd (formerly Jiangsu Hengrui Medicine Co., Ltd) and BGI Genomics. The authors and the funders collaborated in study design, collection, analysis, and interpretation of data, and writing of the report. The funders had no role in the decision to submit the article for publication.

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Administrative, technical, or material support: all authors

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Approval of the final manuscript: all authors

The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Acknowledgments

We thank all the patients, their families, and the institutions for supporting these studies. Aichen Chen, Shujing Gao, Wenxi Jiang, Zeqing Ma, Yitong Li, and Chao Ren were greatly appreciated for their dedicated efforts on data collection. Hongbo Zheng, Qilong Gong, and Tao Yu from Genecast Biotechnology, Wuxi, China were greatly appreciated for their dedicated efforts on biomarker analyses and data interpretation.

Prior Presentation

The results from this study were reported, in part, at the ASCO 2021 Virtual Congress (poster presentation, abstr 4028).

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Figure legends

Figure 1 Patients disposition

SD, Stable disease. Efficacy endpoints were assessed in patients who completed the two cycles of study neoadjuvant chemoimmunotherapy and had tumor resection. Overall survival would also be assessed in the intention-to-treat population, which included all patients signed informed consent. Safety was assessed in all patients who received the study drug at least once.

Figure 2 Multiplex immunofluorescence analysis of immune cells in the tumor microenvironment before and after neoadjuvant treatment

Paired resection specimens (pre-treatment and post-treatment) from 23 patients (10 CPR, 4 MPR, and 9 IPR) were subjected to multiplex immunofluorescence staining with a five-color multiplex panel containing the markers PD-1 (magenta), PD-L1 (orange), CD8 (red), CD68 (cyan) and CD163 (green). (A) Changes in number of immune populations for pre- and post-treatment samples for the different immune markers and marker combinations. (B-D) a trend towards a higher CD8+ (B), CD8+PD-1+ (C), and CD8+PD-L1+ (D). T-cell infiltrate was observed in post-treatment tumor specimens compared to pre-treatment specimens, especially in patients with CPR or MPR. (E-G) representative fluorescence images of three patients (GZ-ESCC-14, JY-ESCC-03 and GY-ESCC-16) illustrating the higher number of CD8+, CD8+PD-1+, and CD8+PD-L1+ T-cell infiltrate after neoadjuvant chemoimmunotherapy. CPR, complete pathologic response; MPR, major pathologic response; IPR, incomplete pathologic response.

Tables

Table 1 Patients characteristics

	All patients (n=56)
Age, years	61 (40 to 70)
Sex	
Male	42 (75.0%)
Female	14 (25.0%)
ECOG performance status	
0	39 (69.6%)
1	17 (30.4%)
Cigarette-smoking history	
Never	19 (33.9%)
Former	16 (28.6%)
Current	21 (37.5%)
Alcohol-drinking history	
Never	31 (55.4%)
Former	18 (32.1%)
Current	7 (12.5%)
Comorbidities	
No	45 (80.4%)
Yes	11 (19.6%)
Hypertension	7 (12.5%)
Diabetes	4 (7.1%)

Coronary heart disease	1 (1.8%)
Cardiothoracic Surgery	1 (1.8%)
Tumor	
T1	1 (1.8%)
T2	14 (25.0%)
T3	38 (67.9%)
T4	2 (3.6%)
Node	
N0	9 (16.1%)
N1	22 (39.3%)
N2	21 (37.5%)
N3	4 (7.1%)
Primary tumor location	
Upper	1 (1.8%)
Middle	27 (48.2%)
Lower	28 (50.0%)
cTNM stage	
Ⅱ	13 (23.2%)
Ⅲ	38 (67.9%)
ⅣA	5 (8.9%)
PD-L1 combined positive score*	
<1	15 (53.6%)
1 to 9	6 (21.4%)
≥10	7 (25.0%)

* PD-L1 combined positive score are available in 28 patients who completed neoadjuvant chemoimmunotherapy and tumor resection.

Data are n (%) or median (range). ECOG, Eastern Cooperative Oncology Group.

Table 2. Associations of baseline characteristics, dose reduction and treatment delay during NCI, and objective response per RECIST v1.1 with pathologic response

	CPR (n=18)	MPR (n=12)	IPR (n=21)	p value
Age (years)	61.5 (46.0-68.0)	60.0 (40.0-70.0)	59.0 (44.0-70.0)	0.460
Sex				0.400
Male	15 (36.6%)	8 (19.5%)	18 (43.9%)	
Female	3 (30.0%)	4 (40.0%)	3 (30.0%)	
BMI	21.90 (17.50-25.00)	19.74 (17.48-24.49)	21.91 (16.30-29.92)	0.290
Weight loss within 3 months	0 (0-7.50)	0.75 (0-4.00)	2.50 (0-15.00)	0.350
ECOG PS				0.500
0	14 (38.9%)	7 (19.4%)	15 (41.7%)	
1	4 (26.7%)	5 (33.3%)	6 (40.0%)	
Cigarette-smoking history				0.950
Never	4 (26.7%)	4 (26.7%)	7 (46.7%)	
Former	6 (40.0%)	3 (20.0%)	6 (40.0%)	

Current	8 (38.1%)	5 (23.8%)	8 (38.1%)	
Alcohol-drinking history				0.880
Never	8 (30.8%)	7 (26.9%)	11 (42.3%)	
Former	8 (44.4%)	3 (16.7%)	7 (38.9%)	
Current	2 (28.6%)	2 (28.6%)	3 (42.9%)	
Comorbidities				0.520
No	15 (35.7%)	11 (26.2%)	16 (38.1%)	
Yes	3 (33.3%)	1 (11.1%)	5 (55.6%)	
Longest diameter of target lesion (mm)	86.0 (22.0-138.5)	70.5 (18.0-116.0)	90.0 (30.0-138.0)	0.380
Tumor				0.610
T1	1 (100%)	0	0	
T2	4 (30.8%)	3 (23.1%)	6 (46.2%)	
T3	11 (31.4%)	9 (25.7%)	15 (42.9%)	
T4	2 (100%)	0	0	
Node				0.650

N0	2 (22.2%)	2 (22.2%)	5 (55.6%)	
N1	8 (40.0%)	4 (20.0%)	8 (40.0%)	
N2	5 (27.8%)	6 (33.3%)	7 (38.9%)	
N3	3 (75.0%)	0	1 (25.0%)	
Grade of differentiation				0.170
Gx	1 (33.3%)	2 (66.7%)	0	
G1	3 (75.0%)	0	1 (25.0%)	
G2	10 (27.0%)	9 (24.3%)	18 (48.6%)	
G3	4 (57.1%)	1 (14.3%)	2 (28.6%)	
cTNM stage				0.086
Ⅱ	4 (30.8%)	1 (7.7%)	8 (61.5%)	
Ⅲ	10 (30.3%)	11 (33.3%)	12 (36.4%)	
Ⅳ	4 (80.0%)	0	1 (20.0%)	
Primary tumor location				0.360
Lower	10 (38.5%)	4 (15.4%)	12 (46.2%)	
Middle	7 (29.2%)	8 (33.3%)	9 (37.5%)	

Upper	1 (100%)	0	0	
Treatment delay in second cycle of NIC				0.460
No	15 (39.5%)	9 (23.7%)	14 (36.8%)	
Yes	3 (23.1%)	3 (23.1%)	7 (53.8%)	
Dose reduction in second cycle of chemotherapy				0.006
No	18 (40%)	12 (26.7%)	15 (33.3%)	
Yes	0	0	6 (100%)	
PD-L1 combined positive score (n=28)				0.200
<1	5 (33.3%)	2 (13.3%)	8 (53.3%)	
1-9	5 (83.3%)	0	1 (16.7%)	
≥10	2 (28.6%)	2 (28.6%)	3 (42.9%)	
Objective response per RECIST v1.1				0.280
Complete response	3 (42.9%)	3 (42.9%)	1 (14.3%)	
Partial response	10 (37.0%)	7 (25.9%)	10 (37.0%)	
Stable disease	5 (29.4%)	2 (11.8%)	10 (58.8%)	

Data are n (%) or median (range). CPR, complete pathologic response; MPR, major pathological response; IPR, incomplete pathological response;

NIC, neoadjuvant chemoimmunotherapy.

Table 3 Adverse events during neoadjuvant chemoimmunotherapy

	All patients (n=56)	
	Grade 1 or 2	**Grade 3**
Treatment-related adverse events		
Any	42 (75.0%)	6 (10.7%)
Serious	0	5 (8.9%)
Leading to treatment delay	8 (14.3%)	3 (5.4%)
Treatment-related hematological toxicity		
White blood cell decreased	19 (33.9%)	1 (1.8%)
Neutrophil count decreased	8 (14.3%)	1 (1.8%)
Platelet count decreased	1 (1.8%)	1 (1.8%)
Febrile neutropenia	1 (1.8%)	0
Treatment-related non-hematological toxicity		
Vomiting	18 (32.1%)	1 (1.8%)
Alopecia	18 (32.1%)	0
Malaise	14 (25.0%)	0
Rash maculo-papular	11 (19.6%)	1 (1.8%)
Nausea	12 (21.4%)	0
Dizziness	12 (21.4%)	0
Diarrhea	9 (16.1%)	2 (3.6%)
Anorexia	7 (12.5%)	0
Pruritus	5 (8.9%)	0
Constipation	5 (8.9%)	0
RCCEP	5 (8.9%)	0

Fever	4 (7.1%)	0
Abdominal pain	3 (5.4%)	0
Anemia	3 (5.4%)	0
Abdominal distension	2 (3.6%)	0
Paresthesia	2 (3.6%)	0
Hyperthyroidism	1 (1.8%)	1 (1.8%)
Headache	2 (3.6%)	0
Dyspepsia	2 (3.6%)	0
Belching	1 (1.8%)	0
Enterocolitis	0	1 (1.8%)
Myocarditis	1 (1.8%)	0
Hyperhidrosis	1 (1.8%)	0
Laryngeal inflammation	1 (1.8%)	0
Myalgia	1 (1.8%)	0
Cough	1 (1.8%)	0
Insomnia	1 (1.8%)	0
Pain	1 (1.8%)	0
Stomach pain	1 (1.8%)	0
Gingival bleeding	1 (1.8%)	0
Periodontal disease	1 (1.8%)	0
Immune-related adverse events	21 (37.5%)	2 (3.6%)
Rash maculo-papular	7 (12.5%)	0
RCCEP	5 (8.9%)	0
Nausea	4 (7.1%)	0

Vomiting	3 (5.4%)	1 (1.8%)
Diarrhea	3 (5.4%)	0
Pruritus	3 (5.4%)	0
Anorexia	3 (5.4%)	0
Hyperthyroidism	2 (3.6%)	0
Malaise	2 (3.6%)	0
Dizziness	2 (3.6%)	0
White blood cell decreased	1 (1.8%)	0
Enterocolitis	0	1 (1.8%)
Abdominal distension	1 (1.8%)	0
Insomnia	1 (1.8%)	0
Alopecia	1 (1.8%)	0
Gingival bleeding	1 (1.8%)	0
Periodontal disease	1 (1.8%)	0

Data are n (%). RCCEP, reactive cutaneous capillary endothelial proliferation.

Table 4 Surgical profile

	Patients (n=51)
Anastomotic procedure	
Hand-sewn Anastomosis	16 (31.4%)
Mechanical Anastomosis	35 (68.6%)
Convert open	1 (2.0%)
Unexpected Admission to ICU	0
Readmit within 30 days of discharge	1 (2.0%)
The time of thoracic part (minute)	85 (35 to 156)
The time of cervical and abdominal (minute)	111 (75 to 209)
Operative time in total (minute)	200 (115 to 315)
Estimated intraoperative blood loss (mL)	50 (17 to 450)
Time to commence intake po. (day)	8 (3 to 25)
Postoperative ICU stay (day)	1 (0 to 6)
Postoperative hospital stay (day)	11 (6 to 48)
Postoperative comorbidity	14 (27.5%)
Pulmonary complications	9 (17.6%)
Pneumonia	7 (13.7%)
Pleural Effusion requiring drainage	3 (5.9%)
Pneumothorax requiring CT reinsertion	2 (3.9%)
Atelectasis requiring bronchoscopy	1 (2.0%)
Recurrent laryngeal nerve paresis/hoarseness	5 (9.8%)
Anastomotic leak requiring. only medical mgmt.	3 (5.9%)
Atrial arrhythmia requiring treatment	2 (3.9%)

Surgical site infection	1 (2.0%)
Uroschesis	1 (2.0%)
Anemia	1 (2.0%)

Data are n (%) or median (range).

Participants

- Resectable thoracic esophageal squamous cell carcinoma with clinical stages of T2N1-3M0/T3N0-3M0/T4N0-3M0 (stage II-IVA)

56 Enrolled and received at least one cycle of study neoadjuvant chemoimmunotherapy

↓

51 Completed two cycles of study neoadjuvant chemoimmunotherapy and tumor resection

↓

56 Included in the intent-to-treat population
56 Included in the safety set
51 Included in the surgical and pathologic evaluation

- Median age: 61 years
  Male: 42; Female: 14

Intervention

camrelizumab, 200 mg, day 1 +
nab-paclitaxel, 260 mg/m² in total, day 1 and day 8 +
cisplatin, 75 mg/m² in total, days 1-3

Two 21-day cycles

↓ approximately 6 weeks later

minimally invasive McKeown esophagectomy including extensive two-field lymphadenectomy

↓ 3 to 8 weeks later

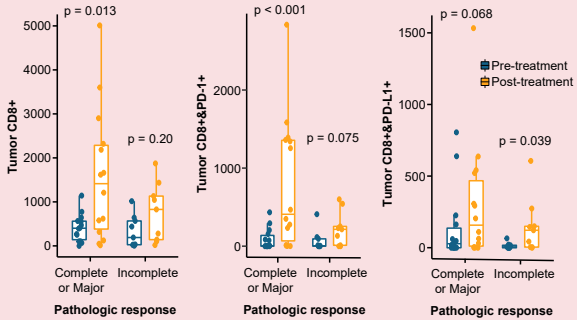
adjuvant therapy or observation according to investigator recommendation and patient decision

Primary endpoint

Complete pathologic response rate in the primary tumor

Findings

- Complete pathologic response rate in the primary tumor:
  35.3% (95% CI, 21.7% to 48.9%)
- Complete pathologic response rate in the primary tumor and lymph nodes
  31.4% (95% CI, 18.2% to 44.6%)
- R0 resection rate: **100%**



CD8+, CD8+PD-1+, and CD8+PD-L1+ T cells increased significantly after 2 cycles of neoadjuvant chemoimmunotherapy

Novelty & Impact Statement: IJC-21-2681.R2

Adverse events linked to neoadjuvant chemoradiotherapy (CRT) for locally advanced, resectable esophageal squamous cell carcinoma (ESCC) significantly impact patient outcomes. Hence, there is critical need for radiation-free therapies for ESCC. Here, the use of neoadjuvant chemoimmunotherapy (NIC) plus chemotherapy was assessed in patients with resectable ESCC. Preoperative camrelizumab plus nab-paclitaxel-cisplatin resulted in complete pathologic response (CPR) in primary tumors and lymph nodes in more than 31 percent of patients – comparable to CPR rates for CRT. Adverse events with NIC, however, were less severe than CRT, warranting additional investigation of NIC plus chemotherapy for resectable, locally advanced ESCC.