Editorial Commentary

Could combination immunotherapy give light to resectable esophageal squamous cell carcinoma?

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The ESCORT-Neo trial reported the efficacy and safety compared the paclitaxel and cisplatin (CDDP) (TP) to camrelizumab (Cam) with chemotherapy [albumin-bound paclitaxel and CDDP (nab-TP) and TP] for the patients with resectable esophageal squamous cell carcinoma (ESCC) (1). The dual primary endpoints were the pathological complete response (pCR) rates and event-free survival (EFS), and this issue reported the final analysis of pCR rates. The Cam + nab-TP and Cam + TP groups showed significantly higher pCR rates than the TP group of 28.0% *vs.* 4.7% (P<0.001) and 15.4% *vs.* 4.7% (P=0.003), respectively, and met their primary endpoint of pCR; however, EFS is not yet mature. Also, the Cam + nab-TP and Cam + TP groups showed higher margin-free resection rates, 99.1%, 95.7%, and 92.2%, respectively, and major pathological response rates were 59.1%, 36.2%, and 20.9%, respectively. According to the results of the CROSS (2) and NEOCRTEC5010 trials (3), the standard of care (SOC) for resectable ESCC has been neoadjuvant chemoradiotherapy (NACRT) for decades. However, as these trials only compared NACRT with surgery alone, the differences between NAC and NACRT remain unclear. In the CMISG1701 (4) and JCOG1109 (5) trials, combining RT with doublet chemotherapy increased the rate of pCR but also led to higher non-cancer mortality without demonstrating a survival benefit. Notably, JCOG1109 found that triplet chemotherapy with docetaxel (DTX), CDDP, and 5-fluorouracil (DCF) offered the longer survival time than NACRT (5) (*Table 1*). In the ESCORT-NEO trial, NAC with doublet chemotherapy was used as SOC, which seems appropriate in this context. As a more intensive systemic therapy, DTX was added in the JCOG1109 trial, while the immune checkpoint inhibitor (ICI) was combined in the ESCORT-NEO trial. DCF therapy resulted in significant hematologic and gastrointestinal toxicity; the incidence of grade ≥3 febrile neutropenia and nausea was 0.8% and 1.5% in the Cam + nab-TP group and 0.8% and 0% in the Cam + TP group, compared with 16% and 21% in the DCF therapy. However, some immune-related adverse events were observed when combined with Cam, though they were manageable. The postoperative complication rates were 34.2%, 38.8%, and 32.0%, respectively. That indicates that combining ICI with NAC did not increase the patients' risk before and during surgery. Combining NAC with an ICI improved pCR without significantly increasing adverse events, positioning it as a promising candidate for the next SOC.

It remains unclear whether NAC combined with ICI is superior to NACRT. However, a retrospective study by researchers in Shanghai reported (6) that NAC with ICI improved survival outcomes than NACRT. The high pCR achieved by NACRT did not correlate with prognosis. In the PALACE-1 trial (7), combining ICI with NACRT

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Table 1 The overview of perioperative treatment for ESCC

Items	Trial											
	CROSS (2)		NEOCRTEC5010 (3)		CMISG1701 (4)		JCOG1109 (5)			ESCORT-NEO/NCCES01 (1)		
Treatment	Neo-TC-RT	Surgery	Neo-CDDP + VNR-RT	Surgery	Neo-TP-RT	TP	CF	DCF	Neo-CF-RT	Nab + TP + Cam	TP + Cam	TP
Patients	T1N1 or T2-3N0-1M0		cT1-4N1M0/T4N0M0		cT3-4aN0-1M0		cstage IB, II, III (non-T4)			cT1b-3N1-3M0 or T3N0M0		
N	178	188	224	227	132	132	199	202	200	132	130	129
pCR rate (%)	29.0	0	43.2	0	27.7	2.9	2.2	18.6	36.7	28.0	15.4	4.7
OS (m)	49.4	24.0	100.1	66.5	NR	43.2	5.6 y	NR	7.0 y	–	–	–

ESCC, esophageal squamous cell carcinoma; Neo, neoadjuvant; TC, carboplatin plus paclitaxel; RT, radiotherapy; CDDP, cisplatin; VNR, vinorelbine; TP, cisplatin plus paclitaxel; CF, cisplatin plus 5-fluorouracil; DCF, docetaxel plus cisplatin plus 5-fluorouracil; nab-TP, cisplatin plus albumin-bound paclitaxel; Cam, camrelizumab; c, clinical; pCR, pathological complete response; OS, overall survival; m, months; y, years; NR, not reached.

Table 2 The overview of the phase II trial of immunotherapy combination treatment for ESCC

Items	Trial					
	PALACE-1 (7)	NICE1 (12)	NIC-ESCC2019 (13)	KEEP-G 03 (14)	Keystone001 (15)	Phase II of Pembro (16)
Treatment	Neo-TP + pembrolizumab-RT	Neo-nab + TP + Cam	Neo-nab + TP + Cam	Neo-nab-TP + sintilimab + S-1	Neo-TP + pembrolizumab	Neo-TP + pembrolizumab-RT
N	18	60	56	30	49	28
pCR rate (%)	56.0	39.2	31.4	20.0	42.2	46.1

ESCC, esophageal squamous cell carcinoma; Neo, neoadjuvant; TP, cisplatin plus paclitaxel; RT, radiotherapy; nab-TP, cisplatin plus albumin-bound paclitaxel; Cam, camrelizumab; pCR, pathological complete response.

increased the pCR rate to 55%. However, other reports have shown limited efficacy gains when ICI is added to NACRT. Moreover, the JCOG1804E trial demonstrated the promising efficacy of triplet chemotherapy with ICI for resectable ESCC patients. Although it was a small study, a pCR rate of approximately 40% was reported with the combination of FLOT and nivolumab (8-10), suggesting that adding further chemotherapy may improve outcomes.

The ESCORT-NEO trial results still leave some questions unanswered. Firstly, the pCR rate differs by about 10% between the combination of the Cam + nab-TP group and the Cam + TP group. This difference may be caused by steroid use, although steroids are commonly administered to prevent emesis in CDDP-containing regimens. An *in vivo* study has reported that high-dose corticosteroids suppress the differentiation of memory T cells and are less effective than low-dose steroids (11). It remains unclear whether the difference in efficacy is truly due to steroids or by chance. Further investigation is needed. Secondly, it is unclear whether a significant improvement in the pCR rate is directly associated with a longer EFS. With NAC, local response is associated with systemic control, so improved EFS is anticipated; however, results are still awaited.

Nonetheless, based on these findings, future developments should explore the incorporation of ICI into NAC or NACRT (*Table 2*), determine whether NAC should involve a doublet or triplet regimen, and assess the appropriate steroid dosage. Quin and colleagues have successfully demonstrated promising outcomes by combining ICI plus doublet chemotherapy for resectable ESCC patients.

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Footnote

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