Protocol study:

Periopearative immunoagent (tislelizumab) plus chemotherapy for locally advanced resectable thoracic oesophageal squamous cell carcinoma trail: A prospective single-arm, phase II study (PILOT trial)

Version number: V1.0
Version date: September 06, 2023

Objectives: Neoadjuvant immunotherapy with chemotherapy (nICT) has been the recommended treatment for locally advanced esophageal squamous cell carcinoma (ESCC). However, high-level evidence of nICT followed by esophagectomy in locally advanced resectable ESCC patients are still lacking. The aim of this study was to analyze esophageal cancer patients who previously underwent nICT followed by esophagectomy to determine whether additional adjuvant therapy is associated with improved survival outcomes.

Design and Methods: Seventy-three eligiled patients with pathologically confirmed thoracic esophageal squamous cell carcinoma and at clinical T1b-3N1-3M0 or T3N0M0 according to the eighth edition of American Joint Committee on Cancer staging will be allocated to neoadjuvant immunotherapy (tislelizumab 200mg d1, q3w ×2 cycles) a nd chemotherapy (nad-paclitaxel 260 mg/m^2 d1 + carboplatin AUC = 5 d1, q3w ×2 cycles) treatment. Patients with resected (R0) were assigned to receive tislelizumab (at a dose of 200 mg every 3 weeks for 30 weeks) in pCR patients or adjuvant immunotherapy and chemothearpy for two cycles, and then tislelizumab (at a dose of 200 mg every 3 weeks for 24 weeks) in non-pCR patients.The primary endpoint for this study is 2-year disease-free survival (DFS) in non-pCR patients.The secondary endpoints include pCR rate, major pathological response (MPR) rate, 2-year DFS in pCR patients, R0 resection rate, adverse events, and overall survival (OS).

Discussion: The results of the PILOT trial will first provide adjuvant immunotherapy in neoadjuvant immunotherapy with chemotherapy treatment for ESCC, also to explore whether adjuvant immunotherapy offers additional benefit in pCR patients or adjuvant immunotherapy and chemothearpy offers additional benefit in non-pCR patients after nICT during the perioperative setting. Meanwhile, the treatment protocols will be compared in terms of efficacy and safety, and 2-year DFS in non-pCR patients and pCR petants. We hypothesize that perioperative immunotherapy will provide preliminary evidence of the efficacy and safety of adjuvant tislelizumab as an innovation therapy for patients with locally advanced ESCC.

Keywords: Esophageal squamous cell carcinoma (ESCC); nivolumab; neoadjuvant;

adjuvant; chemotherapy

1.0 Background

According to the latest data from the National Cancer Center of China, the incidence and mortality of esophageal cancer (EC) were 25.3 and 19.4 per 10000 people, respectively, ranking the sixth and fourth among malignant tumors in China [1]. About 50% of esophageal cancer cases in the world occur in China, of which more than 90% are esophageal squamous cell carcinoma, which is more prone to lymph node metastasis than esophageal adenocarcinoma [2]. Approximately 50% of EC is diagnosed as locally advanced disease, esophagectomy alone is far from enough due to the high recurrence or metastasis rates [3].

The CROSS study and NEOCRTEC5010 study confirmed that neoadjuvant chemoradiotherapy (nCRT) can significantly improve the long-term survival of ESCC patients after surgery [4-6]. Patients who received nCRT in the CROSS study had a recurrence and metastasis rate of 34.7% during a median follow-up of 2 years after surgery, of which hematogenous metastasis was 22% [7]. Similarly, the long-term follow-up results of NEOCRTEC5010 study showed that 33.0% of patients who had received nCRT still had recurrence and metastasis during the 3-year follow-up after surgery, and distant blood metastasis (21.4%) was more common [8]. All these evidences suggest that more efficient systemic treatment options are needed to further improve the efficacy of locally advanced resectable ESCC in the future.

Several phase II clinical studies have confirmed that neoadjuvant immunotherapy combined with chemotherapy (nICT) is safe and effective in the treatment of locally advanced resectable ESCC, which achieves similar pathological complete response (pCR) rate (18.8-39.2%) as nCRT [9-12]. In the previous Nice study [13], the KEEP G 03 study [14] and the TD-NICE study [9], the pCR rates of patients with locally advanced thoracic ESCC treated with neoadjuvant immunotherapy combined with chemotherapy were 39.2%, 20.0% and 50.0%, respectively. It is even higher than the latest DCF neoadjuvant chemotherapy regimen discussed in JCOG1109, with a pCR of 19.8% [15]. The neoadjuvant regimen of tislelizumab combined with chemotherapy in the TD-NICE trial resulted in a higher pCR rate compared with 49% (CROSS study) and 43.2% (NEOCRTEC5010 study)

for preoperative induction chemoradiotherapy. Real-world data show that patients with pCR may have better survival benefits, but distant metastasis and recurrence of non-pCR patients are still problems that need to be solved, and new methods of perioperative treatment are also being explored.

Patients with non-pCR and positive lymph nodes after neoadjuvant chemoradiotherapy have a high risk of recurrence after surgery. Several retrospective studies have investigated the effects of adjuvant chemotherapy after neoadjuvant therapy followed by surgery reducing the distant metastasis and improving the OS in ypT+N+ ESCC patients [16-18]. Similarly, CheckMate577 showed that nivolumab could significantly prolong disease free survival (DFS) in non-pCR patients after nCRT, and patients with squamous cell carcinoma benefited more than those with adenocarcinoma, with a 2-year DFS of 58%[19]. Nevertheless, the question remains that whether adjuvant immunotherapy and chemotherapy offer additional benefit in patients who have received nCRT/nCT.

Hence, we launched a prospective single-arm, phase II trial (PILOT trial) to assess the safety and efficacy of neoadjuvant tislelizumab combined with chemotherapy for locally advanced resectable ESCC patients. Moreover, we also intend to evaluate whether adjuvant administration of immunotherapy combined with chemotherapy could bring survival benefit in non-pCR patients after nICT, as compared with adjuvant immunotherapy treatment in pCR patients, which will answer the questions that CheckMate 577 and TD-NICE did not cover.

2.0 Design and Methods

2.1 Study design and recruitment

The PILOT trial was a prospective, single-arm phase II study of neoadjuvant tislelizumab combined with chemotherapy in patients with locally advanced resectable thoracic ESCC, adjuvant immunotherapy combined with chemotherapy for non-pCR patients, and sequential adjuvant immunotherapy therapy for all patients. The study will be conducted in Shanghai Chest hospitals in China, recruiting 73 patients. The trial will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol has been reviewed and approved by the Institution Review Committee [KS(Y)23255]. All patients will provide written informed consent before enrollment. The protocol is designated PILOT (version 1.1; dated September 6, 2023). Recruitment started in September 2023 and is estimated to continue until September 2026.

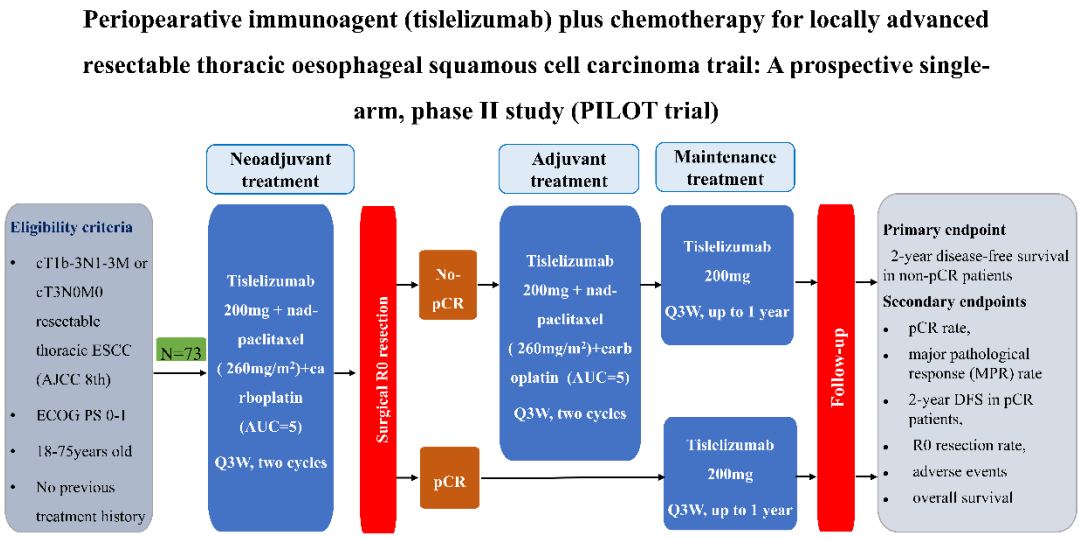

Figure 1. Study Design Drawing

This study is a standardized perioperative immunotherapy trial for locally advanced resectable thoracic ESCC. Eligible patients received neoadjuvant immunotherapy (tislelizumab 200mg d1, q3w× 2 cycles) and chemotherapy (nad-paclitaxel 260 mg/m^2 d1 + carboplatin AUC = 3–5 d1, q3w ×2 cycles) treatment. The efficacy was evaluated according to RECIST 1.1. Patients with a clinical complete response (cCR) and clinical partial response (cPR) undergo surgery after 4–6 weeks. If patients were

evaluated for clinical progressive disease (cPD) and clinically stable disease (cSD), they would receive a new treatment regimen after a multidisciplinary team (MDT) discussion. Subsequently, all the patients underwent surgery after 4–6 weeks. After surgery, patients with pCR would always undergo immunotherapy (Tislelizumab 200 mg q21d) and maintenance treatment for one year, and patients with non-pCR would receive immunotherapy (Tislelizumab 200 mg q21d) and chemotherapy （nad-paclitaxel 260 mg/m2 d1 + carboplatin AUC = 3–5 d1, q3w ×2 cycles ）, and then sequential maintenance immunotherapy treatment for one year. The other patients who did not undergo R0 resection received a new treatment regimen after MDT.

2.2 Study Endpoints

2-year disease-free survival (DFS) in non-pCR patients was considered the primary endpoint and was defined as the time from the first day of surgery to the first occurrence of local or distant recurrence and metastasis or death from any cause.The secondary endpoints are pCR rate, major pathological response (MPR) rate, 2-year DFS in pCR patients, R0 resection rate, adverse events, and overall survival (OS). pCR is defined as complete response of both primary tumor and lymph nodes in the resected specimen. Exploratory endpoints include quality of life (QOL) investigation. If R0 resection was achieved, disease progression other than distant metastasis during neoadjuvant therapy was not considered an event. Recurrence was defined as the appearance of one or more new lesions (confirmed by imaging or cytologic or pathological assessment, local, regional, or distant from the primary resection site) as assessed by the investigator.

2.4 Study population

Eligibility criteria

Patients with locally advanced (T1b-3N1-3M0 or T3N0M0, AJCC 8th) ESCC who have been histologically-confirmed, reviewed by two experienced thoracic surgeons and considered surgically resectable.

2.4.1 Inclusion criteria

1) The patient volunteers to participate in the study, signs a consent form, has good

compliance, and obeys the follow-up, and is willing and able to follow the protocol during the study;

2) Histologically-confirmed squamous cell carcinoma; tumors of the esophagus are located in the thoracic cavity;

3) Have not received systemic and local treatment for esophageal cancer;

4) Pre-treatment staging as cT1b-3N1-3M0 or T3N0M0, American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th edition;

5) Male or female, aged ≥18 and ≤75 years;

6) The Eastern Cooperative Oncology Group (ECOG) performance status (PS) score is 0 –1;

7) R0 resection is expected;

8) Adequate cardiac function. All patients should perform electrocardiogram (ECG), and those with a cardiac history or ECG abnormality should perform echocardiography with the left ventricular ejection fraction >50%;

9) Adequate respiratory function with forced expiratory volume in 1 second (FEV1) ≥ 1.2 L, FEV1% ≥ 50% and lung diffusing capacity for carbon monoxide (DLCO) ≥ 50% shown in pulmonary function tests;

10) Adequate bone marrow function (white blood cells > 4×10^9/L, neutrophil > 1.5×10^9/L, hemoglobin > 90g/L, platelets > 100×10^9/L). Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 3×upper level of normal (ULN);

11) Adequate liver function (total bilirubin <1.5×ULN, AST and ALT <2.5×ULN);

12) Adequate renal function (glomerular filtration rate (GFR) >60 mL/min; serum creatinine (SCr) ≤120 μmol/L];

13) Fertile female subjects are required to have a negative serum or urine pregnancy test no later than 72 hours before starting the study drug administration, and to

use effective contraception (such as an IUD, contraceptive pill, or condom) during the trial period and for at least 3 months after the last dose; For male subjects whose partners are women of reproductive age, effective contraception should be used during the trial period and within 3 months after the last dose;

2.4.2 Exclusion criteria

Patients who meet any of the following conditions will be excluded:

1) Unresectable factors, including those who are unresectable for tumor reasons or have surgical contraindications, or who refuse surgery;

2) Patients with supraclavicular lymph node metastasis;

3) Poor nutritional status, BMI<18.5Kg/m2; Patients could continue to be considered for enrollment if corrected with symptomatic nutritional support before enrollment and after assessment by the principal investigator

4) Allergy to any drugs;

5) Have received or are receiving any of the following treatments; a) any radiotherapy, chemotherapy or other antineoplastic drugs directed at the tumour; b) being treated with an immunosuppressive drug or systemic hormone for immunosuppression (at a dose of >10mg/ day of prednisone or equivalent) within 2 weeks before the first dose of the study drug; Inhaled or topical steroids and corticosteroid replacement at doses >10mg/ day of prednisone or equivalent were allowed in the absence of active autoimmune disease; c) received live attenuated vaccine within 4 weeks before the first dose of study drug; d) major surgery or severe trauma within 4 weeks before the first dose of study drug;

6) Human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) active infection or known HIV seropositivity; including HBV or HCV surface antigen positive (RNA)

7) Uncontrolled cardiac symptoms or diseases, including but not limited to: (1) heart failure above NYHA class II, (2) unstable angina, (3) myocardial infarction

within 1 year, (4) clinically significant supraventricular or ventricular arrhythmias without or poorly controlled after clinical intervention;

8) Severe infection (CTCAE>2) occurred within 4 weeks before the first dose of study drug, such as severe pneumonia requiring hospitalization, bacteremia, and infectious complications; Prophylactic antibiotics were excluded if there was active pulmonary inflammation on chest imaging at baseline, if there were signs and symptoms of infection within 14 days before the first dose of the study drug, or if treatment with oral or intravenous antibiotics was required

9) Participation in other drug clinical studies within 4 weeks before randomization;

10) Patients with interstitial pneumonia or interstitial lung disease, or previous history of interstitial pneumonia or interstitial lung disease requiring hormone therapy, or other subjects with pulmonary fibrosis, organized pneumonia (such as bronchiolitis obliterans), pneumoconiosis, drug-related pneumonia, idiopathic pneumonia that may interfere with the judgment and treatment of immune related pulmonary toxicity, or subjects with active pneumonia or severe lung function damage revealed by CT during screening; Active pulmonary tuberculosis;

11) Patients with any active autoimmune disease or history of autoimmune disease and possible recurrence [including but not limited to autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis, hyperthyroidism, hypothyroidism (patients who can be controlled only by hormone replacement therapy can be enrolled)]; Patients with skin diseases that do not require systemic treatment, such as leukoplakia, psoriasis, alopecia, patients with type I diabetes that can be controlled by insulin treatment, or patients with a history of asthma, but have completely relieved in childhood and do not need any intervention, can be enrolled; Asthma patients who needed bronchodilators for intervention could not be enrolled; Patients have previously received an anti-PD-1， PD-L1 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways;

12) Other malignancies that had been diagnosed within 5 years before the first dose of a study drug were considered unless cancers with a low risk of metastasis or death (5-year survival rate, >90%), such as adequately treated basal-cell or squamous-cell skin cancer or carcinoma in situ of the cervix, were considered.

13) Pregnant or lactating women;

14) The investigators determined that there were other factors that might have led to the forced discontinuation of the study, such as other serious medical conditions (including mental illness) requiring co-treatment, alcohol, substance abuse, family or social factors, and factors that might have affected the safety or adherence of the subjects.

2.5 Intervention（nICT）

On the first day, a fixed dose of 200mg tislelizumab was injected intravenously for about 30-60 min on day 1, followed by sequential nad-paclitaxel (260mg/m^2) combined with carboplatin (AUC=5), once every 3 weeks for 2 cycles. Dosage adjustment is not permitted for tislelizumab, but chemotherapy is allowed in case of severe febrileneutropenia or neutropenia, thrombocytopenia and anemia. Treatment will be interrupted or postponed if any serious AE (SAE) occurs, and treatment could be resumed until the established standards for resumption of treatment are met.

2.6 Surgery

Approximately 4–6 weeks after neoadjuvant treatment, patients will be re-evaluated by the investigators according to the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1. If there was no evidence of metastatic disease, esophagectomy will be performed by two rich experience surgeons. The McKeown procedure can be performed using the da Vinci surgical robot, thoracoscope, or laparoscope, or by using an open approach, as judged appropriate by the surgeon.

Two-field thoracoabdominal lymph node dissection was used for patients with middle and lower thoracic tumors, and three-field lymph node dissection was used for patients with upper thoracic tumors. The lymph nodes dissected groups include: upper thoracic esophagus (105), right recurrent laryngeal nerve (106recR), left recurrent

laryngeal nerve(106recL), sub-carina (107), right trachea-bronchus (106tbR), left trachea-bronchus (106tbL), middle thoracic esophagus (108), lower thoracic esophagus (110), supraphrenic (111), right cardia (1), left cardia (2), lesser curvature of the stomach (3), and left gastric artery (7). At least dissected lymph nodes were dissected. The lymph nodes adjacent to the left and right recurrent laryngeal nerves must be dissected and clear exposed. The dissection will be performed in accordance with the Japanese Classification of Esophageal Cancer, Eleventh Edition. The total number of lymph nodes dissected was no less than 15.

2.7 Pathology Report

The pathological report is consulted by two senior pathologists, including the depth of infiltration of the primary lesion, histological type, pathological status of the upper and posterior margins, and involvement of peripheral and lymph nodes. The postoperative pathological evaluation will be based on the CROSS test. The tumor regression grade (TRG) [20] and ypTNM staging will be evaluated.

2.8 Adjuvant immunotherapy

Patients who underwent R0 resection were divided into pathological complete response (pCR) and non-pathological complete response (non-pCR) according to the pathological results. Subjects with non-R0 resection will terminate the subsequent study treatment program and be given adjuvant radiotherapy.

pCR group: tislelizumab was administered once every 3 weeks until imaging disease recurrence or metastasis, intolerable toxicity, start of new anti-tumor treatment, subject's initiative to withdraw, and investigator's decision to withdraw from the study. Postoperative adjuvant tislelizumab was administered within 4-8 weeks after surgery, and the maximum duration was not more than 1 year.

Non-pCR group: tislelizumab combined with chemotherapy (albumin-bound paclitaxel and carboplatin) for 2 cycles, tislelizumab alone was used from the third cycle, once every 3 weeks until disease recurrence or metastasis, subject's initiative request to withdraw, and investigator's judge that the subject needs to withdraw from the study. The maximum duration of tislelizumab maintenance therapy was not more than 1 year.

3.0 Follow-up

Follow-up will be first performed 1 month after surgery. From then on, follow-up visits will be every 3 months in the first 2 years. The detailed examination items include standard laboratory tests (blood routine, tumor biomarker), a CT scan of thorax, an ultrasound of the neck and abdomen.

If the patient has signs of recurrence (such as related clinical manifestations), additional tumor evaluations are performed during the treatment; possible reoperations and/or further cancer treatments are also documented. During the follow-up period without tumor recurrence, other cytotoxic agents are not allowed. Patient recurrence and survival will be followed up to the patient's death, the last date on which the patient is known to survive, or 2 year after the primary effectiveness analysis.

4.0 Data monitoring

The data and safety monitoring board consisted of three physicians who were independent of the sponsor and declared no competing interests. Active surveillance was conducted every 3 months, and interim analyses were planned after recruitment of half the planned patients.

The safety-related endpoints included neoadjuvant and adjuvant treatment-related adverse events (TRAEs), immune-related adverse events (irAEs), resection rate, and surgical complications. TRAEs and irAEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE5.0). Serious adverse events (SAEs) were defined as grade 3–5 TRAEs. If SAEs occur during the trial, the investigator will immediately take appropriate protective measures or discontinue the treatment, report to the principal investigator within 24 hours, fill out and sign the SAE Report Form. The resection rate referred to the ratio of patients who underwent surgical resection to the intention-to-treat population. Surgical complications within 30 days after operation were coded using the Clavien - Dindo classification. All investigators must comply with the standard operating procedures (SOPs) for the management of study drugs.

5.0 Statistical Analysis Plan

The previous CheckMate577 study suggested that the 2-year DFS was 58% for non-pcr patients with locally advanced esophageal squamous cell carcinoma who received neoadjuvant concurrent chemoradiotherapy followed by radical surgery. Assuming that after perioperative chemoimmunotherapy and immune maintenance, the 2-year DFS increases to 75%, the trial required 55 eligible non pCR patients with a level of significance of 90% ($\alpha = 0.2$) and a power of 90% ($\beta = 0.05$). According to the previous retrospective data analysis of our center, the pCR rate of patients with the neoadjuvant chemotherapy regimen followed by surgery was 26.5%, referring to the published data of multi-center real-world study of neoadjuvant chemotherapy in China (pCR 25.8%), and then 18 patients was needed. A total of 73 patients were enrolled in this study.

The statistical analysis for primary endpoint was that 2-year DFS in non-pCR patients will be calculated by the Kaplan-Meier method.The statistical analysis for secondary endpoints: 2-year DFS in pCR patients, R0 resection rate and overall survival (OS) will be calculated by the Kaplan-Meier method and compared by the log-rank test. The Cox proportional hazard model will be used to evaluate the survival independent factors. Continuous variables were presented as the mean and standard deviation (SD). Categorical variables were presented as percentages and compared using the chi-square test. The differences in proportions between the two groups were evaluated by Fisher's exact test. Wilcoxon test was used to compare the non-parametric datasets. All statistical analysis will be calculated using SPSS (version 24.0, Chicago, IL, USA) statistical analysis software programming. P values less than 0.05 will be considered statistically significant.

6.0 Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions relatedto the accuracy or integrity of any part of the work areappropriately investigated and resolved. The trial will beconducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol has been reviewed and approved by the Ethics Committees of Shanghai Chest hospital of Shanghai Jiao Tong University (No.IS23059). All patients will provide written informed consent before enrollment.

7.0 Reference

1. Sung H, Ferlay J, Siegel RL,et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021; 71(3): 209-249.
2. Zheng R, Zhang S, Zeng H, et al Cancer incidence and mortality in China, 2016. Journal of the National Cancer Center. 2022; 2(1): 1-9.
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012; 366:2074-2084.
4. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015; 16:1090-1098.
5. Yang H, Liu H, Chen Y, 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; 36:2796-2803.
6. Yang H, Liu H, Chen Y, et al. Long-term Efficacy of Neoadjuvant Chemoradiotherapy Plus Surgery for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: The NEOCRTEC5010 Randomized Clinical Trial. JAMA Surg. 2022; 157(5):458-459.
7. Oppedijk, V, van der Gaast, A, van Lanschot, JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014; 32(5):385-91.
8. Liu S, Wen J, Yang H, et al. Recurrence patterns after neoadjuvant chemoradiotherapy compared with surgery alone in oesophageal squamous cell carcinoma: results from the multicenter phase III trial NEOCRTEC5010. Eur J Cancer. 2020;138:113–21.
9. Yan X, Duan H, Ni Y, 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.

10. Liu J, Li J, Lin W, Shao D, Depypere L, Zhang Z, Li Z, Cui F, Du Z, Zeng Y, Jiang S, He P, Gu X, Chen H, Zhang H, Lin X, Huang H, Lv W, Cai W, Liang W, Liang H, Jiang W, Wang W, Xu K, Cai W, Wu K, Lerut T, Fu J, He J. Neoadjuvant camrelizumab plus chemotherapy for resectable, locally advanced esophageal squamous cell carcinoma (NIC-ESCC2019): A multicenter, phase 2 study. Int J Cancer. 2022;151(1):128-137.
11. Zhang Z, Hong ZN, Xie S, Lin W, Lin Y, Zhu J, Yang X, Lin Z, Lin J, Kang M. Neoadjuvant sintilimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: a single-arm, single-center, phase 2 trial (ESONICT-1). Ann Transl Med. 2021;9(21):1623..
12. Li C, Zhao S, Zheng Y, Han Y, Chen X, Cheng Z, Wu Y, Feng X, Qi W, Chen K, Xiang J, Li J, Lerut T, Li H. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). Eur J Cancer. 2021;144:232-241.
13. Liu J, Yang Y, Liu Z, Fu X, Cai X, Li H, Zhu L, Shen Y, Zhang H, Sun Y, Chen H, Yu B, Zhang R, Shao J, Zhang M, Li Z. 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.
14. Chen X, Xu X, Wang D, Liu J, Sun J, Lu M, Wang R, Hui B, Li X, Zhou C, Wang M, Qiu T, Cui S, Sun N, Li Y, Wang F, Liu C, Shao Y, Luo J, Gu Y. Neoadjuvant sintilimab and chemotherapy in patients with potentially resectable esophageal squamous cell carcinoma (KEEP-G 03): an open-label, single-arm, phase 2 trial. J Immunother Cancer. 2023;11(2):e005830.
15. Kato K. Ito Y, Daiko H, et al. A randomized controlled phase III trial comparing two chemotherapy regimen and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NExT study. J Clin Oncol. 2022;40:suppl 238.
16. Xufeng Guo, Zhexin Wang, Hong Yang, et al. Impact of Lymph Node Dissection on Survival after Neoadjuvant Chemoradiotherapy for Locally Advanced

Esophageal Squamous Cell Carcinoma: From the Results of NEOCRTEC5010, a Randomized Multicenter Study. Ann Surg. 2023; 277(2):p259-266.

17. Park SY, Kim HK, Jeon YJ, Lee J, Cho JH, Choi YS, Shim YM, Zo JI. The Role of Adjuvant Chemotherapy after Neoadjuvant Chemoradiotherapy Followed by Surgery in Patients with Esophageal Squamous Cell Carcinoma. Cancer Res Treat. 2023 Apr 24.
18. Lee Y, Samarasinghe Y, Lee MH, Thiru L, Shargall Y, Finley C, Hanna W, Levine O, Juergens R, Agzarian J. Role of Adjuvant Therapy in Esophageal Cancer Patients After Neoadjuvant Therapy and Esophagectomy: A Systematic Review and Meta-analysis. Ann Surg. 2022;275(1):91-98.
19. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, Mendez G, Feliciano J, Motoyama S, Lièvre A, Uronis H, Elimova E, Grootscholten C, Geboes K, Zafar S, Snow S, Ko AH, Feeney K, Schenker M, Kocon P, Zhang J, Zhu L, Lei M, Singh P, Kondo K, Cleary JM, Moehler M; CheckMate 577 Investigators. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021;384(13):1191-1203.
20. Chirieac LR, Swisher SG, Ajani JA, Komaki RR, Correa AM, Morris JS, Roth JA, Rashid A, Hamilton SR, Wu TT. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer. 2005 Apr 1;103(7):1347-55.
21. Tang H, Wang H, Fang Y, Zhu JY, Yin J, Shen YX, Zeng ZC, Jiang DX, Hou YY, Du M, Lian CH, Zhao Q, Jiang HJ, Gong L, Li ZG, Liu J, Xie DY, Li WF, Chen C, Zheng B, Chen KN, Dai L, Liao YD, Li K, Li HC, Zhao NQ, Tan LJ. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy for locally advanced esophageal squamous cell carcinoma: a prospective multicenter randomized clinical trial. Ann Oncol. 2023 Feb;34(2):163-172.
22. Reynolds JV, Preston SR, O'Neill B, et al. Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): preliminary results of phase III RCT of CROSS versus perioperative

chemotherapy (modifified MAGIC or FLOT protocol) (NCT01726452). J Clin Oncol. 2021; 39(15 suppl):4004.

23. Sun Z, Zheng J, Xu X, Zhao X, Ma X, Ye Q. Comparison of clinical outcomes of conservative treatment and surgery for esophageal cancer patients who achieve a clinical complete response following neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. Ann Transl Med. 2022 Dec;10(24):1378.
24. Xi M, Yang Y, Zhang L, et al. Multi-institutional Analysis of Recurrence and Survival After Neoadjuvant Chemoradiotherapy of Esophageal Cancer: Impact of Histology on Recurrence Patterns and Outcomes. Ann Surg 2019;269:663-70.