0003-4975/$36.00
https://doi.org/10.1016/j.athoracsur.2024.02.021

Immunotherapy for Resectable Locally Advanced Esophageal Carcinoma

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ABSTRACT

BACKGROUND The current standard of care for locally advanced esophageal and gastroesophageal junction (GEJ) cancers includes neoadjuvant chemoradiotherapy or perioperative chemotherapy with surgical resection; however, disease-free survival in these patients remains poor. Immune checkpoint inhibitors (ICIs) are approved for adjuvant treatment of locally advanced esophageal and GEJ cancers, but their benefit in the perioperative and neoadjuvant settings remains under investigation.

METHODS We used the PubMed online database to conduct a literature search to identify studies that investigated immunotherapy for locally advanced esophageal and GEJ carcinoma. A review of ClinicalTrials.gov yielded a list of ongoing trials.

RESULTS Adjuvant nivolumab for residual disease after neoadjuvant chemoradiotherapy and surgery is the only approved immunotherapy regimen for locally advanced esophageal cancer. Early-phase trials investigating the addition of neoadjuvant or perioperative ICIs to standard-of-care multimodality approaches have observed pathologic complete response rates as high as 60%. Response rates are highest for ICIs plus chemoradiotherapy for esophageal squamous cell carcinoma and dual checkpoint inhibition in mismatch repair-deficient adenocarcinomas. Safety profiles are acceptable, with a pooled adverse event rate of 27%. Surgical morbidity and mortality with immunotherapy are similar to historical controls with no immunotherapy, and R0 resection rates are high. When reported, disease-free survival among patients treated with perioperative immunotherapy is promising.

CONCLUSIONS Outside of clinical trials, immunotherapy for resectable esophageal carcinoma is limited to the adjuvant setting. Phase III trials investigating neoadjuvant and perioperative immunotherapy are now underway and will provide much-needed data on survival that may ultimately lead to practice-changing recommendations.

(Ann Thorac Surg 2024;118:130-40)

Esophageal cancer is the sixth most common cause of cancer-related mortality, with esophageal squamous cell carcinoma (ESCC) the most common histologic subtype globally and esophageal adenocarcinoma (EAC) the dominant subtype in the Western hemisphere.[1] The current standard of care for locally advanced esophageal and gastroesophageal junction (GEJ) cancers includes surgery and neoadjuvant chemoradiotherapy or perioperative chemotherapy.[2] The specific therapy regimen is selected on the basis of tumor histologic profile (EAC vs ESCC), location in the upper gastrointestinal tract, extent of disease, and institutional preference. With contemporary regimens, median overall survival (OS) is 43 to 50 months for locally advanced EAC and as high as 82 months for locally advanced ESCC.[3,4] However, recurrences are common, even among patients who complete all therapies, and most patients with esophageal cancer die of their disease.

The Supplemental Tables can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2024.02.021] on https://www.annalsthoracicsurgery.org.

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Abbreviations and Acronyms

AE = adverse event
CPS = combined positive score
CTLA-4 = cytotoxic T-lymphocyte–associated protein 4
DFS = disease-free survival
EAC = esophageal adenocarcinoma
EFS = event-free survival
ESCC = esophageal squamous cell carcinoma
FDA = Food and Drug Administration
FLOT = fluorouracil, leucovorin, oxaliplatin, and docetaxel
GEJ = gastroesophageal junction
HR = hazard ratio
ICI = immune checkpoint inhibitor
LAG-3 = lymphocyte activation gene 3
MMR = mismatch repair
MPR = major pathologic response
MSI-H = microsatellite instability high
OS = overall survival
pCR = pathologic complete response
PD-1 = programmed cell death protein-1
PD-L1 = programmed cell death ligand-1
PFS = progression-free survival
TMB = tumor mutational burden
TME = tumor microenvironment

Immunotherapy—primarily, immune checkpoint inhibitors (ICIs)—targeting programmed cell death protein-1 (PD-1) or programmed cell death ligand-1 (PD-L1) have shown remarkable success in the control of select solid tumors.[5] Based on the First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590) trial, pembrolizumab, an anti-PD-1 monoclonal antibody, was the first ICI approved by the United States Food and Drug Administration (FDA) in advanced esophageal or GEJ carcinoma.[6] In this multicenter trial, patients who received pembrolizumab plus chemotherapy had significantly better OS and progression-free survival (PFS) than patients who received chemotherapy alone.

The results of 2 other phase III trials, A Study to Evaluate Efficacy in Subjects With Esophageal Cancer Treated With Nivolumab and Ipilimumab or Nivolumab Combined With Fluorouracil Plus Cisplatin Versus Fluorouracil Plus Cisplatin (CheckMate 648)[7] and Efficacy Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Against Chemotherapy in Stomach Cancer or Stomach/Esophagus Junction Cancer (CheckMate 649),[8] subsequently led to FDA approval of nivolumab plus chemotherapy as first-line treatments for patients with advanced ESCC and EAC, respectively.

There is now interest in adding immunotherapy to multimodality regimens for resectable locally advanced esophageal cancers. The Investigational Immuno-therapy Study of Nivolumab or Placebo in Participants With Resected Esophageal or Gastroesophageal Junction Cancer (CheckMate 577) was the first phase III trial to establish adjuvant nivolumab as the standard of care after neoadjuvant chemoradiotherapy and complete resection for esophageal cancer patients without pathologic complete response (pCR).[9] Adjuvant nivolumab remains the only approved ICI for patients receiving neoadjuvant chemoradiotherapy, and no immunotherapy regimens have been approved for patients receiving perioperative chemotherapy.

However, numerous phase I and II trials have investigated the addition of immunotherapy to standard regimens, and interim analyses of perioperative phase III immunotherapy trials were recently presented. In this review, we outline immunotherapy trials in locally advanced esophageal and GEJ carcinoma, compare pathologic, survival, and surgical outcomes against standard-of-care regimens, and discuss future directions for multimodality treatment in the resectable disease setting.

MATERIAL AND METHODS

We conducted a literature review of the PubMed database using the search terms “esophageal cancer,” “esophageal adenocarcinoma,” esophageal squamous cell carcinoma,” “gastroesophageal carcinoma,” “immunotherapy,” and “surgery.” Esophageal and GEJ carcinomas were included. Gastric cancers were excluded (although relevant trials investigating GEJ and gastric cancers were included). We limited articles to those published in English. ClinicalTrials.gov was searched to identify trials investigating immunotherapy for resectable locally advanced esophageal cancer.

RESULTS

MECHANISMS OF ICIS. Immunotherapy agents are monoclonal antibodies that stimulate the immune system by inhibition of checkpoint proteins and their ligands, which subsequently enhances activation of T cells critical to direct tumor cytotoxicity.[10] At present, there are 4 immune checkpoint targets with FDA-approved ICIs: (1) cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); (2) PD-1; (3) PD-L1; and (4) lymphocyte activation gene-3 (LAG-3) (Figure 1, Supplemental Table 1).

Recent studies have explored the synergistic effect of PD-(L)1 inhibitors with chemotherapy and radiotherapy and observed a profound impact on the immune system by enhancing tumor antigen release, activating immune cells, and increasing tumor-infiltrating lymphocytes.[11,12] This reprogramming of the tumor microenvironment (TME) can transform tumors from a “cold” state, with few immune cells, to a “hot” state, with robust immune cell infiltration, creating an environment in which ICIs may stimulate a response. This is especially

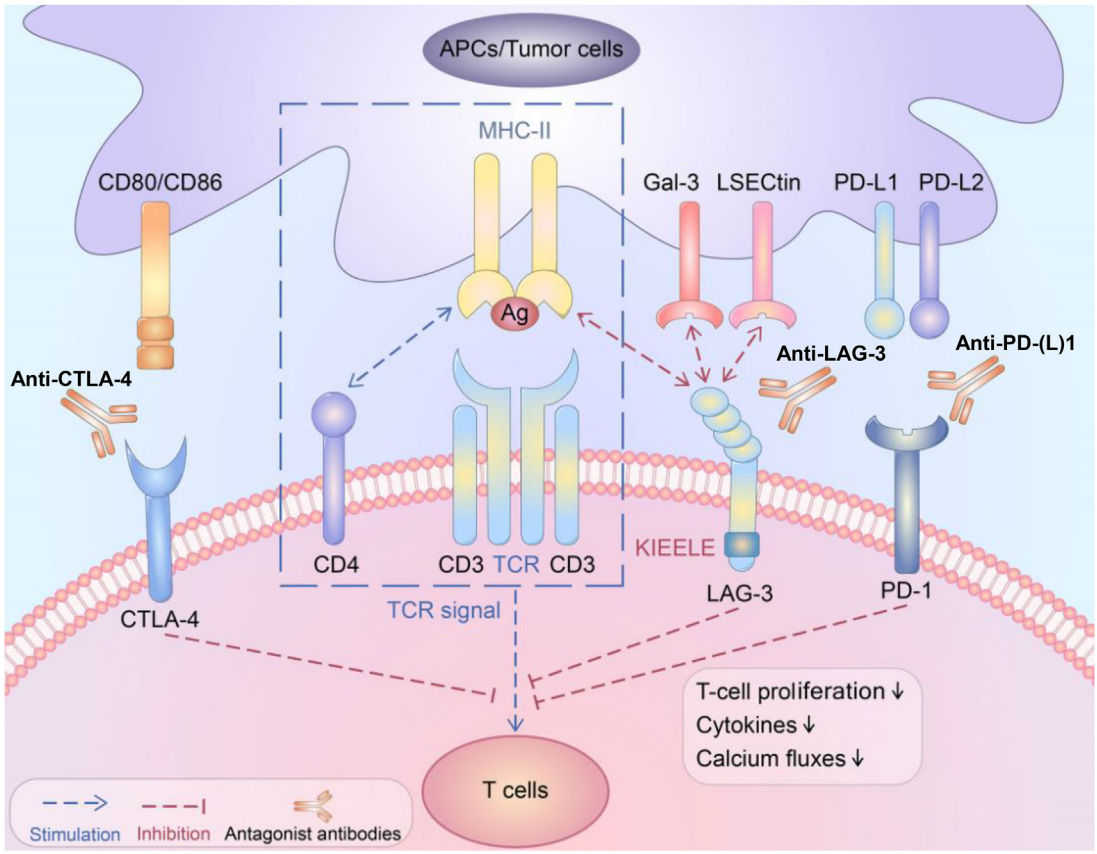

FIGURE 1 Mechanism of action of currently approved classes of immune checkpoint inhibitors (ICIs). (Ag, antigen; APCs, antigen-presenting cells; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; Gal-3, galectin-3; LAG-3, lymphocyte-activation gene 3; LSECtin, liver and lymph node sinusoidal endothelial cell C-type lectin; MHC-II, major histocompatibility complex class II; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; TCR, T-cell receptor.) Copyright © 2022 Wei and Li. Reused with permission under a Creative Commons Attribution License (CC BY) from Wei Y, Li Z. LAG3-PD-1 combo overcome the disadvantage of drug resistance. *Front Oncol*. 2022;12:831407. https://doi.org/10.3389/fonc.2022.831407

important in esophageal cancer, because investigations have demonstrated an immunosuppressive TME.[13]

BIOMARKERS IN ESOPHAGEAL CANCER. The addition of ICIs to chemotherapy in patients with advanced esophageal cancer has improved survival and changed practice for the first time in more than a decade.[7,8] Biomarkers predictive of response to ICIs include PD-L1 expression, deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H), and tumor mutational burden (TMB).[14]

PD-L1 combined positive score. In esophageal cancer, PD-L1 expression is evaluated using the combined positive score (CPS), or the ratio of PD-L1-staining cells (lymphocytes, macrophages, tumor cells) over the total number of viable tumor cells.[15] Clinical trials report different cutoffs for CPS; the most common is a CPS of 5. The phase III CheckMate 649 trial observed improved survival in the nivolumab plus chemotherapy arm (vs placebo plus chemotherapy) for patients with advanced EAC and PD-L1 CPS of $\geq$5.[8] As a result, National Comprehensive Cancer Network guidelines recommend nivolumab plus chemotherapy as first-line for advanced EAC with a CPS $\geq$5.[2] Similar recommendations for advanced ESCC are based on the findings of CheckMate 648.[7]

In CheckMate 577, patients with locally advanced disease with a CPS of $\geq$5 who received adjuvant nivolumab for residual disease after neoadjuvant chemoradiotherapy and surgical resection had significantly better disease-free survival (DFS) than those receiving placebo; however, this benefit was less pronounced among patients with a CPS of <5.[9] This was a post hoc analysis, and given the findings for the entire cohort, nivolumab is recommended for all patients regardless of CPS.[2]

PD-L1 CPS has been a marker of response to PD-(L)1 inhibitors in esophageal cancer, but has several limitations, including intratumoral heterogeneity, variability

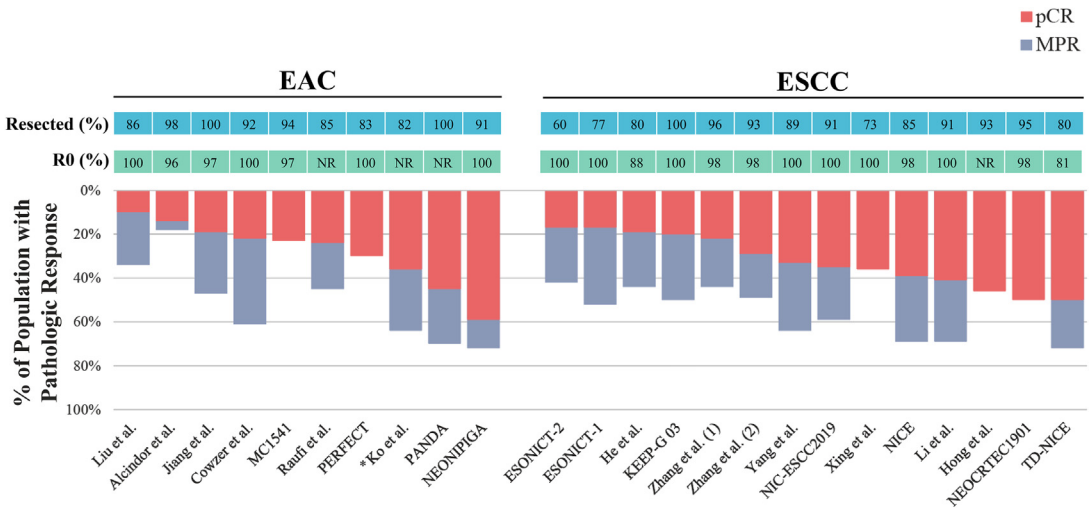

FIGURE 2 Pathologic response and surgical outcomes after neoadjuvant immunotherapy with chemotherapy and/or radiotherapy in resectable esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) across completed neoadjuvant and perioperative clinical trials. *In the Ko and associates trial,[27] 5 of 28 patients had ESCC. Pathologic complete response (pCR) and major pathologic response (MPR) displayed as waterfall plot from smallest pCR rate (left) to largest (right). (ESONICT-1, Neoadjuvant sintilimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: a single-arm, single-center, phase 2 trial; ESONICT-2, Toripalimab combined with docetaxel and cisplatin neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma: a single-center, single-arm clinical trial; KEEP G 03, Sintilimab in Combination With Chemotherapy in Neoadjuvant Treatment of Potentially Resectable Esophageal Cancer; MC1541, Pembrolizumab, Combination Chemotherapy, and Radiation Therapy Before Surgery in Treating Adult Patients With Locally Advanced Gastroesophageal Junction or Gastric Cardia Cancer That Can Be Removed by Surgery; NEOCRTEC1901, Combination of Toripalimab and Neoadjuvant Chemoradiotherapy in Esophageal Cancer; NEONIPIGA, Pre-operative Nivolumab and Ipilimumab, Followed by Post-operative Nivolumab, for MSI/dMMR Oesogastric Adenocarcinoma; NICE, A phase II study of neoadjuvant immunotherapy combined with chemotherapy (camrelizumab plus albumin paclitaxel and carboplatin) in resectable thoracic esophageal squamous cell cancer; NIC-ESCC2019, Neoadjuvant camrelizumab plus chemotherapy for resectable, locally advanced esophageal squamous cell carcinoma; NR, not reported; PANDA, Neoadjuvant Capecitabine, Oxaliplatin, Docetaxel and Atezolizumab in Resectable Gastric and GE-junction Cancer; PERFECT, Neoadjuvant Chemoradiotherapy Combined With Atezolizumab for Resectable Esophageal Adenocarcinoma: A Single Arm Phase II Feasibility Trial; TD-NICE, Tislelizumab combined with chemotherapy as neoadjuvant therapy for surgically resectable esophageal cancer.)

in pathologic assessment, and dynamic changes in expression throughout a patient's disease course.[16]

Mismatch repair. Mismatch repair (MMR) is an important DNA repair tool to fix replication errors, the loss of which (dMMR) leads to hyper mutation and a large neoantigen burden.[17] These mutations accumulate at microsatellites, referred to as microsatellite instability. MSI-H tumors have more immunogenic neoantigens and a TME marked by inflammation, which are predictive of response to ICIs.[18] Although 6% to 24% of resected GEJ adenocarcinomas are MSI-H, non-GEJ cancers are rarely MSI-H.[19] Given the findings of recently published trials, guidelines now recommend MSI/MMR testing in all newly diagnosed patients.[2]

Tumor mutational burden. TMB is the total number of somatic mutations per coding area of the tumor genome, and a higher TMB is associated with more neoantigen formation, leading to a better response upon initiation of ICI therapy.[20] Although TMB is a guideline-endorsed biomarker for esophageal cancer,[2] <10% of esophageal tumors are TMB-high,[21] and it is rarely used to drive therapeutic decision making.

Other biomarkers. Biomarkers typically associated with gastric cancer—human epidermal growth factor receptor 2 (HER2), Epstein-Barr virus, and claudin 18.2—are now under investigation in EAC.[22-24] Results from Pembrolizumab/Placebo Plus Trastuzumab Plus Chemotherapy in Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-811/KEYNOTE-811) demonstrated that pembrolizumab plus trastuzumab and chemotherapy in metastatic HER2-positive esophageal cancer is safe and effective.[22] Epstein-Barr virus-positive gastric cancers have the highest neoantigen burden of all subtypes, and PD-L1 is expressed on up to 50% of tumor cells and 94% of immune cells.[23] Although the impact of Epstein-Barr virus in esophageal cancer is currently mixed, this marker

may play an important role with the expansion of immunotherapy. Last, claudin 18.2 is another potential antibody target, because it is normally expressed in gastric epithelia and has been found in up to 18% of EACs.[24]

Overall, there are currently no specific biomarkers indicative of response to immunotherapy for esophageal cancer. As more clinical trials are designed, it is imperative that correlative studies of predictive biomarkers are included.

CURRENT EVIDENCE FOR IMMUNOTHERAPY FOR RESECTABLE ESOPHAGEAL CANCER.

Neoadjuvant immunotherapy. The rationale behind the use of neoadjuvant immunotherapy is to expand tumor-resident T-cell clones through tumor antigen exposure while the tumor remains intact.[25] This may enhance the breadth and depth of the T-cell response, decreasing the likelihood of recurrence after surgery, a principle demonstrated in other tumor types.[26] The theoretical drawbacks of an induction approach include missing the surgical window, immune-mediated complications resulting in delays in surgical resection, and increased operative difficulty; however, this has not been shown in the available data. At present, all completed and ongoing clinical trials in this space are early-phase studies (Supplemental Table 2), and there are no phase III results for induction immunotherapy.

The data from these studies are immature; the primary outcomes available are pCR and major pathologic response (MPR) (Figure 2).[27-43] As we await results of large, randomized studies and survival data, meta-analyses provide some insight. Ge and associates[44] analyzed phase II trials of neoadjuvant chemoimmunotherapy for locally advanced esophageal cancer and found a pooled pCR rate of 31.4% (95% CI, 27.6%-35.3%) and pooled MPR rate of 48.9% (95% CI, 42.0%-55.9%).[44] When subdivided by histologic profile, the pooled pCR rate was 32.4% (95% CI, 28.2%-36.8%) for patients with ESCC and 25.2% (95% CI, 16.3%-35.1%) for patients with EAC. The pCR rate in this analysis was similar to the neoadjuvant chemoradiotherapy arm of Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS) (29%)[3] but superior to the perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) arm of the 5-FU, Leucovorin, Oxaliplatin and Docetaxel (FLOT) Versus Epirubicin, Cisplatin and 5-FU (ECF) in Patients With Locally Advanced, Resectable Gastric Cancer (FLOT-4) trial (16%).[4]

Neoadjuvant immunotherapy for ESCC. ESCC is known to be radiosensitive and is most frequently treated with induction chemoradiotherapy. In the phase II single-arm Combination of Toripalimab and Neoadjuvant Chemoradiotherapy in Esophageal Cancer (NEOCRTEC1901) trial, 44 patients with locally advanced ESCC received concurrent chemoradiotherapy and toripalimab (anti-PD-1) before surgical resection.[29] All patients received the neoadjuvant regimen, and 42 patients underwent surgery (R0 rate, 98%). The primary end point of pCR was 50% (95% CI, 35-65%), compared with an historical control of 36% in patients treated with chemoradiotherapy at the same institution; however, the difference was not significant ($P = .19$). Multiple phase II Chinese trials have investigated neoadjuvant immunotherapy and chemotherapy without radiotherapy, with variable pCR rates (17%-50%) (Figure 2). In contrast, the pCR rate for traditional neoadjuvant chemotherapy alone in patients with ESCC is <5%.[45]

Neoadjuvant immunotherapy for EAC. At present, the addition of ICIs to induction chemoradiotherapy for EAC has not been beneficial. The addition of atezolizumab (anti-PD-L1) to induction chemoradiotherapy was explored in the phase II Neoadjuvant Chemoradiotherapy Combined With Atezolizumab for Resectable Esophageal Adenocarcinoma: A Single Arm Phase II Feasibility Trial (PERFECT) trial, which enrolled 40 patients with resectable EAC.[27] Patients received CROSS-based neoadjuvant chemoradiotherapy and atezolizumab, followed by surgery. The regimen was feasible: 85% of patients received all 5 cycles of atezolizumab, and 83% underwent resection. pCR was achieved in 10 patients (30%), which is similar to historical response rates for chemoradiotherapy alone.[3] This cohort was compared with a propensity score-matched cohort that underwent neoadjuvant chemoradiotherapy. The pCR rate ($P = .51$) and OS ($P = .43$) were not significantly different between the cohorts.

An ongoing phase II/III trial (Nivolumab and Ipilimumab in Treating Patients With Esophageal and Gastroesophageal Junction Adenocarcinoma Undergoing Surgery; EA2174, NCT03604991) is investigating multiple regimens, including single and doublet ICI, for patients with T1 N1-3 M0 or T2-3 N0-2 M0 EAC. Patients are first randomized to receive neoadjuvant chemoradiotherapy alone or chemoradiotherapy plus nivolumab. After surgery, all patients are randomized again to receive adjuvant nivolumab, with or without ipilimumab. Initial results have demonstrated comparable adverse events (AEs) between treatment arms.

In the absence of available data from randomized trials, Wong and associates[46] used the National Cancer Database to explore the addition of neoadjuvant immunotherapy to chemoradiotherapy. This retrospective analysis included patients with resectable EAC or ESCC who received neoadjuvant immunotherapy plus chemoradiotherapy or neoadjuvant chemoradiotherapy alone, followed by esophagectomy. In total, 1.6% patients (165 of 10,348)

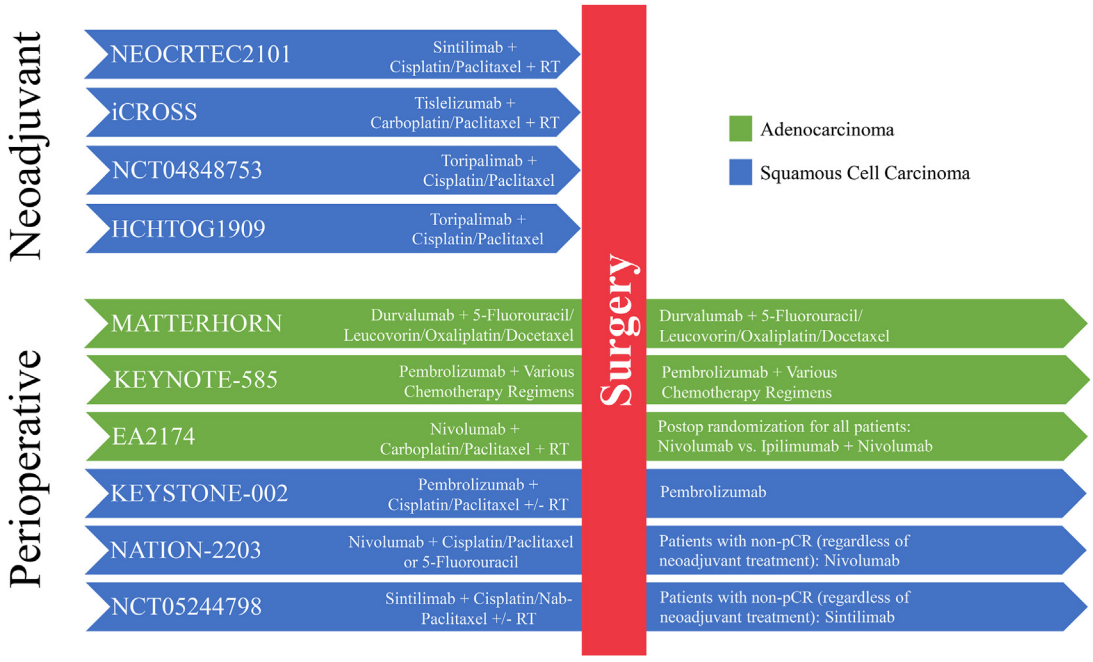

FIGURE 3 Ongoing phase III clinical trials investigating immunotherapy in resectable locally advanced esophageal cancer. (EA2174, Nivolumab and Ipilimumab in Treating Patients With Esophageal and Gastroesophageal Junction Adenocarcinoma Undergoing Surgery; HCHTOG1909, A Phase III, Randomized Controlled Study of Neo-adjuvant Toripalimab (JS001) in Combination With Chemotherapy Versus Neo-adjuvant Chemotherapy for Resectable Esophageal Squamous Cell Carcinoma; iCROSS, Neoadjuvant Immunotherapy Plus CRT Versus Neoadjuvant CRT for Locally Advanced Resectable ESCC; KEYNOTE-585, Study of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants With Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma; KEYSTONE-002, Pembrolizumab Plus Neoadjuvant Chemotherapy vs. Neoadjuvant Chemoradiotherapy for Locally Advanced ESCC; MATTERHORN, A Randomized, Double-blind, Placebo-controlled, Phase III Study of Neoadjuvant-Adjuvant Durvalumab and FLOT Chemotherapy Followed by Adjuvant Durvalumab in Patients With Resectable Gastric and Gastroesophageal Junction Cancer (GC/GEJC); NATION-2203, Study of Neoadjuvant Nivolumab or Placebo Plus Chemotherapy Followed by Surgery and Adjuvant Treatment in Subjects With Resectable ESCC; NCT04848753, Perioperative Toripalimab (JS001) Combined With Neoadjuvant Chemotherapy in Patients With Resectable Locally Advanced Thoracic Esophageal Squamous Cell Carcinoma; NCT05244798, Sintilimab Plus NCT or NCRT Versus NCRT for ESCC; NEOCRTEC2101, PD-1 Inhibitor Combined With Neoadjuvant Chemoradiotherapy Plus Surgery for Locally Advanced ESCC; pCR, pathologic complete response; postop, postoperative; RT, radiotherapy.)

who met the inclusion criteria received induction immunotherapy. Independent predictors of receipt of immunotherapy included younger age, adenocarcinoma histology, and treatment at an academic center. Receipt of immunotherapy was associated with higher rates of pCR (29% vs 21%; P = .018) and nodal downstaging (50% vs 40%; P = .017). Immunotherapy was associated with longer median OS (69.1 vs 56.3 months; P = .005). In a propensity score-matched analysis, immunotherapy remained associated with improved survival; however, more granularity is needed to understand which subgroups benefit from this approach.

PERIOPERATIVE IMMUNOTHERAPY. The benefit of postoperative immunotherapy after preoperative ICI regimens is unknown. The success of perioperative cytotoxic regimens, such as FLOT, provide a rationale for this approach, and several ongoing phase I/II trials are exploring this strategy (Figure 2[47-53], Supplemental Table 3). Hong and associates[52] enrolled 28 patients with clinical stage IB-III ESCC in a single-arm phase II study of preoperative chemoradiotherapy and pembrolizumab, followed by surgery and adjuvant pembrolizumab for up to 2 years.[52] The 1-year OS was 82%. The primary end point of pCR was 46%, and DFS was longer in patients with pCR (hazard ratio, 0.33); however, the difference was not significant (P = .1).

To better understand the added survival benefit of immunotherapy with standard neoadjuvant/perioperative regimens, the Phase 1/2 Study of anti-PD-L1 in Combination with Chemo(radio)therapy for Oesophageal Cancer (LUD2015-005), an open-label phase II study, investigated neoadjuvant durvalumab plus neoadjuvant

capecitabine/oxaliplatin, perioperative FLOT, or neoadjuvant CROSS chemoradiotherapy in patients with operable gastroesophageal cancer.[54] Of 33 patients who underwent surgery, 23 (70%) received adjuvant durvalumab. At 2 years, OS was 82%, 78%, and 78% in the durvalumab plus capecitabine/oxaliplatin, FLOT, and CROSS arms, respectively, an improvement over the 2-year OS for the FLOT (68%)[4] and CROSS (67%)[3] trials.

With traditional regimens, the proportion of patients achieving pCR in EAC is often lower than in ESCC, a trend that continues with immunotherapy.[3,4] In one trial, patients with resectable locally advanced GEJ or gastric adenocarcinoma were administered 4 preoperative and postoperative cycles of toripalimab plus FLOT; 25% of patients had a pCR (primary end point), and 43% had an MPR.[55] Although modest, the pCR rate in the original FLOT trial was 16%. Another trial (Peri-operative Immuno-Chemotherapy in Operable Oesophageal and Gastric Cancer, ICONIC), using a nearly identical design, investigated avelumab. Only 15% of patients had a pCR, and the trial closed early, because it was unlikely to meet the prespecified pCR goal of 25%.[56]

Cowzer and associates[50] used a more individualized approach in EAC by adding durvalumab to induction fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and positron emission tomography-directed chemoradiotherapy, followed by surgery and adjuvant durvalumab.[50] Although the pCR rate of 22% was similar to previous trials, 12-month and 24-month survival was particularly encouraging at 92% and 85%,[50] demonstrating that pCR may not be the ideal surrogate to evaluate the efficacy of immunotherapy in esophageal cancer.[57]

Ongoing perioperative immunotherapy trials. Interim results were recently published from the phase IIb Study of Atezolizumab + FLOT vs. FLOT Alone in Patients With GC/GEJ and High Immune Responsiveness (DANTE) trial investigating perioperative FLOT, with or without atezolizumab, for GEJ and gastric adenocarcinoma.[58] Completion rates of preoperative and postoperative therapy and surgical characteristics were similar between arms. Pathologic downstaging favored the atezolizumab arm (pT0, 23% vs 15%; pN0, 68% vs 54%). Patients with PD-L1 CPS $\geq$10 (pCR rate, 46% vs 24% [CPS <10]) or MSI-H (pCR rate, 50% vs 27% [MSI-low]) tumors experienced a greater benefit from atezolizumab. A similar approach is under investigation in the phase III A Randomized, Double-blind, Placebo-controlled, Phase III Study of Neoadjuvant-Adjuvant Durvalumab and FLOT Chemotherapy Followed by Adjuvant Durvalumab in Patients With Resectable Gastric and Gastroesophageal Junction Cancer (GC/GEJC) (MATTERHORN) trial, in which 948 patients with resectable GEJ or gastric carcinoma were randomized to receive perioperative durvalumab or placebo with standard-of-care perioperative FLOT.[59] Initial results demonstrated a significantly higher pCR rate with durvalumab (19% vs 7%; $P < .001$), but the primary end point of EFS has not been met.

Another phase III trial, Study of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants With Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-585/KEYNOTE-585), randomized 1007 patients to perioperative pembrolizumab plus chemotherapy or perioperative chemotherapy alone for locally advanced GEJ or gastric adenocarcinoma.[60] Interim results show an improvement in pCR with pembrolizumab (13% vs 2%; $P < .001$) and an EFS rate favoring the ICI arm (median, 44.4 vs 25.3 months; hazard ratio [HR], 0.81; $P = .0198$).

Three phase III trials in Asia are currently recruiting or will soon recruit patients with locally advanced ESCC to a variety of perioperative regimens including immunotherapy. (Figure 3). These ongoing studies may provide practice-changing outcome data for resectable ESCC.

ADJUVANT IMMUNOTHERAPY. Currently, the only FDA-approved protocol for immunotherapy for resectable esophageal cancer is CheckMate 577.[9] This was a multicenter, randomized-controlled phase III trial in which patients with completely resected stage II or III esophageal or GEJ cancer, who had received neoadjuvant chemoradiotherapy and had residual disease, were randomized to receive nivolumab or placebo for up to 1 year. Nivolumab led to better DFS compared with placebo (22.4 vs 11.0 months; HR, 0.69; 95% CI, 0.56-0.86; $P < .001$). DFS with nivolumab was even more pronounced in patients with ESCC (median DFS, 29.7 [nivolumab] months vs 11.0 [placebo] months; HR, 0.61), compared with those with EAC (median DFS, 19.4 [nivolumab] months vs 11.1 [placebo] months; HR, 0.75). All patients in the nivolumab arm received at least 1 dose, but only 43% of patients completed 1 year of adjuvant therapy.

IMMUNOTHERAPY FOR SUBGROUP-SPECIFIC CONSIDERATIONS.

dMMR/MSI-H. MSI-H tumors have a unique biology distinct from microsatellite stable tumors, are often chemotherapy resistant, and exhibit meaningful sensitivity to ICIs.[61] A meta-analysis of studies investigating resectable esophagogastric cancer demonstrated that MSI-H is a favorable prognostic biomarker and signaled that delaying curative surgery with neoadjuvant chemotherapy may be detrimental.[62] Therefore, upfront surgical resection is a reasonable option.

Given their sensitivity to ICIs, dMMR/MSI-H tumors are being treated with neoadjuvant ICIs in multiple

trials. Pre-operative Nivolumab and Ipilimumab, Followed by Post-operative Nivolumab, for MSI/dMMR Oeso-gastric Adenocarcinoma (NEONIPIGA), a single-arm phase II study, evaluated neoadjuvant ipilimumab and nivolumab, followed by surgery and adjuvant nivolumab in resectable dMMR/MSI-H GEJ/gastric tumors, and demonstrated unprecedented pCR and MPR rates of 59% and 83%.[51] TremelImumab aNd Durvalumab For the Non-operatIve Management (NOM) of MSI-high Resectable GC/GEJC (INFINITY), an ongoing single-arm phase II trial, evaluated 12 weeks of neoadjuvant dual-checkpoint inhibition (durvalumab plus tremelimumab) in a similar population and found equally promising rates of pCR (60%) and MPR (80%).[63]

As a result, the National Comprehensive Cancer Network designated neoadjuvant or perioperative ICI for resectable, locally advanced dMMR/MSI-H GEJ/gastric tumors in August 2023.[2] Therefore, upfront dMMR/MSI testing is imperative in the workup of all newly diagnosed patients to avoid ineffective systemic therapy and surgical delays.

Human epidermal growth factor receptor 2. Despite multiple negative studies with dual HER2 blockade in locally advanced and metastatic GEJ/gastric adenocarcinoma, the addition of pembrolizumab to trastuzumab and chemotherapy in KEYNOTE-811 significantly improved PFS in these patients and established a new standard of care.[22] Given these promising results, investigation of this regimen in locally advanced resectable disease is a logical future trial.

SAFETY OUTCOMES IN IMMUNOTHERAPY. Immunotherapy regimens are generally well tolerated. The most common immune-related AEs from ICIs are skin reaction (15.8%), hypothyroidism (9.7%), infusion-related reactions (5.9%), hepatitis (5.3%), and pneumonitis (4.5%).[64] A meta-analysis showed that the pooled incidence of any AE among patients with resectable locally advanced esophageal carcinoma was 26.9% (95% CI, 16.7-38.3%); however, there was significant heterogeneity among studies.[44] The largest trial to report safety data on immunotherapy was CheckMate 577.[9] Grade 3/4 treatment-related AEs were more common with adjuvant nivolumab than placebo (13% vs 6%). The most common AEs of any grade were fatigue, diarrhea, pruritus, and rash in the nivolumab arm, and diarrhea and fatigue in the placebo arm. Grade 3/4 immune-related AEs were rare, occurring in <1% of patients in both arms. In the recently reported KEYNOTE-585 study, grade ≥3 treatment-related AE were considerably higher but similar between the pembrolizumab plus chemotherapy (65%) and placebo plus chemotherapy (63%) arms.[60] MATTERHORN found similar proportions of grade 3/4 AEs (58% for durvalumab plus FLOT vs 56% for placebo plus FLOT).[59]

SURGICAL CONSIDERATIONS AFTER INDUCTION IMMUNOTHERAPY. Esophagectomy carries a significant risk of complications, with severe morbidity occurring in 17% of patients and 30-day mortality of 2.4%.[65] Postoperative complications after induction immunotherapy plus chemotherapy or chemoradiotherapy and surgery vary across phase II trials, but the addition of immunotherapy does not appear to increase morbidity or mortality. The most common postoperative complications after neoadjuvant immunotherapy-containing regimens are pneumonia and anastomotic leak, occurring in ~10% to 20% of patients,[29,66] which is similar to historical benchmarks after neoadjuvant chemotherapy with or without radiotherapy.[65] Furthermore, induction immunotherapy demonstrates no difference in intraoperative blood loss or length of stay compared with induction therapy without ICI.[46,66,67]

Operative times are not significantly different between cohorts with and without immunotherapy.[66] Rates of complete resection are high for chemoimmunotherapy and chemoradiotherapy-immunotherapy, with most phase II trials reporting R0 resection rates of >95% (Figure 2). In MATTERHORN, the surgery and R0 resection rates in the durvalumab arm (87% and 86%) were not significantly different than in the placebo arm (84% and 86%).[59] In CROSS, 92% of patients who received neoadjuvant chemoradiotherapy had a complete resection (vs 69% with surgery alone); in FLOT, 78% to 85% of patients had a complete resection.[3,4] These results suggest that rates of R0 resection after neoadjuvant immunotherapy plus chemotherapy and/or radiotherapy are not inferior to standard-of-care regimens; however, further data from forthcoming phase III trials are needed.

Finally, the addition of immunotherapy does not result in a clinically significant increase in time to surgery or surgical attrition.[46,59,66] Patients typically proceed to surgery ~7 to 8 weeks from the end of neoadjuvant immunotherapy, which is not significantly different from traditional neoadjuvant regimens.[66] Currently available data show that, on average, ~90% (range, 60%-100%) of patients undergo surgical resection after induction therapy across a variety of combination regimens and ICI agents (Figure 2).

COMMENT

FUTURE DIRECTIONS FOR LOCALLY ADVANCED ESOPHAGEAL CANCER TREATMENT. At present, most clinical trials of immunotherapy for locally advanced esophageal cancer have used PD-1 or PD-L1 inhibitors. However, not all patients benefit from these therapies, and investigators have been searching for alternative

treatments and biomarkers. A recently completed phase II trial examined the safety and efficacy of neoadjuvant chemoradiotherapy plus sotigalimab, a cluster of differentiation 40 (CD40) agonist that activates multiple immune cells to improve anti-tumor responses.[28] Of 34 patients with clinical stage II to IVA esophageal cancer who received this regimen, 36% had a pCR and 64% had an MPR. Additionally, circulating tumor DNA has shown promise as a prognostic biomarker in esophageal cancer[68] and will likely play an important role in patient selection in the future.

Vaccine therapy is a novel treatment approach that has demonstrated feasibility in a pan-cancer setting[69] and is now under investigation for esophageal cancer. In a phase I trial, Neoantigen Vaccine in Esophagus Cancer Patients Following Neoadjuvant Therapy and Surgical Resection (NCT05307835) in China, patients with resectable esophageal cancer will undergo perioperative therapy with surgical resection. After adjuvant therapy, patients will receive a personalized neoantigen cancer vaccine based on the antigen profile of their resected tumor.

Another personalized approach that gained attention at the 2023 European Society for Medical Oncology Meeting is active surveillance for patients with a complete clinical response after neoadjuvant therapy. In the Surgery As Needed for Oesophageal cancer (SANO) trial, patients with a complete clinical response after neoadjuvant chemoradiotherapy were randomized to active surveillance or standard surgery.[70] At 2 years, the active surveillance arm had noninferior OS and better short-term quality of life compared with the standard surgery arm.

CONCLUSIONS. Immunotherapy for locally advanced esophageal cancer is a relatively nascent field that is rapidly evolving. Currently, adjuvant nivolumab for residual pathologic disease after neoadjuvant chemoradiotherapy and surgery is the only FDA-approved ICI regimen for esophageal cancer. However, many recent phase I and II trials have provided promising pCR and MPR rates without additional operative morbidity or mortality compared with existing regimens. Although pathologic response is currently the best end point available until survival data matures, it must be interpreted with caution in patients with esophageal cancer. Phase III trials investigating immunotherapy in the neoadjuvant and perioperative settings are now underway, and their results will help guide future practice.

The authors wish to thank David Sewell for his superb editing and handling of the manuscript submission.

FUNDING SOURCES

Funding was received from the National Institutes of Health, National Cancer Institute grants R01CA217169 and R01CA240472 to David R. Jones and Cancer Center Support Grant P30CA008748 to Memorial Sloan Kettering Cancer Center. Yelena Y. Janjigian has received research funding from Memorial Sloan Kettering Cancer Center Cycle for Survival, the United States Department of Defense, Fred's Team, and the National Cancer Institute.

DISCLOSURES

Smita Sihag is a member of the AstraZeneca Advisory Board. Daniela Molena serves on a steering committee for AstraZeneca, as a consultant for Johnson & Johnson, Bristol-Myers Squibb, AstraZeneca, and Boston Scientific, and has been an invited speaker for Merck and Genentech. Samuel L. Cytryn reports stock ownership in BioNTech, Pfizer, and Moderna within the past 12 months. Yelena Y. Janjigian reports research funding from Bayer, Bristol-Myers Squibb, Eli Lilly, Genentech/Roche, Merck, and RGENIX, advisory board or consulting with AbbVie, AmerisourceBergen, AskGene Pharma, Arcus Biosciences, Astellas, AstraZeneca, Basilea Pharmaceutica, Bayer, Bristol-Myers Squibb, Clinical Care Options, Daiichi-Sankyo, Eli Lilly, Geneos Therapeutics, GlaxoSmithKline, Guardant Health, Imedex, Imugene, Lynx Health, Merck, Merck Serono, Mersana Therapeutics, Michael J Hennessy Associates, Paradigm Medical Communications, PeerView Institute, Pfizer, Research to Practice, RGENIX, Seagen, Silverback Therapeutics, and Zymeworks, and stock options in RGENIX. Abraham J. Wu reports research support from CivaTech Oncology, Inc, honoraria from Nanovi A/S, serves on the Simphotek, Inc Scientific Advisory Board, and has stock in Simphotek, Inc. Stephanie G. Worrell is a member of the Bristol-Meyers Squibb Advisory Board and consults for Intuitive Surgical, Inc. David R. Jones serves as a consultant or speaker for or has received grant support from Merck, AstraZeneca, Genentech, More Health, and DAVA Oncology. The other authors have no conflicts of interest to disclose.

REFERENCES

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 Cancer J Clin*. 2021;71:209-249.

2. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 1.2024. Accessed March 12, 2024. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

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. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393:1948-1957.

5. Ma W, Xue R, Zhu Z, et al. Increasing cure rates of solid tumors by immune checkpoint inhibitors. *Exp Hematol Oncol*. 2023;12:10.

6. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398:759-771.

7. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med*. 2022;386:449-462.

8. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398:27-40.

9. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med*. 2021;384:1191-1203.

10. Sun Q, Hong Z, Zhang C, Wang L, Han Z, Ma D. Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends. *Signal Transduct Target Ther*. 2023;8:320.

11. Galluzzi L, Humeau J, Buqué A, Zitvogel L, Kroemer G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol*. 2020;17:725-741.

12. Zhang Z, Liu X, Chen D, Yu J. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. *Signal Transduct Target Ther*. 2022;7:258.

13. Zheng Y, Chen Z, Han Y, et al. Immune suppressive landscape in the human esophageal squamous cell carcinoma microenvironment. *Nat Comm*. 2020;11:6268.

14. Wang D-R, Wu X-L, Sun Y-L. Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response. *Signal Transduct Target Ther*. 2022;7:331.

15. Kulangara K, Zhang N, Corigliano E, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med*. 2019;143:330-337.

16. Grossman JE, Vasudevan D, Joyce CE, Hildago M. Is PD-L1 a consistent biomarker for anti-PD-1 therapy? The model of balstilimab in a virally-driven tumor. *Oncogene*. 2021;40:1393-1395.

17. Yuza K, Nagahashi M, Watanabe S, Takabe K, Wakai T. Hypermutation and microsatellite instability in gastrointestinal cancers. *Oncotarget*. 2017;8:112103-112115.

18. Mestrallet G, Brown M, Bozkus CC, Bhardwaj N. Immune escape and resistance to immunotherapy in mismatch repair deficient tumors. *Front Immunol*. 2023;14:1210164.

19. van Velzen MJM, Derks S, van Grieken NCT, Haj Mohammad N, van Laarhoven HWM. MSI as a predictive factor for treatment outcome of gastroesophageal adenocarcinoma. *Cancer Treat Rev*. 2020;86:102024.

20. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol*. 2020;21:1353-1365.

21. Yarchoan M, Albacker LA, Hopkins AC, et al. PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. *JCI Insight*. 2019;4:e126908.

22. Janjigian YY, Kawazoe A, Bai Y, et al. 15110—Pembrolizumab plus trastuzumab and chemotherapy for HER2+2b; metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: survival results from the phase III, randomized, double-blind, placebo-controlled KEYNOTE-811 study. Abstract presented at: ESMO Congress 2023, October 20-24, 2023, Madrid Spain.

23. Derks S, Liao X, Chiaravalli AM, et al. Abundant PD-L1 expression in Epstein-Barr virus-infected gastric cancers. *Oncotarget*. 2016;7:32925-32932.

24. Moentenich V, Gebauer F, Comut E, et al. Claudin 18.2 expression in esophageal adenocarcinoma and its potential impact on future treatment strategies. *Oncol Lett*. 2020;19:3665-3670.

25. Versluis JM, Long GV, Blank CU. Learning from clinical trials of neoadjuvant checkpoint blockade. *Nat Med*. 2020;26:475-484.

26. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973-1985.

27. van den Ende T, de Clercq NC, van Berge Henegouwen MI, et al. Neoadjuvant chemoradiotherapy combined with atezolizumab for resectable esophageal adenocarcinoma: a single-arm phase II feasibility trial (PERFECT). *Clin Cancer Res*. 2021;27:3351-3359.

28. Ko AH, Noel M, Chao J, et al. 1229P: A multicenter phase II study of sotigalimab (CD40 agonist) in combination with neoadjuvant chemoradiation for resectable esophageal and gastroesophageal junction (GEJ) cancers. *Ann Oncol*. 2022;33:S1111.

29. Chen R, Liu Q, Li Q, et al. A phase II clinical trial of toripalimab combined with neoadjuvant chemoradiotherapy in locally advanced esophageal squamous cell carcinoma (NEOCRTEC1901). *eClinicalMedicine*. 2023;62:102118.

30. Liu Y, Han G, Li H, et al. Camrelizumab combined with FLOFOX as neoadjuvant therapy for resectable locally advanced gastric and gastroesophageal junction adenocarcinoma: updated results of efficacy and safety. *J Clin Oncol*. 2021;39(suppl):4036-4036.

31. Jiang H, Yu X, Li N, et al. Efficacy and safety of neoadjuvant sintilimab, oxaliplatin and capecitabine in patients with locally advanced, resectable gastric or gastroesophageal junction adenocarcinoma: early results of a phase 2 study. *J Immunother Cancer*. 2022;10:e003635.

32. Verschoor YL, Kodach L, van den Berg J, et al. Neoadjuvant atezolizumab plus docetaxel/oxaliplatin/capecitabine in non-metastatic gastric and gastroesophageal junction adenocarcinoma: the PANDA trial. *J Clin Oncol*. 2022;40(suppl):4059-4059.

33. Liu J, Yang Y, Liu Z, 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:e004291.

34. Liu J, Li J, Lin W, et al. Neoadjuvant camrelizumab plus chemotherapy for resectable, locally advanced esophageal squamous cell carcinoma (NIC-ESCC2019): a multicenter, phase 2 study. *Int J Cancer*. 2022;151:128-137.

35. Yang G, Su X, Huang Y, et al. Intensive cycles of neoadjuvant camrelizumab combined with chemotherapy in locally advanced esophageal squamous cell carcinoma: a single-arm, phase II trial. *J Transl Med*. 2023;21:411.

36. Zhang Z, Hong ZN, Xie S, et al. 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;9:1623.

37. Zhang Z, Ye J, Li H, et al. Neoadjuvant sintilimab and chemotherapy in patients with resectable esophageal squamous cell carcinoma: a prospective, single-arm, phase 2 trial. *Front Immunol*. 2022;13:1031171.

38. 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.

39. Xing W, Zhao L, Zheng Y, et al. The sequence of chemotherapy and toripalimab might influence the efficacy of neoadjuvant chemo-immunotherapy in locally advanced esophageal squamous cell cancer—a phase II study. *Front Immunol*. 2021;12:772450.

40. He W, Leng X, Mao T, et al. Toripalimab plus paclitaxel and carboplatin as neoadjuvant therapy in locally advanced resectable esophageal squamous cell carcinoma. *Oncologist*. 2022;27:e18-e28.

41. Gao L, Lu J, Zhang P, Hong Z-N, Kang M. Toripalimab combined with docetaxel and cisplatin neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma: a single-center, single-arm clinical trial (ESONICT-2). *J Gastrointest Oncol*. 2022;13:478-487.

42. Li Y, Zhou A, Liu S, et al. Comparing a PD-L1 inhibitor plus chemotherapy to chemotherapy alone in neoadjuvant therapy for locally advanced ESCC: a randomized phase II clinical trial: a randomized clinical trial of neoadjuvant therapy for ESCC. *BMC Med*. 2023;21:86.

43. Chen X, Xu X, Wang D, et al. 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:e005830.

44. Ge F, Huo Z, Cai X, et al. Evaluation of clinical and safety outcomes of neoadjuvant immunotherapy combined with chemotherapy for patients with resectable esophageal cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5:e2239778.

45. Tang H, Wang H, Fang Y, et al. 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;34:163-172.

46. Wong LY, Liou DZ, Backhus LM, Lui NS, Shrager JB, Berry MF. The impact of neoadjuvant immunotherapy on perioperative outcomes and survival after esophagectomy for esophageal cancer. *JTCVS Open*. 2023;14:547-560.

47. Zhu M, Chen C, Foster NR, et al. Pembrolizumab in combination with neoadjuvant chemoradiotherapy for patients with resectable adenocarcinoma of the gastroesophageal junction. *Clin Cancer Res*. 2022;28:3021-3031.

48. Raufi AG, Lee S, May M, et al. Abstract CT009: Phase II trial of perioperative pembrolizumab plus capecitabine and oxaliplatin followed by adjuvant pembrolizumab for resectable gastric and gastroesophageal junction (GC/GEJ) adenocarcinoma. *Cancer Res*. 2022;82(suppl):CT009.

49. Alcindor T, Fiset P-O, Opu T, et al. Perioperative immunochemotherapy (mDCF + avelumab) in locally advanced gastro-esophageal adenocarcinoma: a phase II trial. *J Clin Oncol*. 2023;41(suppl):4055-4055.

50. Cowzer D, Wu AJ, Sihag S, et al. Durvalumab and PET-directed chemoradiation in locally advanced esophageal adenocarcinoma: a phase Ib/II study. *Ann Surg*. 2023;278:e511-e518.

51. André T, Tougeron D, Piessen G, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPIGA phase II study. *J Clin Oncol*. 2023;41:255-265.

52. Hong MH, Kim H, Park SY, et al. A phase II trial of preoperative chemoradiotherapy and pembrolizumab for locally advanced esophageal squamous cell carcinoma (ESCC). *J Clin Oncol*. 2019;37(suppl):4027-4027.

53. Zhang G, Yuan J, Pan C, et al. Multi-omics analysis uncovers tumor ecosystem dynamics during neoadjuvant toripalimab plus nab-paclitaxel and S-1 for esophageal squamous cell carcinoma: a single-center, open-label, single-arm phase 2 trial. *eBioMedicine*. 2023;90:104515.

54. Middleton MR, Karydis I, Lu X, et al. Long-term outcomes from adding durvalumab to neoadjuvant treatment of operable gastroesophageal cancers: results from a multicenter study LUD2015-005. *J Clin Oncol*. 2023;41(suppl):398-398.

55. Li H, Deng J, Ge S, et al. Phase II study of perioperative toripalimab in combination with FLOT in patients with locally advanced resectable gastric/gastroesophageal junction (GEJ) adenocarcinoma. *J Clin Oncol*. 2021;39(suppl):4050.

56. Athauda A, Starling N, Chau I, et al. Perioperative FLOT plus anti-PD-L1 avelumab (FLOT-A) in resectable oesophagogastric adenocarcinoma (OGA): interim safety analysis results from the ICONIC trial. *J Clin Oncol*. 2021;39(suppl):201.

57. Barbetta A, Sihag S, Nobel T, et al. Patterns and risk of recurrence in patients with esophageal cancer with a pathologic complete response after chemoradiotherapy followed by surgery. *J Thorac Cardiovasc Surg*. 2019;157:1249-1259.e5.

58. Al-Batran S-E, Lorenzen S, Thuss-Patience PC, et al. Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. *J Clin Oncol*. 2022;40(suppl):4003.

59. Janjigian YY, Al-Batran S-E, Wainberg ZA, et al. LBA73—Pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastroesophageal junction cancer (GC/GEJC): interim results of the global, phase III MATTERHORN study. Abstract presented at: ESMO Congress 2023; October 20-24, 2023, Madrid, Spain.

60. Shitara K, Rha SY, Wyrwicz LS, et al. LBA74—Pembrolizumab plus chemotherapy vs chemotherapy as neoadjuvant and adjuvant therapy in locally-advanced gastric and gastroesophageal junction cancer: the phase III KEYNOTE-585 study. Abstract presented at: ESMO Congress 2023; October 20-24, 2023, Madrid, Spain.

61. Ratti M, Lampis A, Hahne JC, Passalacqua R, Valeri N. Microsatellite instability in gastric cancer: molecular bases, clinical perspectives, and new treatment approaches. *Cell Mol Life Sci*. 2018;75:4151-4162.

62. Pietrantonio F, Miceli R, Raimondi A, et al. Individual patient data meta-analysis of the value of microsatellite instability as a biomarker in gastric cancer. *J Clin Oncol*. 2019;37:3392-3400.

63. Pietrantonio F, Raimondi A, Lonardi S, et al. INFINITY: a multicentre, single-arm, multi-cohort, phase II trial of tremelimumab and durvalumab as neoadjuvant treatment of patients with microsatellite instability-high (MSI) resectable gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC). *J Clin Oncol*. 2023;41(suppl):358.

64. Zheng J, Huang B, Xiao L, Wu M, Li J. Treatment-and immune-related adverse events of immune checkpoint inhibitors in esophageal or gastroesophageal junction cancer: a network meta-analysis of randomized controlled trials. *Front Oncol*. 2022;12:821626.

65. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. *Ann Surg*. 2019;269:291-298.

66. Sihag S, Ku GY, Tan KS, et al. Safety and feasibility of esophagectomy following combined immunotherapy and chemoradiotherapy for esophageal cancer. *J Thorac Cardiovasc Surg*. 2021;161:836-843.

67. Wang K, Liang Y, Huang J, et al. A propensity score-matched analysis of neoadjuvant chemoimmunotherapy versus surgery alone for locally advanced esophageal squamous cell carcinoma. *J Surg Oncol*. 2023;128:207-217.

68. Ng HY, Ko JMY, Lam KO, et al. Circulating tumor DNA dynamics as prognostic markers in locally advanced and metastatic esophageal squamous cell carcinoma. *JAMA Surg*. 2023;158:1141-1150.

69. Fang Y, Mo F, Shou J, et al. A pan-cancer clinical study of personalized neoantigen vaccine monotherapy in treating patients with various types of advanced solid tumors. *Clin Cancer Res*. 2020;26:4511-4520.

70. van der Wilk BJ, Eyck BM, Wijnhoven BP, et al. LBA75—Neoadjuvant chemoradiotherapy followed by surgery versus active surveillance for oesophageal cancer (SANO-trial): a phase-III stepped-wedge cluster randomised trial. Abstract presented at: ESMO Congress 2023; October 20-24, 2023, Madrid, Spain.