Cancer Management and Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Profile of Nivolumab in the Treatment of Resected Esophageal Squamous Cell Carcinoma: A Review of the Clinical Data

Yuntae Kim[1,2], Shun Yamamoto[1], Ken Kato[1]

[1]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [2]Department of Gastroenterology, St. Luke International Hospital, Tokyo, Japan

Correspondence: Ken Kato, Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan, Tel +81-3-3542-2511, Fax +81-3-3542-3815, Email kenkato@ncc.go.jp

Abstract: Esophageal cancer (EC) is the seventh most common malignancy globally. There are two main histological subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. ESCC is the predominant histological type of esophageal cancer worldwide and has worse prognosis than esophageal adenocarcinoma. However, effective treatment for patients with ESCC remains limited. Moreover, the risk of recurrence remains high in patients with resectable ESCC even with perioperative multidisciplinary treatment, such as chemoradiotherapy or chemotherapy. Nivolumab, a human monoclonal immunoglobulin G4 antibody that inhibits programmed cell death protein 1, has recently been identified as a potential treatment for patients with metastatic esophageal cancer based on the results of the ATTRACTION-3 and CheckMate 648 trials. The CheckMate 577 trial showed survival benefits of postoperative nivolumab monotherapy compared with placebo in patients with resectable locally advanced esophageal cancer who did not achieve a pathological complete response after preoperative chemoradiotherapy. In this review, we discuss the data on the efficacy and safety of postoperative nivolumab and share future perspectives on immune checkpoint inhibitors as perioperative therapy for patients with locally advanced ESCC.

Keywords: esophageal squamous cell carcinoma, immune checkpoint inhibitor, nivolumab, postoperative treatment

Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide, causing more than 500,000 deaths annually.[1] EC can be divided into two main types: esophageal squamous cell carcinoma (ESCC), which is common worldwide (accounting for approximately 90% of cases), particularly in East Asia and East Africa, and esophageal adenocarcinoma (EAC), which is common in Western countries. The major risk factors for ESCC are different from those for EAC, with smoking and alcohol consumption being the major risk factors for ESCC, whereas chronic gastroesophageal reflux disease is the major risk factor for EAC.[2,3] In Western countries, the incidence of ESCC is stable, while that of EAC is increasing.[3–6] EAC is a highly aggressive malignant disease that is almost diagnosed at an advanced stage.[7]

Locally advanced EC is difficult to treat due to its biology and anatomic limitations. Therefore, preoperative treatments have been developed for such patients. Preoperative chemoradiotherapy followed by surgery based on the results of the CROSS trial, mainly in Western countries,[8] and preoperative triplet chemotherapy followed by surgery based on the results of the JCOG1109 (NExT) trial, mainly in Japan and other Asian countries,[9] have been considered the standard of care.

The CROSS study was a randomized, controlled trial comparing preoperative chemoradiotherapy with carboplatin and paclitaxel administered weekly for 5 weeks and concurrent radiotherapy (41.4 Gy/23 fractions) with surgery alone in patients with locally advanced EC. The study showed that the median overall survival (OS) with preoperative chemoradiotherapy followed by surgery was superior to that for surgery alone (49.4 months vs 24.0 months, hazard ratio [HR] 0.657, 95% CI [confidence interval] 0.495–0.871).[8]

Received: 26 January 2023
Accepted: 4 May 2023
Published: 10 May 2023

The JCOG1109 (NExT) trial evaluated patients with resectable locally advanced ESCC who received (1) preoperative chemoradiotherapy consisting of cisplatin and 5-fluorouracil (CF) followed by concurrent radiotherapy (41.4 Gy in 23 fractions) and surgery, or (2) docetaxel, cisplatin, 5-fluorouracil (DCF) followed by surgery, and (3) preoperative CF followed by surgery[10] in a three-arm randomized controlled trial. In this study, OS of patients who received surgery after preoperative DCF therapy was superior to that of patients who received surgery after preoperative CF therapy (3-year OS: 72.1% vs 62.6%, HR 0.68, 95% CI 0.50–0.92). However, OS after preoperative CF plus radiotherapy was not superior to OS after preoperative CF plus surgery (3-year OS: 68.3% vs 62.6%, HR 0.84, 95% CI 0.63–1.12).[9]

The development of therapies for locally advanced EC has primarily focused on preoperative treatment, as described above. However, it has been shown that approximately half of patients with locally advanced EC who receive preoperative therapy relapse after surgery.[8,10] Therefore, effective postoperative therapy has been sought to improve the clinical outcome of patients with locally advanced EC. In this context, nivolumab, a human monoclonal immunoglobulin G4 antibody that inhibits programmed cell death protein 1 (PD-1), showed promise as a treatment for patients with metastatic EC based on the results of the ATTRACTION-3[11] and CheckMate 648[12] studies. It is being developed as a postoperative treatment for patients with locally advanced EC based on the results of the ATTRACTION-311 and CheckMate 577 studies.[13]

In this review, we discuss the efficacy and safety of postoperative nivolumab therapy and the future perspectives of this investigational therapy for locally advanced EC.

Postoperative Nivolumab Treatment

Nivolumab

The treatment of many cancers has been revolutionized by the advent of immune checkpoint inhibitors (ICIs) that target the PD-1/Programmed Death Ligand 1 (PD-L1) pathway. There are two major types of immune responses: positive immune responses that eliminate pathogens and foreign substances, and negative immune responses that prevent tissue damage caused by excessive immune responses after the elimination response has achieved its goal, maintaining a balance in immune homeostasis. The molecules involved in this immune response are called immune checkpoint molecules, which are divided into inhibitory immune checkpoint molecules (PD-1, cytotoxic T lymphocyte-associated antigen 4, etc.) and stimulatory immune checkpoint molecules (CD40 ligand, OX40, inducible T cell costimulatory molecules, etc.). An important mechanism driving tumor progression is the aberrant expression of inhibitory immune checkpoint molecules by tumor cells, which is associated with escape from immune surveillance.

PD-1 is an immunosuppressive receptor that is highly expressed on immune cells, including activated T-cells, B-cells, and natural killer cells. Interaction between PD-1 and PD-L1 or PD-L2 could mediate suppression of T-cell activity via negative regulation of T-cell receptor and CD28 signaling (Figure 1A). PD-L1 is overexpressed in many cell types, including antigen-presenting cells.[14] PD-L1 is also upregulated in many types of cancer, suggesting that the PD-1/PD-L1

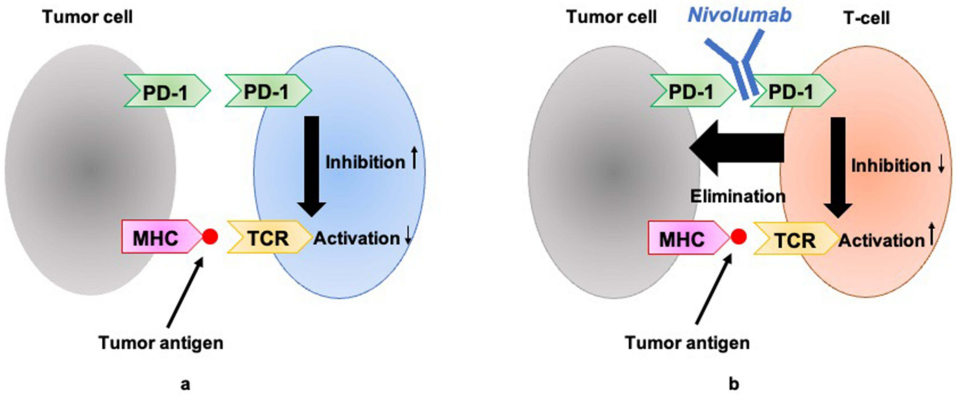

Figure 1 Mechanisms of action of nivolumab. (**A**) Tumor cells Inhibit T-lymphocyte activation. (**B**) Nivolumab inhibits interaction between PD-1 and PD-L1.
Abbreviations: MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

pathway inhibits the antitumor response.[15] PD-L1 overexpression is observed in approximately 20–80% of ESCC patients, and poor clinical outcomes have been reported in these patients.[16]

Nivolumab is a genetically engineered human IgG4 monoclonal antibody specific for PD-1[15] and the glycoprotein consisting of two light chains of 214 amino acid residues and two heavy chains of 440 amino acid residues, with an N-linked glycan chain at the asparagine in the heavy chain. The IgG4 subclass, which has no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), has been selected to prevent PD-L1 and PD-L2 from binding to PD-1.[14,16] The IgG4 subclass has been selected to avoid damaging the bound activated T cells. Nivolumab also increases tumor antigen-specific T-cell proliferation and cytokine secretion in vitro (Figure 1B).[17,18] Nivolumab has been approved to treat advanced squamous and non-squamous non-small cell lung cancer, melanoma, Hodgkin lymphoma, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer, hepatocellular carcinoma, and malignant pleural mesothelioma.[19–28]

CheckMate 577

Nivolumab was initially developed for the treatment of patients with metastatic or recurrent EC. The ATTRACTION-3 and CheckMate 648 trials established the current standard of care, including ICI, for these patients.[11,12] Additionally, nivolumab is being developed for postoperative treatment of resectable locally advanced EC.

CheckMate 577 was a Phase III study comparing nivolumab monotherapy with placebo as postoperative treatment following complete resection of resectable EC or esophagogastric junction cancer (EGJC) in patients who had received preoperative chemoradiotherapy and did not achieve a pathologic complete response (pCR).

CheckMate 577 randomized 794 patients to nivolumab (n=532, 240 mg every 2 weeks for 16 weeks followed by 480 mg every 4 weeks) or placebo (n=262). Randomization was stratified by histology (squamous vs adenocarcinoma), pathological lymph node status (≤pN1 vs ypN0) and PD-L1 expression (≥1% vs <1%).[13]

The primary endpoint was disease-free survival (DFS). Secondary endpoints were OS and OS rates at 1, 2 and 3 years. Safety profiles were evaluated in all patients who received at least one dose of the assigned regimen. The study required a minimum of 440 DFS events to have 91% power to detect a mean HR of 0.72 with a two-sided alpha of 0.05, allowing for a prespecified interim analysis.

Prespecified interim analyses included data collected from the date of randomization through the clinical data cutoff date of May 12, 2020. Median follow-up was 24.4 months. Asians comprised 15% of patients; ECOG performance status was 0 (58%) or 1 (42%). Clinical stage at initial presentation was II in 35% and III in 65%. Tumors were located in the esophagus (60%) or at the esophagogastric junction (40%). Seventy-one percent of patients had EAC, 29% had ESCC, and 57% had pathologic lymph node status ≥ ypN1. PD-L1 expression was ≥ 1% in 16% and < 1% in 72% of patients.

In a pre-specified interim analysis, median DFS was significantly longer in the nivolumab group than in the placebo group (22.4 months [95% CI 16.6–34.0] vs 11.0 months [95% CI 8.3–14.3]; HR 0.69 [95% CI 0.56–0.86], p=0.0003). In a histologic subgroup analysis, the median DFS for ESCC patients was 29.7 months in the nivolumab group versus 11.0 months in the placebo group (HR 0.61), which tended to be superior to that for EAC patients (19.4 months versus 11.1 months, HR 0.75). A pre-specified subgroup analysis also showed a trend toward longer DFS in the nivolumab arm.

Fatigue (17%), diarrhea (17%), pruritus (10%), rash (10%), hypothyroidism (9%) and nausea (9%) were the most common treatment-related adverse events in the nivolumab group. Serious adverse events were observed in 8% of patients treated with nivolumab compared to 3% of patients treated with placebo. The incidence of treatment-emergent adverse events leading to discontinuation was 9% in the nivolumab group and 3% in the placebo group. Post-operative nivolumab treatment was well tolerated and had an acceptable safety profile.

The CheckMate 577 results suggest that postoperative nivolumab may be a useful standard of care for patients with locally advanced EC and EGJC who do not achieve pCR after preoperative chemoradiation and surgery.

However, the CheckMate 577 study raises several important questions. First, complete data on OS have not yet been reported. Patients with recurrent ESCC may receive nivolumab monotherapy or nivolumab-containing therapy after relapse. Therefore, the superiority of OS as well as DFS in the postoperative nivolumab group over the placebo group is important information to determine the treatment strategy for patients with locally advanced EC. Second, there are no data on patients with EC who underwent surgery after preoperative chemoradiotherapy and achieved pCR. Since

approximately 30–40% of patients who receive preoperative chemoradiation achieve pCR,[8,9,29] efficacy and safety data are needed on the use of postoperative nivolumab monotherapy in this population. Recently, durvalumab, a selective high-affinity human IgG1 monoclonal antibody that targets PD-L1 and blocks its binding to PD-1 and CD80, allowing T cells to recognize and kill tumor cells,[30] is also in development for the perioperative treatment of ESCC. A randomized, double-blind, Phase II trial was reported comparing postoperative durvalumab to placebo in patients with resectable locally advanced ESCC. In this study, there was no benefit in the postoperative durvalumab group compared to the placebo group with respect to DFS (HR 1.76, 95% CI 0.42–7.40) or OS (HR 2.26, 95% 0.41–12.34) in ESCC patients who achieved pCR.[31] The results of this Phase II study suggest that postoperative ICI therapy may not provide clinical benefit to patients who achieve pCR. Third, the CheckMate 577 trial did not provide data on EC patients who underwent surgery after preoperative chemotherapy. Radiotherapy can cause the release of inflammatory cytokines and chemokines that reprogram the immune microenvironment of the tumor by promoting the infiltration of effector T cells into the tumor.[32] Thus, preoperative radiotherapy may stimulate the immune system and contribute to the effectiveness of postoperative nivolumab therapy. Further studies are needed to evaluate the efficacy of adding postoperative nivolumab after preoperative chemotherapy, such as DCF based on the JCOG1109 trial, followed by surgery. Finally, there is a need for biomarkers that can predict the efficacy of ICIs, including nivolumab. The CheckMate 577 trial includes a subgroup analysis of DFS according to PD-L1 expression as measured by the combined positive score (CPS). The HR was reported to be 0.62 (95% CI 0.46–0.83) in the CPS ≥5 group and 0.89 (95% CI 0.65–1.22) in the CPS <1 group.[13] The results of this subgroup analysis suggest that the CPS for PD-L1 expression may be a useful biomarker for the efficacy of postoperative nivolumab therapy. The utility of this score in patients with metastatic or recurrent EC has already been demonstrated in the KEYNOTE-181 study.[33] In addition, its utility in patients with metastatic or recurrent ESCC who received nivolumab monotherapy was also reported in ASCO-GI 2022. This retrospective study evaluated the correlation of progression-free survival with CPS for PD-L1 expression in detail. It reported an HR of 1.33 (95% CI 0.66–2.68) for a CPS cut-off of 5, an HR of 0.85 (95% CI 0.52–1.38) for a CPS cut-off of 10, an HR of 0.79 (95% CI 0.50–1.26) for a CPS cut-off of 15, and an HR of 0.70 (95% 0.43–1.13) for a CPS cut-off of 20.[34] These results suggest that the CPS for PD-L1 expression may have potential as a biomarker for predicting the clinical benefit of ICIs. However, there are still some questions about the best cut-off point for this score and whether there are other biomarkers that might be more useful. More translational research is needed to answer these questions.

The CheckMate 577 trial showed impressive results in patients with locally advanced EC. However, due to its limitations and setting, more long-term efficacy data, including OS, and more detailed biomarker data are awaited from this trial. In this retrospective study, the correlation between CPS of PD-L1 expression and progression-free survival was evaluated in detail. The results showed an HR of 1.33 (95% CI 0.66–2.68) for a CPS cutoff of 5, HR 0.85 (95% CI 0.52–1.38) for a CPS cutoff of 10, HR 0.79 (95% CI 0.50–1.26) for a CPS cutoff of 15, and HR 0.70. These results suggest that the CPS of PD-L1 expression may be a potential biomarker for predicting the clinical benefit of ICI. However, some questions remain regarding the optimal cutoff value for this score and whether there are other more useful biomarkers. More translational research is needed to answer these questions.

The CheckMate 577 trial showed excellent results in patients with locally advanced EC. However, due to its limitations and setting, longer-term efficacy data including OS and more detailed biomarker data from this trial are eagerly awaited.

The Optimal Biomarkers of Nivolumab Under Research

Nivolumab is being developed for the treatment of patients with locally advanced and metastatic ESCC, but there are few data on useful biomarkers to select the more beneficial population, PD-L1 expression has been one of the promising candidates as a predictive biomarker for ICI use in other cancer types.[35] To assess PD-L1 expression, many clinical trials have often used the tumor proportion score (TPS) or CPS. The TPS is defined as the number of PD-L1 positive tumor cells divided by the total number of tumor cells multiplied by 100. The CPS is defined as the number of PD-L1 positive tumor cells, macrophages and lymphocytes divided by the total number of tumor cells multiplied by 100. However, the relationship between PD-L1 expression and efficacy has been investigated, and the results of these studies in patients with advanced ESCC have been inconsistent.[11,12,33,34] The subgroup analysis of the CheckMate 577 trial showed that

postoperative nivolumab monotherapy appeared to have better clinical benefit in patients with CPS ≥ 5 compared to patients with CPS < 5.[13] Given these data, more useful biomarkers are needed for patients who received ICI-containing treatments.

Recently, however, the balance of PD-1 expression between CD8+ effector T cells and Treg cells in the tumor microenvironment has been reported as a potential biomarker of ICI in lung and gastric cancer.[36] Japanese investigators retrospectively reported the clinical utility of the balance of PD-1 expression between CD8+ effector T cells and regulatory T cells for predicting the efficacy of nivolumab monotherapy in patients with treated advanced ESCC.[37] The ratio of regulatory T cell PD-1 expression to CD8+ effector T cells was significantly higher in non-responders than in responders (p=0.036). PFS in the low ratio group was significantly longer than in the high ratio group (median PFS: 3.2 months vs 1.8 months, HR [95% CI]: 0.56[0.34–0.92], p=0.02). OS in the ratio-low group tended to be longer than in the ratio-high group (median OS: not reached vs 10.2 months, HR [95% CI]: 0.64 [0.31–1.30], p=0.21).

This balance of PD-1 expression between regulatory T cells and effector T cells was biologically meaningful and this biomarker analysis showed the theoretical results in patients with advanced ESCC. This promising biomarker is expected to be beneficial for patients with resected advanced ESCC and may identify the optimal population for postoperative nivolumab monotherapy. Therefore, further prospective biomarker studies are needed to select the optimal postoperative treatment strategy.

Ongoing Nivolumab-Related Trials of Preoperative Therapy

Postoperative nivolumab therapy is effective in patients with locally advanced EC, but approximately half of these patients relapse or die.[13] Therefore, besides postoperative therapy, preoperative therapy must be developed for greater clinical benefit. The development of preoperative therapy, including ICI, for patients with resectable locally advanced EC is underway worldwide (Table 1). A Phase I trial (ClinicalTrials.gov Identifier: NCT03044613) is ongoing to evaluate the safety and efficacy of induction nivolumab alone versus preoperative chemoradiation plus nivolumab plus surgery in patients with resectable EC or gastroesophageal cancer.[38] Treatment-related adverse events occurred in 12 of 16 patients (75.0%), with 4 (25.0%) patients experiencing Grade 3 adverse events (dyspnea, upper respiratory tract infection, transaminitis, rash). However, 14 (87.5%) patients were able to receive the full scheduled dose of nivolumab. pCR rate was reported as 31.3% (5/16 patients). A multicenter phase I/II trial (ClinicalTrials.gov Identifier: NCT03278626)

Table 1 Perioperative Nivolumab-Related Clinical Trials

Clinical Trial	Phase	Histology	Patients, n	Regimen	pCR (%)	DFS (Months)
Postoperative treatment CheckMate 577	III	ESCC, EAC	794	Postoperative nivolumab vs placebo	NA	22.4
Preoperative treatment NCT03044613 Arm A	II	ESCC, EAC	16	Induction nivolumab + preoperative CRT + concurrent nivolumab	31.3	NA
NCT03278626	I/II	ESCC	12	Induction nivolumab + preoperative CRT + concurrent nivolumab	33.3	NA
FRONTiER Cohort A/B	I	ESCC	13	Preoperative CF + nivolumab	7.7	NA
FRONTiER Cohort C/D	I	ESCC	12	Preoperative DCF + nivolumab	25.0	NA

Abbreviations: CF, cisplatin and 5-fluorouracil; CRT, chemoradiotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

evaluated the safety and efficacy of nivolumab in combination with chemoradiotherapy in 6 patients with locally advanced ESCC.[39] There were no unacceptable toxicities and the most frequent grade 3–4 treatment-related adverse events were lymphopenia (83.3%) and leukopenia (33.3%). In addition, two patients (33.3%) achieved a complete clinical response.

Another phase I trial, JCOG1804E (FRONTiER), evaluated nivolumab plus CF, nivolumab plus DCF, and nivolumab plus 5-FU + LOCOVORIN + OXALIPLatin + docetaxel (FLOT) as preoperative chemotherapy in patients with resectable, locally advanced ESCC. The short-term results of CF plus nivolumab and DCF plus nivolumab have been reported, showing pCR rates of 7.7% (1/13) and 25.0% (3/12), respectively. The pCR rates were 7.7% (1/13) and 25.0% (3/12), respectively. Only one patient developed dose-limiting toxicity (grade 3 dyspnea and rash) after surgery.[40,41] There are also two ongoing trials with unreported data: one phase I/II trial (ClinicalTrials.gov Identifier: NCT03544736) is evaluating the safety and feasibility of nivolumab with radiation therapy or chemoradiotherapy in different settings. The study includes one cohort of perioperative nivolumab plus neoadjuvant chemoradiotherapy for operable ECs. Another single-arm phase II trial (ClinicalTrials.gov Identifier: NCT03987815) will evaluate the safety and feasibility of nivolumab monotherapy for T2 or T3-node negative ESCC prior to curative surgery.

Considering the pathologic response rates in patients treated with preoperative chemoradiotherapy and triplet chemotherapy,[8,9] preoperative chemoradiotherapy plus nivolumab may have some additive effect, but preoperative chemotherapy plus nivolumab may be even more effective. However, data on preoperative therapy including nivolumab are limited, and further studies, including long-term results with FLOT plus nivolumab, are needed.

Conclusion

The placebo-controlled CheckMate 577 trial has demonstrated the clinical benefits of postoperative nivolumab in patients with resectable locally advanced EC, mainly ESCC, who did not achieve a pCR after preoperative chemoradiotherapy. However, some patients with locally advanced EC have had disease recurrence after perioperative treatment. Therefore, further intensive development of treatments is needed.

Abbreviations

ASCO, American Society of Clinical Oncology; CD40 cluster of differentiation; CF, cisplatin and 5-fluorouracil; CI, confidence interval; CPS, combined positive score; CRT, chemoradiotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil; DFS, disease-free survival; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio; ICIs, immune checkpoint inhibitors; JCOG, Japan Clinical Oncology Group; MHC, major histocompatibility complex; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; NA, not applicable; TCR, T-cell receptor.

Disclosure

Yuntae Kim reports no conflicts of interest in this work. Shun Yamamoto reports having received honoraria from ONO and BMS, MSD. Ken Kato reports having received consulting fees from BMS and MSD, BeiGene, Roche, AstraZeneca, Bayer, honoraria from ONO and BMS, Taiho, and research funding from ONO and BMS, MSD, BeiGene, Chugai, Shionogi, AstraZeneca, BAYER, all of which is unrelated to the submitted work. The authors report no other conflicts of interest in this work.

References

1. World Health Organization. GLOBOCAN 2020 estimated cancer incidence, mortality and prevalence worldwide. Available from: http://globocan.iarc.fr/. Accessed May 4, 2023.
2. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. *Cancer Epidemiol Biomarkers Prev*. 2016;25:16–27. doi:10.1158/1055-9965.EPI-15-0578
3. Rustgi AK, El- Serag HB. Esophageal carcinoma. *N Engl J Med*. 2014;371:2499–2509. doi:10.1056/NEJMra1314530
4. Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology*. 2018;154:360–373. doi:10.1053/j.gastro.2017.08.023

5. Njei B, McCarty TR, Birk JW. Trends in esophageal cancer survival in United States adults from 1973 to 2009: a SEER database analysis. *J Gastroenterol Hepatol*. 2016;31:1141–1146. doi:10.1111/jgh.13289
6. Murphy G, McCormack V, Abedi-Ardekani B, et al. International cancer seminars: a focus on esophageal squamous cell carcinoma. *Ann Oncol*. 2017;28:2086–2093. doi:10.1093/annonc/mdx279
7. Thrift AP. The epidemic of oesophageal carcinoma: where are we now? *Cancer Epidemiol*. 2016;41:88–95. doi:10.1016/j.canep.2016.01.013
8. 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. doi:10.1056/NEJMoa1112088
9. 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(4_suppl):238. doi:10.1200/JCO.2022.40.4_suppl.238
10. Ando N, Kato H, Igaki H, et al. A randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for clinical stage II/III squamous cell carcinoma of the thoracic esophagus (JCOG 9907). *Ann Surg Oncol*. 2012;19(1):68–74. doi:10.1245/s10434-011-2049-9
11. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, Phase 3 trial. *Lancet Oncol*. 2019;20(11):1506–1517. doi:10.1016/S1470-2045(19)30626-6
12. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *N Engl J Med*. 2022;386(5):449–462. doi:10.1056/NEJMoa2111380
13. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021;384(13):1191–1203. doi:10.1056/NEJMoa2032125
14. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med*. 2016;375(18):1767–1778. doi:10.1056/NEJMra1514296
15. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. *Nat Rev Immunol*. 2018;18(3):153–167. doi:10.1038/nri.2017.108
16. Guo W, Wang P, Li N, et al. Prognostic value of PD-L1 in esophageal squamous cell carcinoma: a meta-analysis. *Oncotarget*. 2017;9(17):13920–13933. doi:10.18632/oncotarget.23810
17. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28(19):3167–3175. doi:10.1200/JCO.2009.26.7609
18. Hamanishi J, Mandai M, Ikeda T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-Resistant ovarian cancer. *J Clin Oncol*. 2015;33(34):4015–4022. doi:10.1200/JCO.2015.62.3397
19. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006–2017. doi:10.1056/NEJMoa1414428
20. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627
21. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311–319. doi:10.1056/NEJMoa1411087
22. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373(19):1803–1813. doi:10.1056/NEJMoa1510665
23. Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016;375(19):1856–1867. doi:10.1056/NEJMoa1602252
24. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, Phase 2 trial. *Lancet Oncol*. 2017;18(3):312–322. doi:10.1016/S1470-2045(17)30065-7
25. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18(9):1182–1191. doi:10.1016/S1470-2045(17)30422-9
26. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, Phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–2502. doi:10.1016/S0140-6736(17)31046-2
27. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390(10111):2461–2471. doi:10.1016/S0140-6736(17)31827-5
28. Okada M, Kijima T, Aoe K, et al. Clinical Efficacy and Safety of Nivolumab: results of a Multicenter, Open-label, Single-arm, Japanese Phase II study in Malignant Pleural Mesothelioma (MERIT). *Clin Cancer Res*. 2019;25(18):5485–5492. doi:10.1158/1078-0432.CCR-19-0103
29. 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(27):2796–2803. doi:10.1200/JCO.2018.79.1483
30. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res*. 2015;3(9):1052–1062. doi:10.1158/2326-6066.CIR-14-0191
31. Park S, Sun JM, Choi YL, et al. Adjuvant durvalumab for esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy: a placebo-controlled, randomized, double-blind, phase II study. *ESMO open*. 2022;7(1):100385. doi:10.1016/j.esmoop.2022.100385
32. McLaughlin M, Patin EC, Pedersen M, et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. *Nat Rev Cancer*. 2020;20(4):203–217. doi:10.1038/s41568-020-0246-1
33. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. *J Clin Oncol*. 2020;38(35):4138–4148. doi:10.1200/JCO.20.01888
34. Mikuni H, Yamamoto S, Sawada R, et al. Correlation of combined positive score of PD-L1 expression and clinical efficacy for advanced esophageal squamous cell carcinoma treated with nivolumab monotherapy. *J Clin Oncol*. 2022;40:289. doi:10.1200/JCO.2022.40.4_suppl.289
35. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–1639. doi:10.1056/NEJMoa1507643

36. Kumagai S, Togashi Y, Kamada T, et al. The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. *Nat Immunol*. 2020;21(11):1346–1358. doi:10.1038/s41590-020-0769-3
37. Mikuni H, Watanabe GS, Kumagai S, et al. Activation status of CD8+ T and Treg cells in the tumor microenvironment potentially predicts the clinical in advanced esophageal squamous cell carcinoma. Poster presented at: European Society for Medical Oncology (ESMO) Congress; September 10; 2022; Paris, France.
38. Kelly RJ, Smith KN, Anagnostou V, et al. Neoadjuvant nivolumab plus concurrent chemoradiation in stage II/III esophageal/gastroesophageal junction cancer. *J Clin Oncol*. 2019;37(4_suppl):142. doi:10.1200/JCO.2019.37.4_suppl.142
39. Wu JJ, Atkinson EC, Leichman LP, et al. A phase I/II multisite study of nivolumab and carboplatin/paclitaxel with radiation therapy (RT) in patients with locally advanced esophageal squamous cell carcinoma (ESCC). *J Clin Oncol*. 2020;38(4_suppl):372. doi:10.1200/JCO.2020.38.4_suppl.372
40. Yamamoto S, Kato K, Daiko H, et al. Feasibility study of nivolumab as neoadjuvant chemotherapy for locally esophageal carcinoma: fRONTiER (JCOG1804E). *Future Oncol*. 2020;16(19):1351–1357. doi:10.2217/fon-2020-0189
41. Matsuda S, Yamamoto S, Kato K, et al. FRONTiER: a feasibility trial of nivolumab with neoadjuvant CF or DCF, FLOT therapy for locally advanced esophageal carcinoma (JCOG1804E)—Short-term results for cohorts C and D. *J Clin Oncol*. 2022;40:286. doi:10.1200/JCO.2022.40.4_suppl.286