Current perspectives of the Japanese Esophageal Oncology Group on the development of immunotherapy for esophageal cancer

Toru Kadono¹,², Shun Yamamoto¹ and Ken Kato¹,*

¹Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, and ²Department of Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

*For reprints and all 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. E-mail: kenkato@ncc.go.jp

Received 15 January 2022; Editorial Decision 31 July 2022; Accepted 3 August 2022

Abstract

Esophageal cancer is the seventh most common cancer worldwide and continues to have a poor prognosis. Starting with the development of immune checkpoint inhibitors for patients with metastatic melanoma, many clinical trials have been conducted to evaluate the efficacy and safety of immune checkpoint inhibitors against various malignancies. Although few effective drugs are available for patients with advanced esophageal cancer, two immune checkpoint inhibitors, nivolumab and pembrolizumab, have been approved as second-line treatments for advanced esophageal squamous cell carcinoma. Recently, immune checkpoint inhibitors have shown promising results as post-operative therapies and first-line treatments for advanced esophageal cancer. Nivolumab has been approved as a post-operative therapy based on the CheckMate-577 trial, and nivolumab, ipilimumab and pembrolizumab have been approved as first-line treatments based on the CheckMate-648 trial and the KEYNOTE-590 trial. In addition, many trials of immune checkpoint inhibitors plus pre-operative treatment or definitive chemoradiotherapy are ongoing. The Japan Esophageal Oncology Group was established in 1978 and has conducted numerous clinical trials, most of which have examined multimodality treatments. In the era of immunotherapy, Japan Esophageal Oncology Group is conducting a clinical trial studying multimodality treatment with an immune checkpoint inhibitor. JCOG1804E (FRONTiER) is a phase I trial to evaluate the safety and efficacy of nivolumab plus pre-operative chemotherapy followed by surgery. These results might improve the clinical outcomes of esophageal cancer patients.

Key words: esophageal squamous cell carcinoma, immune checkpoint inhibitor, nivolumab, pembrolizumab, pre-operative treatment, post-operative treatment

Introduction

Worldwide, patients with esophageal SCC (ESCC) account for about 87% of all EC patients. However, the dominant histological subtypes differ according to geographical region and culture. For example, in North America and Europe, the most common histological subtype is esophageal AC (EAC); in Eastern Asian countries, the most common histological subtype is ESCC (1). In Japan, ESCC patients account for 90% of all EC patients (2,3); consequently, the
Table 1. Results of phase III clinical trials evaluating ICIs for EC

| Agent (Trial) | Line | Location | Histology | No. of pts | Regimen | Response rate | Median PFS | Median OS | Ref |
|---------------|------|----------|-----------|------------|---------|---------------|------------|-----------|-----|
| **Metastatic or recurrent setting** | | | | | | | | | |
| Nivolumab (ATTRACTION-3) | 2 | E | SCC | 419 | Nivolumab | 19% | 1.7 months | 10.9 months | (41) |
| Pembrolizumab (KEYNOTE-181) | 2 | E/EGJ | SCC/AC (SCC 63%) | 628 | Pembrolizumab | 13.1% | 2.1 months | 7.1 months | (49) |
| Camrelizumab (ESCORT) | 2 | E | SCC | 457 | Pembrolizumab | 16.7% | 2.2 months | 8.2 months | (57) |
| Tislelizumab (RATIONALE-302) | 2 | E | SCC | 512 | Pembrolizumab | 16.7% | 2.2 months | 8.2 months | (58) |
| Pembrolizumab (KEYNOTE-590) | 1 | E/EGJ | SCC/AC (SCC 73%) | 749 | CF + Pembrolizumab | 45.0% | 6.3 months | 12.4 months | (50) |
| Nivolumab (CheckMate-648) | 1 | E | SCC | 970 | CF + Nivolumab | 53% | 6.9 months | 15.4 months | (56) |
| **Resectable, locally advanced setting** | | | | | | | | | |
| Nivolumab (CheckMate-577) | Adjuvant | E/EGJ | SCC/AC (SCC 29%) | 794 | Nivolumab | - | 22.4 months’ NE | - | (46) |

Abbreviations: pts, patients; E, esophagus; EGJ, esophagogastric junction; SCC, squamous cell carcinoma; AC, adenocarcinoma; CF, cisplatin plus fluorouracil; CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; NE, not evaluated.

Japanese Esophageal Oncology Group (JEOG) has focused on the development of treatments (mainly multi-modal) for ESCC. Treatment drugs for EC are limited, and the prognosis in patients with EC remains poor. Recently, immune checkpoint inhibitors (ICIs) have been developed in various cancers and shown antitumor activity in EC. Here, we show the development of ICIs in EC according to disease stage and discuss the prospect of ICIs Table 1 and 2.

ICIs for advanced EC

Systemic chemotherapy is required for patients with recurrences or metastasis to palliate symptoms and improve survival. Although few studies have validated the efficacy of palliative chemotherapy for EC, chemotherapy combined with platinum and fluorouracil was recognized as a standard therapy (3,4,20,21).

The recent development of ICIs, such as anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) and anti-programmed death-1 (PD-1), was a breakthrough in cancer treatment. Tumor-specific antigens are expressed on tumor cells as a result of genetic and epigenetic alterations; these antigens are recognized by dendritic cells or antigen-presenting cells. Subsequently, the antigens are presented to T-cells, and activated T-cells kill the tumor cells. In an interaction between T-cells and tumor cells, the degree of the T-cell response is regulated by a balance between activating and inhibitory signals, known as immune checkpoints (24,25). PD-1 expressed on the surface of T-cells interacts with programmed death-ligand 1 (PD-L1) on cancer cells and immune cells, downregulating T-cell activation and leading to T-cell apoptosis (26,27). Therefore, blockade of the PD-1/PD-L1 pathway produces anti-tumor effects, and PD-1/PD-L1 inhibitors have conferred clinical benefits in patients with various cancers (28–38).

Nivolumab

Nivolumab is a humanized monoclonal IgG4 PD-1 antibody. The ATTRACTION-1 phase II trial assessed the efficacy and safety of nivolumab monotherapy for patients with advanced EC refractory or intolerant to standard therapies, such as fluorouracil and platinum or taxane. In 65 ESCC patients, the ORR, which was the study’s primary endpoint, was 17% (95% CI: 10–28%), and the median PFS and OS were 1.5 months (95% CI: 1.4–2.8 months) and
Nivolumab monotherapy have become the second-line standard treatment, this treatment showed progressive disease at the best response of about half of ESCC patients and no useful biomarkers were detected in the ATTRACTION-3 trial. Therefore, the biomarker analysis was needed for this population. In the KEYNOTE-180 and KEYNOTE-181 trials, PD-L1 expression using combined positive score was a promising biomarker for pembrolizumab monotherapy; there were no data on PD-L1 (CPS) and efficacy of nivolumab monotherapy. Regarding this clinical question, a retrospective study showed a trend toward a better PFS with a higher CPS cut-off (CPS 5: HR, 1.33: CPS 10: HR, 0.85; CPS 20: HR, 0.70). Therefore, CPS might be a potential biomarker for evaluating the efficacy of nivolumab in patients with advanced ESCC (44). Additionally, further studies are needed to identify optimal biomarkers other than CPS for nivolumab, and JEOG members are presently conducting the ANTARES study (UMIN000043703) to explore useful new biomarkers using blood, biopsy and fecal samples.

Following the success of nivolumab monotherapy for patients with advanced EC, nivolumab combined with chemotheraphy or ipilimumab which is an anti-CTLA-4 monoclonal antibody was developed. CTLA-4 is expressed on T-cells and regulates T-cell activation by counteracting and inhibiting CD28. Interactions between CTLA-4 and CD28 inactivate T-cells. Interactions between CTLA-4 and CD28 inactivate T-cells. Further studies are needed to identify optimal biomarkers other than CPS for nivolumab, and JEOG members are presently conducting the ANTARES study (UMIN000043703) to explore useful new biomarkers using blood, biopsy and fecal samples.

The CheckMate-648 phase III trial examined nivolumab plus ipilimumab or nivolumab plus CF versus CF as a first-line chemotherapy in patients with metastatic or recurrent ESCC. The primary endpoints were OS and PFS in patients with PD-L1 ≥ 1%. The nivolumab plus CF arm had a significantly longer OS (15.4 months vs. 9.1 months, HR: 0.54, 99.5% CI: 0.37–0.80, P < 0.0001) and PFS (6.9 months vs. 4.4 months, HR: 0.65, 98.5% CI: 0.46–0.92, P = 0.0355) than the CF arm in patients with PD-L1 ≥ 1%. The nivolumab plus ipilimumab arm also had a significantly longer OS (13.7 months vs. 9.1 months, HR: 0.64, 98.6% CI: 0.46–0.90, P = 0.001) than the CF arm in patients with PD-L1 ≥ 1%, but the PFS was comparable (4.0 months vs. 3.6 months, HR: 0.73, 95% CI: 0.50–1.05, P = 0.07).

### Table 2. Ongoing trials of ICIs for EC

| Trial                        | Agent       | Line | Phase | No. of pts | Treatment Arm(s)                        | Ref |
|------------------------------|-------------|------|-------|------------|-----------------------------------------|-----|
| **Metastatic or recurrent setting** | RATIONALE-306 | Tislelizumab | I      | III        | 649                                     |     |
|                              | Pembrolizumab | I    | III   | 862        | Pembrolizumab + Lenvatinib + Chemotherapy |     |
|                              | Pembrolizumab | I    | III   | 600        | Pembrolizumab + Chemotherapy             |     |
|                              | Pembrolizumab | I    | III   | 612        | Pembrolizumab + Chemotherapy             |     |
| Unresectable, locally advanced setting | TENERGY | Atezolizumab | Following dCRT | II | 50 | dCRT followed by Atezolizumab | (60) |
|                              | NOBEL       | Nivolumab | Combined with dCRT | II | 60 | dCRT + Nivolumab                  |     |
|                              | SKYSCRAPER-07 | Tislelizumab | Following dCRT | III | 750 | dCRT followed by Tislelizumab + Atezolizumab |     |
|                              | Placebo     | Atezolizumab | Combined with dCRT | III | 600 | Placebo + Atezolizumab         | (61) |
|                              | KUNLUN      | Durvalumab | Combined with dCRT | III | 600 | dCRT + Durvalumab                |     |
|                              | KEYNOTE-975 | Pembrolizumab | Combined with dCRT | III | 600 | dCRT + Pembrolizumab             |     |
| Resectable, locally advanced setting | CRUCIAL | Nivolumab | Combined with dCRT | II | 130 | dCRT + Nivolumab                 |     |
|                              | FRONTIER (JCOG1804E) | Nivolumab | Neoadjuvant | I | 36 | DCF + Nivolumab                  | (72) |
|                              |             |       |       |            | FLOT + Nivolumab                    |     |

Abbreviations: pts, patients; dCRT, definitive chemoradiotherapy; CF, cisplatin plus fluorouracil; FLOT, docetaxel, oxaliplatin, leucovorin plus fluorouracil.
4.4 months, HR: 1.02, 95% CI: 0.73–1.43, P = 0.8958) (56). The combination of nivolumab plus chemotherapy and nivolumab plus ipilimumab were approved as a first-line treatment for patients with advanced EC regardless of PD-L1 expression in May 2022.

Pembrolizumab

Pembrolizumab is another humanized IgG4 monoclonal PD-1 antibody that was first evaluated in the KEYNOTE-028 phase I trial of patients with PD-L1-positive advanced solid tumors. In this trial, 78% of the patients had ESCC, and 87% patients had received two or more prior lines of chemotherapy. The ORR, median PFS and OS were 30% (95% CI: 13–53%), 1.8 months (95% CI: 1.7–2.9 months) and 7.0 months (95% CI: 4.3–17.7 months), respectively (47).

The KEYNOTE-180 phase II trial to evaluate the efficacy and safety of pembrolizumab was conducted for patients who received two or more prior lines of chemotherapy with advanced metastatic ESCC or EAC. The proportion of ESCC was 52.1%, and 47.9% of patients had PD-L1 positive tumors (PD-L1-positivity was defined as CPS ≥10). The ORR, median PFS and OS were 9.9% (95% CI: 5.2–16.7%), 2.0 months (95% CI: 1.9–2.1 months) and 7.1 months, HR: 0.78, 95% CI: 0.63–0.96, P = 0.0095) (48). Grade 3–5 treatment-related adverse events were reported in 12.4% of the patients, and the most common adverse events in any grade were fatigue, rash, pruritus, hypothyroidism and diarrhea. Since pembrolizumab showed a promising response and manageable safety profile in the phase II trial, the KEYNOTE-181 phase III trial was conducted. Patients who had one prior line of standard chemotherapy with ESCC or EAC were randomized to receive pembrolizumab or the investigator’s choice of chemotherapy (paclitaxel, docetaxel or irinotecan) as a second-line in this randomized, open-label, global phase III trial. The primary endpoints were OS in patients with CPS ≥10, in patients with ESCC and in all the patients. In this trial, the proportions of Asians, patients with ESCC and patients with a CPS ≥10 were 38.6, 63.8 and 35.3 at baseline, respectively. The pembrolizumab arm in patients with a CPS ≥10 had a better median OS, compared with the chemotherapy arm (9.3 months vs. 6.7 months, HR: 0.69, 95% CI: 0.52–0.93, P = 0.0074); however, the median OS of the ESCC patients was not superior to that for the chemotherapy arm (8.2 months vs. 7.1 months, HR: 0.78, 95% CI: 0.63–0.96, P = 0.0095). Grade 3–5 treatment-related adverse events were reported in 18% of patients in the pembrolizumab arm, compared with 40.9% of the patients in the chemotherapy arm (49). Based on these results, pembrolizumab was approved as a second-line treatment for recurrent, locally advanced or metastatic ESCC with a CPS ≥10.

These results suggested that chemotherapy combined with pembrolizumab as a first-line chemotherapy might improve patient outcome. The KEYNOTE-590 phase III trial was a randomized, double-blind, placebo-controlled trial evaluating chemotherapy with CF plus pembrolizumab versus chemotherapy for patients with locally advanced unresectable or metastatic EC or esophageogastric junction AC. The primary endpoints were OS in patients with ESCC and a CPS ≥10, OS and PFS in patients with ESCC, OS and PFS in patients with a CPS ≥10, and OS and PFS in all the patients. Seven hundred and forty-nine patients were assigned, and the proportion of patients with SCC was 73.5% in the chemotherapy plus pembrolizumab arm and 72.9% in the chemotherapy arm. The chemotherapy plus pembrolizumab arm had a better median OS than the chemotherapy arm in all the patients (12.4 months vs. 9.8 months, HR: 0.73, 95% CI: 0.62–0.86, P < 0.0001), in the CPS ≥10 cohort (13.5 months vs. 9.4 months, HR: 0.62, 95% CI: 0.49–0.78, P < 0.0001), in the patients with ESCC (12.6 months vs. 9.8 months, HR: 0.72, 95% CI: 0.60–0.88, P < 0.0006) and in the patients with ESCC and a CPS ≥10 (13.9 months vs. 8.8 months, HR: 0.57, 95% CI: 0.43–0.75, P < 0.0001). The median OS was also better in the chemotherapy plus pembrolizumab arm in all the patients (6.3 months vs. 5.8 months, HR: 0.65, 95% CI: 0.55–0.76, P < 0.0001), in the CPS ≥10 cohort (7.5 months vs. 5.5 months, HR: 0.51, 95% CI: 0.41–0.65, P < 0.0001) and in the ESCC patients (6.3 months vs. 5.8 months, HR: 0.65, 95% CI: 0.54–0.78, P < 0.0001). Grade 3–5 treatment-related adverse events were reported in 72% of the patients in the chemotherapy plus pembrolizumab arm, compared with 68% of patients in the chemotherapy arm (50). The combination of chemotherapy plus pembrolizumab was approved as a first-line treatment for patients with advanced EC regardless of CPS score in November 2021.

The results of the above trials for pembrolizumab and nivolumab suggest that the histological subtype might be a predictive marker of the efficacy of ICIs for patients with metastatic EC. A subgroup analysis in the KEYNOTE-181 trial showed that patients with ESCC seemed to have better survival benefits (HR: 0.77, 95% CI: 0.63–0.96) than those with EAC (HR: 1.12, 95% CI: 0.83–1.47) (49). In addition, the CheckMate-577 trial showed a similar tendency for survival benefits in ESCC (HR: 0.61, 95% CI: 0.42–0.88) and EAC (HR: 0.75, 95% CI: 0.59–0.96) (46). Some biological studies have shown the occurrence of ESCC to be associated with smoking, and smoking is strongly associated with high PD-L1 expression and a high tumor mutational burden (51–53). These results may explain why ESCC patients receiving ICIs experience a greater clinical benefit than EAC patients. However, on the other hand, the KEYNOTE-590 trial reported a similar benefit between other ESCC patients (HR: 0.72, 95% CI: 0.60–0.88) and EAC patients (HR 0.74, 95% CI: 0.52–1.02). Consistent biological mechanisms according to histology have not been established, and further biological studies are warranted.

Other ICIs and current treatment developments

Camrelizumab is an anti-PD-1 IgG4 antibody that was investigated for patients with metastatic or recurrent ESCC or China. The phase III ESCORT trial compared camrelizumab with a regimen of the investigator’s choice with docetaxel or irinotecan as the second-line treatment. A total of 457 patients were randomly allocated, and the median OS was superior in the camrelizumab arm (8.3 months, 95% CI: 6.8–9.7 months), compared with the chemotherapy arm (6.2 months, 95% CI: 5.7–6.9 months), with an HR of 0.71 (95% CI: 0.57–0.87, P = 0.001) (57). In addition, the RATIONALE-302 phase III trial compared tsilzeilibumab, which is an anti-PD-1 antibody, with chemotherapy (paclitaxel, docetaxel or irinotecan) as a second-line chemotherapy for patients with metastatic or recurrent ESCC. Overall, 512 patients were randomized to each group, and the tsilzeilibumab arm had a significantly longer OS than the chemotherapy arm in the intention-to-treat population (8.6 months vs. 6.3 months, HR: 0.70, 95% CI: 0.57–0.85, P = 0.0001) (58).

As ongoing trials, the RATIONALE-306 phase III is to evaluate the safety and efficacy of tiselizumab plus chemotherapy (platinum plus fluorouracil, platinum plus capcitabine or platinum plus paclitaxel) versus chemotherapy as a first-line chemotherapy for patients with metastatic or recurrent ESCC. (NCT03783442). Moreover, the LEAP-014 phase III (NCT04949256) evaluating the safety and efficacy of addition of lenvatinib to pembrolizumab, fluorouracil and platinum as a first-line chemotherapy is ongoing. As a second or later line chemotherapy, a multi-cohort phase II
The standard treatments for advanced or unresectable locally advanced ESCC are almost the same in Japan and Western countries. However, the standard treatment for resectable locally advanced ESCC differs. The standard treatment in Western countries consists of pre-operative CRT plus an esophagectomy, based on the results of the CROSS trial (10).

Nivolumab

The high recurrence rate of resectable locally advanced EC, even after pre-operative CRT, remains a problem, especially for EC without pathological complete resection (45). Nivolumab has been developed as a post-operative therapy to improve the outcome of patients with resectable locally advanced EC. The phase III, global, randomized, double-blind, placebo-controlled CheckMate 577 trial compared nivolumab with a placebo as a post-operative treatment. Patients with stage II/III EC or esophagogastric junction cancer with AC or SCC receiving pre-operative CRT followed by complete resection and with confirmed residual pathological disease were randomized to receive nivolumab or the placebo. The primary endpoint was the disease-free survival (DFS). A total of 794 patients were assigned, and patients with SCC accounted for 29% of the patients in each group. The nivolumab group had a significantly better median DFS compared with the placebo group (22.4 months vs. 11.0 months, HR: 0.69, 96.4% CI: 0.56–0.86, P < 0.001). The DFS was longer in the nivolumab group regardless of the histological type. Grade ≥ 3 treatment-related adverse events were 13% in the nivolumab group and 6% in the placebo group. The most common adverse events were fatigue, diarrhea, pruritus and rash in the nivolumab group (46).

Post-operative nivolumab monotherapy conferred clinical benefits in the CheckMate 577 trial; however, its use as a standard treatment in Japan remains problematic. The standard treatment for resectable locally advanced ESCC in Japan is pre-operative chemotherapy with DCF and esophagectomy with D2-3 lymph node dissection based on the JCOG1109 trial (12). On the other hand, in the CheckMate 577 trial, CRT was used as a pre-operative therapy, and the main histology was AC; as well, the types of surgery included not only esophagectomy but also proximal, total or distal gastrectomy with D0-3 lymph node dissection. Because of these differences, novel evidence supporting post-operative nivolumab monotherapy in Japan is still needed. Additionally, no data on OS has been reported. Therefore, further data about the survival benefits or other ongoing clinical trials related to perioperative treatments are needed.

JCOG1804E (FRONTiER) trial

The clinical benefits of nivolumab for patients with ESCC were demonstrated in the ATTRACTION-3 trial, and some trials for non-small cell lung cancer (NSCLC) have shown the efficacy of nivolumab monotherapy and a combination of nivolumab and cytotoxic chemotherapy as a pre-operative therapy (68,69). In addition, the use of an ICI pre-operatively showed a greater efficacy than when used post-operatively in a pre-clinical study (70).

In Japan, the standard pre-operative treatment for resectable, locally advanced ESCC was pre-operative CF followed by surgery; however, pre-operative CF therapy resulted in a histopathological complete response (pCR) rate of only 5% (8). Pre-operative DCF therapy resulted in a superior OS, compared with pre-operative CF therapy, in the JCOG1109 trial. Additionally, not for ESCC patients but for EAC or gastric cancer patients, peri-operative fluorouracil and leucovorin, oxaliplatin and docetaxel (FLOT) therapy has been established as a standard treatment in Western countries (71).
Given this background, not only doublet chemotherapy plus nivolumab but also triplet chemotherapy plus nivolumab are promising treatments. To improve the clinical outcomes of patients with resectable locally advanced ESCC, a multi-cohort phase I study, the JCOG1804E (FRONTiER) study, evaluating the safety and efficacy of pre-operative treatment with nivolumab plus CF, DCF or FLOT is ongoing (72).

First, 24 patients will be divided into cohorts of 6 people each (cohorts A–D) to evaluate safety. Cohort A will receive two courses of cisplatin (80 mg/m^2) and nivolumab (360 mg/body) on day 1 and fluorouracil (800 mg/m^2) on days 1–5 every 3 weeks. Cohort B will receive one prior administration of nivolumab (240 mg/body) 2 weeks before the start of chemotherapy followed by the same regimen as that used in cohort A. Cohort C will receive three courses of docetaxel (70 mg/m^2), cisplatin (70 mg/m^2) and nivolumab (360 mg/body) on day 1 and fluorouracil (750 mg/m^2) on days 1–5 every 3 weeks. Cohort D will receive one prior administration of nivolumab (240 mg/body) 2 weeks before the start of chemotherapy followed by the same regimen as that used in cohort C. Subsequently, an esophagectomy with 2–3 field lymph node dissection will be performed within 84 days of the last dose of pre-operative chemotherapy. Next, 12 patients will be added to cohort E, which will receive four courses of docetaxel (50 mg/m^2), oxaliplatin (85 mg/m^2), leucovorin (200 mg/m^2), fluorouracil (2600 mg/m^2) and nivolumab (240 mg/body) on day 1 every 2 weeks. The primary endpoint will be the incidence of dose-limiting toxicities (DLTs) from the initial dose until the 30th post-operative day, and the secondary endpoints will be the ORR during pre-operative chemotherapy, the pCR rate, the proportion of curative resections, the rate of protocol treatment completion, the PFS/OS and the frequency of adverse events.

The short-term results for cohorts A and B were reported at ASCO-GI 2021. In total, 13 patients were registered in cohort A (n = 6) and cohort B (n = 7). In these cohorts, no DLTs were observed in 12 patients, and one patient in cohort B was excluded because a non-residual resection was not obtained. Grade 3 or more adverse events consisted of neutropenia during pre-operative chemotherapy (46.3%) and anastomotic leakage (8.3%) after surgery. One patient in cohort B had grade 2 adrenal insufficiency; no treatment-related deaths were reported. The R0 resection rate was 92.3% (12/13), and the pathological complete response rate was 33.3% (2/6) in cohort A (73).

Additionally, the short-term results for cohorts C and D were reported at ASCO-GI 2022. In total, 12 patients were registered in cohort C (n = 6) and cohort D (n = 6). No DLTs were observed in cohort C, but one patient in cohort D developed a grade 3 rash and dyspnea. The R0 resection rate was 91.7% (11/12), and the pathological complete response rate was 33.3% (4/12) in both cohorts (74).

Based on the results of cohorts A–D, pre-operative CF or DCF plus nivolumab therapy followed by surgery appears to be well tolerated and to show promising efficacy. However, detailed data on biomarkers or cohort E (pre-operative FLOT plus nivolumab) have not yet been reported, and further investigations are expected.

Current treatment development

A phase I trial to assess the safety, feasibility and efficacy of induction nivolumab prior to CRT plus nivolumab as a neoadjuvant therapy followed by an esophagectomy in patients with stage I/II EC or esophagogastric cancer was conducted. In total, 12 out of 16 patients (75.0%) had adverse events related to any treatment, and 4 patients (25.0%) had grade 3 adverse events of dyspnea, upper respiratory tract infection, transaminitis and rash. The pCR rates for EAC and ESCC were 28.6% (4/14) and 50.0% (1/2), respectively (62). A phase II trial to assess the safety, feasibility and efficacy of neoadjuvant CRT plus pembrolizumab and adjuvant pembrolizumab following surgery for patients with resectable advanced ESCC was also conducted. Although the pCR rate was 46.1%, one death occurred before surgery (hematensis) and two deaths occurred after surgery (acute lung injury) (63). The phase II PERFECT trial examined pre-operative CRT with atezolizumab followed by surgery for patients with resectable EAC. The primary endpoint was the ratio of patients who completed a treatment that included atezolizumab. Thirty-nine patients were enrolled, and 24 patients completed the pre-operative treatment; the pCR rate (Mandard 1) was 39% (9/23) (64). A phase III trial to assess the safety and efficacy of pre-operative CRT with nivolumab, which is an anti-PD-L1 antibody, followed by surgery plus post-operative nivolumab in patients with clinical stage cT1N1M0, cT2-3 N0-2 M0 had a pCR rate of 43% (3/7) and one patient developed grade 2 hypothyroidism (65).

For patients with locally advanced EC who were not candidates for primary surgery, the phase II CRUCIAL trial to evaluate the efficacy and safety of definitive CRT with FOLFOX plus nivolumab followed by sequential nivolumab and CRT plus nivolumab and ipilimumab followed by sequential nivolumab and ipilimumab (NCT03437200) is ongoing.

Conclusion

ICIs have improved the treatment outcomes and have changed the treatment strategies for EC. In Japan, chemotherapy plus nivolumab and nivolumab plus ipilimumab have been approved as first-line treatments based on the CheckMate-648 study. The superiority of pembrolizumab as a second-line treatment in the KEYNOTE-181 trial was limited to patients with a CPS ≥10; however, the KEYNOTE-590 trial showed a superior OS and PFS for the chemotherapy plus pembrolizumab group, compared with the chemotherapy group, as a first-line treatment. The chemotherapy plus pembrolizumab has been approved as a first-line treatment regardless of CPS score in Japan. Some trials of anti-PD-1/PD-L1 inhibitors for resectable/unresectable locally advanced EC, including the JCOG1804E trial, are ongoing.

Conflict of interest statement

Dr Ken Kato has received research grants from ONO PHARMA-CEUTICAL, Shionogi, MSD, Merck Serono, Beigene, Oncolyx Biopharma, Chugai Pharmaceutical and BAYER outside the submitted work. Toru Kadono and Shun Yamamoto have nothing to declare.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 2015;16:36–46.
3. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal society: part 1. Esophagus 2019;16:1–24.
Ito Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus 2019;16:254–43.

Takeuchi H, Miyata H, Gotoh M, et al. A risk model for esophagectomy using data of 3354 patients included in a Japanese nationwide web-based database. Ann Surg 2014;260:259–66.

Kato H, Sato A, Fukuda H, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan clinical oncology group study [JCOG9708]. Jpn J Clin Oncol 2009;39:638–43.

Kato K, Ito Y, Nozaki I, et al. Parallel-group controlled trial of esophagectomy versus chemoradiotherapy in patients with clinical stage I esophageal carcinoma [JCOG0502]. Gastroenterology 2021;161:1878–86.e2.

Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus [JCOG9907]. Ann Surg Oncol 2012;19:68–74.

Hara H, Tahara M, Daiko H, et al. Phase II feasibility study of preoperative chemotherapy with docetaxel, cisplatin, and fluorouracil for esophageal squamous cell carcinoma. Cancer Sci 2013;104:1455–60.

Gebelki V, Burmeister B, Smithers BM, Foo K, Zalberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal cancer: a meta-analysis. Lancet Oncol 2007;8:226–34.

Hashimoto J, Kato K, Ito Y, et al. Phase II feasibility study of preoperative concurrent chemoradiotherapy with cisplatin plus 5-fluorouracil and elective lymph node irradiation for clinical stage III esophageal squamous cell carcinoma. Int J Clin Oncol 2019;24:60–7.

Kato K, Ito Y, Daiko H, et al. A randomized controlled phase III trial comparing two chemotherapy regimens and chemoradiotherapy regimen as neoadjuvant treatment for locally advanced esophageal cancer, JCOG1109 NEXT study. J Clin Oncol 2022;40:238–8.

Minsky D, Pajak T, Ginsberg R, et al. III trial of combined-modality therapy for Esophageal therapy. J Clin Oncol 2014;20:1167–74.

Kato K, Nakajima TE, Ito Y, et al. Phase II study of concurrent chemoradiotherapy at the dose of 50.4 Gy with elective nodal irradiation for stage II–III esophageal carcinoma. Jpn J Clin Oncol 2013;43:608–15.

Ito Y, Takeuchi H, Ogawa G, et al. A single-arm confirmatory study of definitive chemoradiotherapy (dCRT) including salvage treatment in patients (pts) with clinical (c) stage III/IV esophageal carcinoma (EC) [JCOG0909]. J Clin Oncol 2018;36:4051.

Conroy T, Galas MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305–14.

Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan esophageal oncology group (JEOG) trial [JCOG9516]. Jpn J Clin Oncol 2004;34:615–9.

Yokota T, Kato K, Hamamoto Y, et al. Phase II study of chemoselection with docetaxel plus cisplatin and 5-fluorouracil induction chemotherapy and subsequent conversion surgery for locally advanced unresectable oesophageal cancer. Br J Cancer 2016;115:1328–34.

Terada M, Hara H, Daiko H, et al. Phase III study of tri-modality combination therapy with induction docetaxel plus cisplatin and 5-fluorouracil versus definitive chemoradiotherapy for locally advanced unresectable squamous-cell carcinoma of the thoracic esophagus [JCOG1510: TRIANGLE]. Jpn J Clin Oncol 2019;49:1055–60.

Izuka T, Takegawa T, Ide H, et al. Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japanese Esophageal oncology group trial. Jpn J Clin Oncol 1992;22:172–6.

Hayashi K, Ando N, Watanabe H, et al. Phase II evaluation of protracted infusion of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal oncology group (JEOG) trial [JCOG9407]. Jpn J Clin Oncol 2001;31:419–23.

Hirono K, Tsubosa Y, Mizusawa J, et al. Phase III trial of 2-weekly docetaxel combined with cisplatin plus fluorouracil in metastatic esophageal cancer [JCOG0807]. Cancer Sci 2014;105:1189–95.

Kataoka K, Tsuchima T, Mizusawa J, et al. A randomized controlled phase III trial comparing 2-weekly docetaxel combined with cisplatin plus fluorouracil (2-weekly DCF) with cisplatin plus fluorouracil (CF) in patients with metastatic or recurrent esophageal cancer: rationale, design and methods of Japan clinical oncology group study [JCOG1314 (MIRACLE study)]. Jpn J Clin Oncol 2015;45:494–8.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8:467–77.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:232–44.

Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8:793–800.

Freeman BGJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 Immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027–34.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined Nivolumab and Ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–56.

Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study [KEYNOTE-006]. Lancet 2017;390:1853–62.

Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–33.

Socinski MA, Joette RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288–301.

Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2108–21.

Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.

Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 trial. Lancet 2019;394:1915–28.

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;390:2461–71.

Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.

Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017;35:1225–32.

Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in Unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–905.

Kudo T, Hamamoto Y, Kato K, et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol 2017;18:631–9.

Satoh T, Kato K, Ura T, et al. Five-year follow-up of nivolumab treatment in Japanese patients with esophageal squamous-cell carcinoma (ATTRACTION-1/ONO-4538-07). Esophagus 2021;18:835–43.

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;20:1506–17.

Okada M, Kato K, Cho BC, et al. Three-year follow-up and response-survival relationship of nivolumab in previously treated patients with advanced squamous cell carcinoma (ATTRACTION-3). Clin Cancer Res 2022;28:3277–86.
43. Mikuni H, Yamamoto S, Oshima K, et al. Retrospective study of nivolumab monotherapy for advanced esophageal squamous cell carcinoma. J Clin Oncol 2021;39:179–9.

44. Mikuni H, Yamamoto S, Sawada R, et al. Correlation of PD-L1 expression using combined positive score and clinical efficacy for advanced esophageal squamous cell carcinoma treated with nivolumab monotherapy. 2022; ASCO Gastrointestinal Cancers Symposium, Abstract #289.

45. Blum Murphy M, Xiao L, Patel VR, et al. Pathological complete response in patients with esophageal cancer after the trimodality approach: the association with baseline variables and survival—the University of Texas MD Anderson Cancer Center experience. Cancer 2017;123:4106–13.

46. Kelly RJ, Ajani JA, Kudrjawz J, et al. Adjuvant Nivolumab in resected Esophageal or gastroesophageal junction cancer. N Engl J Med 2021; 384:1191–203.

47. Dui T, Pih–Paul SA, Jalal SL, et al. Safety and antitumor activity of the anti– programmed death-1 antibody pembrolizumab in patients with advanced esophageal carcinoma. J Clin Oncol 2018;36:61–7.

48. Shah MA, Kojima T, Hochhauser D, et al. Efficacy and safety of Pembrolizumab for heavily Pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the Esophagus: the phase 2 KEYNOTE-180 study. JAMA Oncol 2019;5:546–50.

49. 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;38:4138–48.

50. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-950): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759–71.

51. Calles A, Liao X, Sholl LM, et al. Expression of PD-1 and its ligands, PD-L1 and PD-L2, in smokers and never smokers with KRAS-mutant lung cancer. J Natl Cancer Inst 1992;71:1065–8.

52. Wang X, Ricciuti B, Nguyen T, et al. Association between smoking history and tumor mutation burden in advanced non-small cell lung cancer. J Thorac Oncol 2015;10:1726–35.

53. Desrichard A, Kuo F, Chowell D, et al. Tobacco smoking-associated alterations in the immune microenvironment of squamous cell carcinomas. J Natl Cancer Inst 2018;110:1386–92.

54. Schwartz RH. Costimulation of T lymphocytes: the role of CD28, CTLA-4, and B7/BBI in interleukin-2 production and immunotherapy. Cell 1992;71:1063–8.

55. Janjigian YY, Bendell J, Calvo E, et al. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophageogastric cancer. J Clin Oncol 2018;36:2836–44.

56. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced Esophageal squamous-cell carcinoma. N Engl J Med 2022; 386:449–62.

57. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator’s choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORt): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol 2020;21:832–42.

58. Shen L, Kato K, Kim SB, et al. Tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic Esophageal squamous cell carcinoma (RATIONALE-302): a randomized phase III study. J Clin Oncol 2022;71.

59. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342–50.

60. Bando H, Kotani D, Tsushima T, et al. TENERGY: multicenter phase II study of Atezolizumab monotherapy following definitive Chemoradiotherapy with 5-FU plus cisplatin in patients with unresectable locally advanced esophageal squamous cell carcinoma. BMC Cancer 2020; 20:1–6.

61. Shah MA, Bennouna J, Dui T, et al. KEYNOTE-975 study design: a phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma. Future Oncol 2021;17: 1143–53.

62. Kelly RJ, Smith KN, Anagnostou V, et al. Neoadjuvant nivolumab plus concurrent chemoradiation in stage III/IV esophageal/gastroesophageal junction cancer. J Clin Oncol 2019;37:142.

63. Hong MH, Kim HR, Park SY, et al. A phase II trial of neoadjuvant chemoradiotherapy and pembrolizumab for locally advanced esophageal squamous cell carcinoma (ESCC). J Clin Oncol 2019;37: 4027.

64. van den Ende T, de Clercq NC, van Berge Henegouwen MI, et al. A phase II feasibility trial of neoadjuvant chemoradiotherapy combined with atezolizumab for resectable esophageal adenocarcinoma: the PERFECT trial. J Clin Oncol 2019;37:4045.

65. Uboha NV, Maloney JD, McCarthy D, et al. Safety of neoadjuvant chemoradiation (CRT) in combination with avelumab (a) in the treatment of resectable esophageal and gastroesophageal junction (EGJ) cancer. J Clin Oncol 2019;37:4041.

66. Then EO, Lopez M, Saleem S, et al. Esophageal cancer: an updated surveillance epidemiology and end results database analysis. World J Oncol 2020;11:55–64.

67. Van Hagen P, Halshof MCCM, Van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074–84.

68. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378:1976–86.

69. Provencio-Pulla M, Nadal-Alforja E, Cobo M, et al. Neoadjuvant chem/oimmunotherapy for the treatment of stages IIIA resectable non– small cell lung cancer (NSCLC): a phase II multicenter exploratory study—NADIM study-SLCG. J Clin Oncol 2018;36:8521.

70. Liu J, Blake SJ, Yong MCR, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. Cancer Discov 2016;6:1382–99.

71. Al-Batran S-E, 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: 1948–57.

72. Yamamoto S, Kato K, Daiko H, et al. Feasibility study of nivolumab as neoadjuvant chemotherapy for locally esophageal carcinoma: FRONTIER (JCOG1804E). Future Oncol 2020;16:1351–7.

73. Yamamoto S, Kato K, Daiko H, et al. FRONTIER: a feasibility trial of nivolumab with neoadjuvant CF or DCF therapy for locally advanced esophageal carcinoma (JCOG1804E)—the short-term results of cohort a and b. J Clin Oncol 2021;39:202–2.