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

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Summary

Background Chemotherapy for patients with advanced oesophageal squamous cell carcinoma offers poor long-term survival prospects. We report the final analysis from our study of the immune checkpoint PD-1 inhibitor nivolumab versus chemotherapy in patients with previously treated advanced oesophageal squamous cell carcinoma.

Methods We did a multicentre, randomised, open-label, phase 3 trial (ATTRACTION-3) at 90 hospitals and cancer centres in Denmark, Germany, Italy, Japan, South Korea, Taiwan, the UK, and the USA. We enrolled patients aged 20 years and older with unresectable advanced or recurrent oesophageal squamous cell carcinoma (regardless of PD-L1 expression), at least one measurable or non-measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, a baseline Eastern Cooperative Oncology Group performance status of 0–1, and who were refractory or intolerant to one previous fluoropyrimidine-based and platinum-based chemotherapy and had a life expectancy of at least 3 months. Patients were randomly assigned (1:1) to either nivolumab (240 mg for 30 min every 2 weeks) or investigator's choice of chemotherapy (paclitaxel 100 mg/m² for at least 60 min once per week for 6 weeks then 1 week off; or docetaxel 75 mg/m² for at least 60 min every 3 weeks), all given intravenously. Treatment continued until disease progression assessed by the investigator per RECIST version 1.1 or unacceptable toxicity. Randomisation was done using an interactive web response system with a block size of four and stratified according to geographical region (Japan *vs* rest of the world), number of organs with metastases, and PD-L1 expression. Patients and investigators were not masked to treatment allocation. The primary endpoint was overall survival, defined as the time from randomisation until death from any cause, in the intention-to-treat population that included all randomly assigned patients. Safety was assessed in all patients who received at least one dose of the assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT02569242, and follow-up for long-term outcomes is ongoing.

Findings Between Jan 7, 2016, and May 25, 2017, we assigned 419 patients to treatment: 210 to nivolumab and 209 to chemotherapy. At the time of data cutoff on Nov 12, 2018, median follow-up for overall survival was 10·5 months (IQR 4·5–19·0) in the nivolumab group and 8·0 months (4·6–15·2) in the chemotherapy group. At a minimum follow-up time (ie, time from random assignment of the last patient to data cutoff) of 17·6 months, overall survival was significantly improved in the nivolumab group compared with the chemotherapy group (median 10·9 months, 95% CI 9·2–13·3 *vs* 8·4 months, 7·2–9·9; hazard ratio for death 0·77, 95% CI 0·62–0·96; p=0·019). 38 (18%) of 209 patients in the nivolumab group had grade 3 or 4 treatment-related adverse events compared with 131 (63%) of 208 patients in the chemotherapy group. The most frequent grade 3 or 4 treatment-related adverse events were anaemia (four [2%]) in the nivolumab group and decreased neutrophil count (59 [28%]) in the chemotherapy group. Five deaths were deemed treatment-related: two in the nivolumab group (one each of interstitial lung disease and pneumonitis) and three in the chemotherapy group (one each of pneumonia, spinal cord abscess, and interstitial lung disease).

Interpretation Nivolumab was associated with a significant improvement in overall survival and a favourable safety profile compared with chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma, and might represent a new standard second-line treatment option for these patients.

Funding ONO Pharmaceutical Company and Bristol-Myers Squibb.

Introduction

Oesophageal cancer is the seventh most common cancer globally, and the sixth most common cause of death from cancer.[1] The relative 5-year survival rate is 8% or less for patients diagnosed with metastatic disease.[2,3]

Research in context

Evidence before this study

We searched PubMed in July, 2019, using the terms "esophageal OR oesophageal" and "PD-1 OR PD-L1" in the title or abstract, with no time limits, to identify articles published in English about immunotherapies with PD-1/PD-L1 inhibitors in patients with oesophageal cancer. To identify results from clinical trials that were not yet published in peer-reviewed journals, we also searched the American Society of Clinical Oncology and European Society for Medical Oncology congress websites for publications between July 1, 2017, and July 1, 2019, using the key words "esophageal squamous OR oesophageal squamous" and "PD-1 OR PD-L1". We selected primary publications from phase 2 or phase 3 studies of PD-1 or PD-L1 monotherapy in patients who had previously received treatment for unresectable advanced or recurrent oesophageal squamous cell carcinoma. Using these search criteria, we identified three studies of PD-1 immune checkpoint inhibitors: the phase 2 ONO-4538-07 (ATTRACTION-1) and phase 2 KEYNOTE-180 studies of nivolumab and pembrolizumab monotherapy, respectively, and the phase 3 KEYNOTE-181 study of pembrolizumab. In the ATTRACTION-1 phase 2 study, nivolumab showed promising antitumour activity with a manageable safety profile in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to standard chemotherapies. In the KEYNOTE-180 phase 2 study, pembrolizumab showed durable antitumour activity and manageable safety in heavily pre-treated patients with metastatic oesophageal squamous cell carcinoma. The final analysis of the KEYNOTE-181 phase 3 study reported no significant difference in overall survival for pembrolizumab versus chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma.

Added value of this study

To our knowledge, ATTRACTION-3 is the first randomised phase 3 study to show a significant improvement in overall survival with a PD-1 inhibitor (nivolumab) versus chemotherapy (paclitaxel or docetaxel) in previously treated patients with advanced oesophageal squamous cell carcinoma. A survival benefit with nivolumab was noted irrespective of tumour PD-L1 expression. Nivolumab was well tolerated and showed a favourable safety profile, with numerically fewer treatment-related adverse events versus chemotherapy. Additionally, an exploratory analysis of health-related quality of life showed significant improvements with nivolumab compared with chemotherapy.

Implications of all the available evidence

The results of this study, along with those from previously published studies, suggest that anti-PD-1 monotherapy offers a favourable benefit–risk profile in patients with previously treated, unresectable advanced or recurrent oesophageal squamous cell carcinoma. Nivolumab might represent a new standard second-line treatment option to address the high unmet need for patients with advanced oesophageal squamous cell carcinoma.

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Oesophageal squamous cell carcinoma is the dominant histological subtype of oesophageal cancer worldwide (approximately 90%)[1,4] and has a molecular profile distinct from that of oesophageal adenocarcinoma.[5,6] The usefulness of palliative chemotherapy for patients with advanced oesophageal squamous cell carcinoma is not well established.[7,8] Fluoropyrimidine and platinum doublet chemotherapy are considered acceptable first-line therapy options for patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.[7–10] In the second-line setting, single-agent chemotherapy is an established option based on patient benefit-risk assessment.[7–10] Although second-line treatments with docetaxel and paclitaxel are used for patients with advanced oesophageal squamous cell carcinoma that has progressed after first-line chemotherapy, they are associated with haematological, gastrointestinal, and neurological toxicities[11] and with poor long-term survival.[12,13] There is therefore an urgent unmet need for new treatment options for this patient population.

Inhibitors of immune checkpoint protein PD-1 enhance antitumour activity of T cells by blocking the interaction between the PD-1 receptor and its ligands.[14,15] Antitumour activity of PD-1 inhibitors has been reported in studies of several types of squamous cell tumours, including oesophageal, head and neck, non-small cell lung, and anal cancers.[16–20] Until recently, no targeted therapies were approved for treatment of advanced oesophageal squamous cell carcinoma. The US Food and Drug Administration approved the PD-1 inhibitor pembrolizumab in 2019 for the treatment of recurrent locally advanced or metastatic oesophageal squamous cell carcinoma in patients whose tumours express PD-L1 (combined positive score ≥10) and who have progressed beyond one or more previous systemic therapy.

PD-L1 expression is enriched in oesophageal squamous cell carcinoma, which might increase tumour susceptibility in these patients to elimination following immune checkpoint inhibition. The reported prevalence of PD-L1 expression in oesophageal squamous cell carcinoma ranges from 15% to 83% in tumour cells, and from 13% to 31% in immune cells.[6,21–24] Nivolumab, a human monoclonal anti-PD-1 antibody, has been approved for the treatment of several solid tumours, and showed promising antitumour activity and a manageable safety profile in a phase 2 study (ATTRACTION-1) of patients with advanced oesophageal squamous cell carcinoma who were refractory or intolerant to fluoropyrimidine-based, platinum-based, and taxane-based chemotherapies.[19] In the randomised, open-label, phase 3 ATTRACTION-3 trial, we compared nivolumab with chemotherapy in patients with unresectable

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advanced or recurrent oesophageal squamous cell carcinoma who were refractory or intolerant to one previous fluoropyrimidine-based and platinum-based chemotherapy. Here, we report the results of the final analysis of ATTRACTION-3 (follow-up for long-term outcomes is ongoing).

Methods

Study design and participants

We did a multicentre, randomised, open-label, phase 3 trial at 90 hospitals and cancer centres in Denmark, Germany, Italy, Japan, South Korea, Taiwan, the UK, and the USA.

Eligible patients were age 20 years or older with unresectable oesophageal cancer, whose major current or previously resected lesion was in the cervical or thoracic oesophagus (including the oesophagogastric junction) and was pathologically confirmed as squamous or adenosquamous cell carcinoma. Patients who were refractory or intolerant to fluoropyrimidine-based and platinum-based chemotherapy who had previously received one treatment regimen, were not indicated for a radical resection, and had a life expectancy of at least 3 months were included. The definition of refractory disease included progressive disease or recurrence during previous chemotherapy (including chemo-radiation) or within 8 weeks after the last dose; within 24 weeks after the last dose if there was a complete response during previous chemotherapy, as confirmed by two or more consecutive assessments per protocol definition; or within 24 weeks after the last dose of neoadjuvant or adjuvant therapy associated with radical resection (R0). Other key inclusion criteria were at least one measurable or non-measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; adequate organ function; and an ability to provide a fresh or archival tumour sample for the determination of PD-L1 status. Baseline laboratory tests required to assess eligibility included white blood cell, neutrophil, and platelet counts; haemoglobin; alanine aminotransferase; aspartate aminotransferase; total bilirubin; and serum creatinine or creatinine clearance. Patients with substantial malnutrition, tumour invasion on organs located adjacent to the oesophagus, interstitial lung disease, pulmonary fibrosis, concurrent autoimmune disease, symptomatic brain or meninx metastases, or grade 2 peripheral neuropathy, and patients refractory to taxane therapy were excluded. Additionally, patients who previously received nivolumab or other therapeutic antibodies or systemic anticancer therapies for regulation of T cells, or systemic corticosteroids or immunosuppressants, antineoplastic drugs, or radiotherapy within 28 days before randomisation were excluded.

The trial was done according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the study protocol (appendix p 21), which was approved by the institutional review board or independent ethics committee at each site. All patients provided written, informed consent before study participation.

Randomisation and masking

We randomly assigned patients (1:1) to either nivolumab or investigator's choice of chemotherapy (paclitaxel or docetaxel). Randomisation was done using an interactive web response system with a block size of four and stratified according to geographical region (Japan *vs* the rest of the world), number of organs with metastases (≤1 *vs* ≥2), and expression of PD-L1 (<1% *vs* ≥1%). Investigators registered patients at each site via the web registration system. An authorised vendor used their original internal system to generate the sequentially numbered containers to ensure random allocation, and to assign patients to study treatments. The web registration system ensured that the container sequence was concealed until the treatment allocation was completed. Patients and investigators were not masked to treatment allocation.

Procedures

Nivolumab was administered intravenously over 30 min at a dose of 240 mg every 2 weeks (each cycle was 6 weeks). Paclitaxel and docetaxel were administered intravenously for at least 60 min; paclitaxel at 100 mg/m² once per week for 6 weeks followed by 1 week off (each cycle was 7 weeks) and docetaxel at 75 mg/m² every 3 weeks (each cycle was 3 weeks), until disease progression assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Patients were permitted to continue treatment beyond initial disease progression in both treatment groups based on the investigators' judgement.

Tumours were assessed using CT or MRI per RECIST version 1.1 at baseline, every 6 weeks from the start of cycle 1 for 1 year, and every 12 weeks thereafter, until either initiation of post-study treatment or progression or recurrence during follow-up. Complete and partial responses were confirmed by two or more successive scans within a minimum of 4 weeks.

Tumour cell PD-L1 expression was assessed on at least 100 viable tumour cells by a central laboratory using immunohistochemistry (PD-L1 IHC 28-8 pharmDx assay; Dako, an Agilent Technologies company, Santa Clara, CA, USA). Adverse events were assessed throughout the treatment period and for 28 days after the end of treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Serious adverse events were assessed throughout the treatment period and for 100 days after treatment discontinuation per CTCAE version 4.0. Treatment was interrupted or delayed in case of adverse event occurrence and resumed if protocol-defined criteria for treatment resumption were

met. Dose reductions were allowed for paclitaxel and docetaxel for toxicities prespecified in the protocol under dose reduction criteria (appendix p 84). Dose reductions were not permitted in the nivolumab group. Additional study procedure details are in the appendix (p 3).

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation until death from any cause. Secondary endpoints were the proportion of patients with an investigator-assessed objective response (the percentage of patients whose best overall response was either a complete response or partial response); best overall response; progression-free survival (defined as the time from randomisation to the first documented tumour progression or death); the proportion of patients with disease control (the percentage of patients whose best overall response was assessed as a complete response, partial response, or stable disease); maximum percentage change from baseline in the sum of the diameters of target lesions; time to response (the time from randomisation to the first confirmed complete or partial response); and duration of response (the time from the first response date to the date of the first documented tumour progression or death). The percentage of patients with ongoing response was calculated based on the number of ongoing responses divided by the number of responders.

Prespecified, exploratory subgroup analyses assessed the association between overall survival and stratification factors or baseline variables: PD-L1 expression (<1%, ≥1%, <5%, ≥5%, <10%, and ≥10%), age (<65 years *vs* ≥65 years), sex (male *vs* female), race (Asian *vs* white), ECOG performance status (0 *vs* 1), previous surgery (no *vs* yes), previous radiotherapy (no *vs* yes), and history of smoking (never, former, or current).

As a prespecified exploratory endpoint, health-related quality of life was assessed based on the three-level version of the EuroQol 5D questionnaire (EQ-5D-3L), comprising the visual analogue scale (VAS) and descriptive system, which is used to generate the utility index. Assessments were done every 6 weeks from the start of cycle 1 until the end of the treatment phase and every 12 weeks during the follow-up phase. Measured outcomes were mean change from baseline using both descriptive analyses and a mixed model for repeated measures (MMRM) to compare between-treatment differences in least square mean changes from baseline; time to deterioration in health-related quality of life; and the proportion of patients who experienced deterioration at fixed timepoints. Changes from baseline of seven points and 0·08 points for the VAS and utility index, respectively, were considered clinically meaningful, and were used as the threshold for determining deterioration.[25] Time to deterioration was defined as time from randomisation until a deterioration from baseline for VAS and utility index scores while on treatment.[25] Detailed methods are in the appendix (p 2).

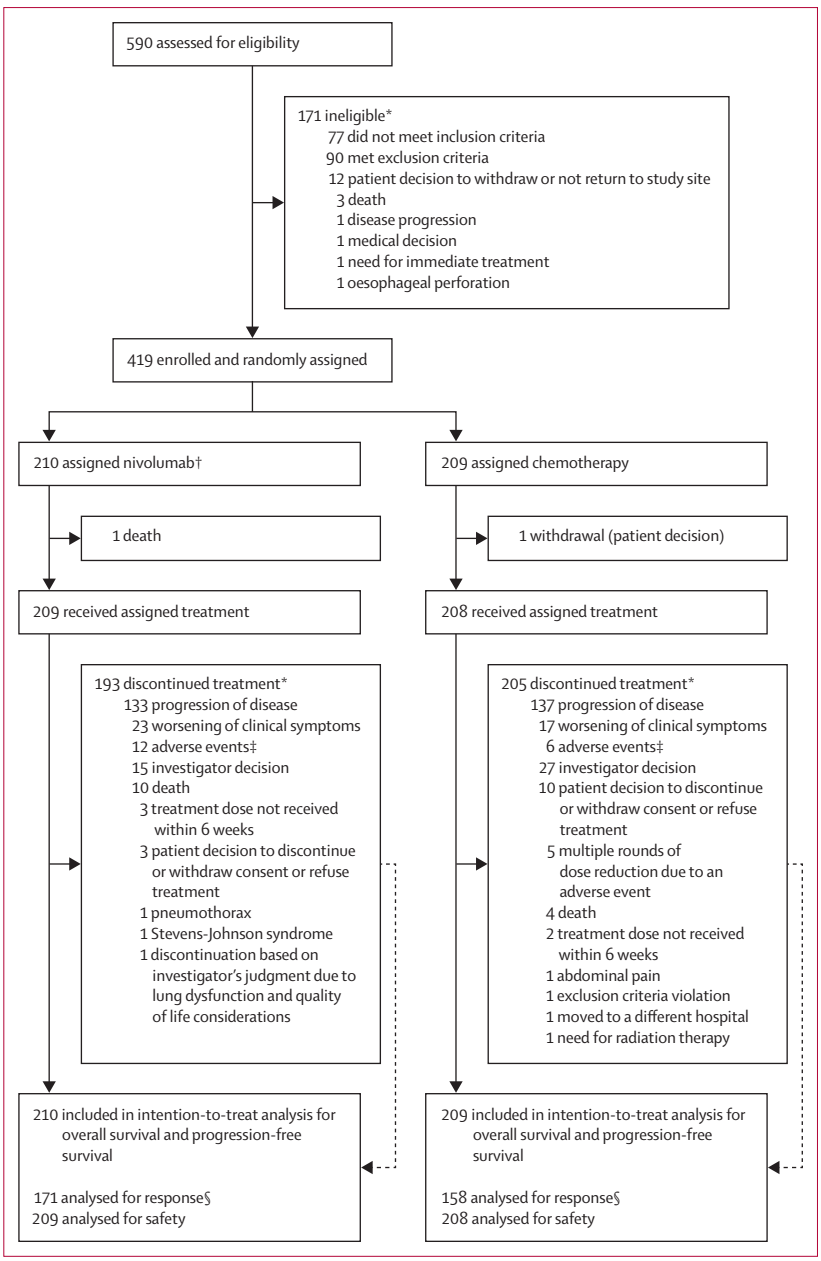

Figure 1: **Trial profile**

*Numbers do not always add up to the total because some patients had more than one reason for exclusion from randomisation or discontinuation from treatment. †Four patients enrolled in the nivolumab group had protocol deviations (one patient did not meet inclusion criteria [refractory or intolerant to one previous fluoropyrimidine and platinum-based therapy], one patient received prohibited medication while on treatment with nivolumab, one patient received concurrent anticancer therapy while on treatment with nivolumab, and one patient's serious adverse event was not reported within the safety follow-up time period required per the protocol). ‡Discontinuation from treatment occurred due to prespecified categories of either onset of grade 3 or higher peripheral neuropathy, grade 2 or higher interstitial lung disease (regardless of causal relationship with study drug); grade 3 or higher bronchospasm, diarrhoea, colitis, neurological toxicity, hypersensitivity reaction, infusion reaction, or uveitis, for which the causal relationship with nivolumab could not be ruled out; or any drug-related liver function test abnormality meeting protocol-defined criteria for discontinuation. §39 patients in the nivolumab group and 51 patients in the chemotherapy group were excluded from the response analysis because of non-measurable disease.

	Nivolumab group (n=210)	Chemotherapy group (n=209)*
Age, years	64 (57–69)	67 (57–72)
<65	112 (53%)	85 (41%)
≥65	98 (47%)	124 (59%)
Sex		
Male	179 (85%)	185 (89%)
Female	31 (15%)	24 (11%)
Race		
Asian	201 (96%)	200 (96%)
White	9 (4%)	9 (4%)
ECOG performance status		
0	101 (48%)	107 (51%)
1	109 (52%)	102 (49%)
Recurrent disease		
No	107 (51%)	120 (57%)
Yes	103 (49%)	89 (43%)
Disease stage† (TNM classification‡)		
II–III	8 (7%)	13 (11%)
IV	94 (88%)	100 (83%)
Unknown	5 (5%)	7 (6%)
Previous therapies		
Surgery	111 (53%)	94 (45%)
Radiotherapy	153 (73%)	142 (68%)
Systemic anticancer therapy	210 (100%)	208 (100%)
Number of organs with metastases§		
≤1	89 (42%)	91 (44%)
≥2	121 (58%)	118 (56%)
Site of metastases		
Lymph node	159 (76%)	163 (78%)
Liver	57 (27%)	54 (26%)
Lung	98 (47%)	92 (44%)
Bone	23 (11%)	25 (12%)
PD-L1 expression¶		
<1%	109 (52%)	107 (51%)
≥1%	101 (48%)	102 (49%)
<5%	136 (65%)	137 (66%)
≥5%	74 (35%)	72 (34%)
<10%	146 (70%)	152 (73%)
≥10%	64 (30%)	57 (27%)
History of smoking		
Never	30 (14%)	32 (15%)
Former	159 (76%)	147 (70%)
Current	21 (10%)	30 (14%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. TNM=tumour, node, and metastases. *Included 65 patients treated with docetaxel and 144 patients treated with paclitaxel. †Summarised at randomisation for patients with non-recurrent oesophageal cancer (nivolumab [n=107] and chemotherapy [n=120]). ‡Union for International Cancer Control TNM Classification of Malignant Tumours, 7th edn. Wiley-Blackwell; 2011. §Per interactive web response system. ¶Per test results.

Table 1: **Baseline characteristics of the intention-to-treat population**

Statistical analysis

The expected average hazard ratio (HR) for nivolumab versus chemotherapy was assumed to be 0·70 (appendix p 71). A total of 331 death events were required to detect superiority of nivolumab over chemotherapy with at least 90% power by the log-rank test at a two-sided significance level of 5%. Assuming an enrolment period of 16 months and a follow-up period of 18 months after randomisation of the last patient, the required number of patients was 390.

Overall survival and progression-free survival were assessed in the intention-to-treat (ITT) population, which included all randomly assigned patients. Objective response, disease control, maximum percentage change from baseline in the sum of the diameters of target lesions, time to response, and duration of response were assessed in all randomly assigned patients who had target lesion measurements at baseline (ie, the response-evaluable population). Safety was assessed in all patients who received at least one dose of the assigned treatment. Both descriptive and MMRM analyses of patient-reported outcomes were done for all randomly assigned patients who had an EQ-5D-3L VAS and utility index assessment at baseline and at least one post-baseline assessment including unscheduled or follow-up visits (ie, the patient-reported outcomes population). Time to deterioration of health-related quality of life was assessed in the ITT population.

Median overall survival, progression-free survival, and duration of response were estimated using Kaplan-Meier methods, and the corresponding two-sided 95% CIs were calculated using the Brookmeyer and Crowley method based on a log-log transformation. The stratified Cox proportional hazards regression model with the randomisation factors as the stratification factors and treatment group as a single covariate was used to assess differences between treatment groups in overall survival and progression-free survival. The proportion of patients who survived at a given timepoint was derived from the Kaplan-Meier method with corresponding two-sided 95% CIs calculated based on the Greenwood formula for variance derivation based on log-log transformation. We used a two-sided stratified log-rank test using randomisation stratification factors with a 5% significance level. When superiority in overall survival was determined, a hierarchical hypothesis testing approach for the key secondary endpoints was used to preserve a study-wise type I error rate at 5%. The key secondary endpoints were tested in the following hierarchical order: first, the proportion of patients with an objective response and second, progression-free survival. The proportional hazards assumption was tested using a Cox model with treatment and treatment by time interaction.

For the proportion of patients with an objective response, the odds ratio (OR) and corresponding two-sided 95% CIs were calculated using the

Cochran-Mantel-Haenszel test with the randomisation factors as the stratification factors. For the proportion of patients with disease control, exact 95% CIs were calculated using the Clopper-Pearson method. For subgroup analyses of overall survival, HRs and corresponding 95% CIs for nivolumab relative to chemotherapy were calculated using the unstratified Cox proportional hazards model. For the primary endpoint of overall survival, the interaction between the treatment group and the individual prespecified baseline demographic and disease characteristics was assessed using a Cox proportional-hazards model. An interaction p value of less than 0·15 was considered significant. To assess any effect associated with the crossing of the overall survival curves, the treatment difference in overall survival was assessed in a post-hoc analysis using a weighted log-rank test from the Fleming-Harrington G(ρ–γ) family with a ρ value of 1 and γ value of 1,[26] accounting for the non-proportional hazards effect. Geographical region, the number of organs with metastases, and tumour PD-L1 expression were used as stratification factors. The difference between treatments in health-related quality of life was assessed using a longitudinal MMRM approach, which included data at timepoints with at least ten patients per treatment group.

Statistical analyses were done using SAS software (version 9.4). Additional statistical methods are summarised in the appendix (p 4). An interim analysis planned in the original protocol was subsequently cancelled per an amendment to the protocol on Nov 7, 2017 (version 9.0). An independent data monitoring committee monitored safety data. This trial is registered with ClinicalTrials.gov, number NCT02569242.

Role of the funding source

The funders of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. All authors had full access to all the data in the study, participated in writing or reviewing the manuscript, and provided final approval for the decision to submit the manuscript for publication.

Results

Between Jan 7, 2016, and May 25, 2017, we assessed 590 patients for eligibility (figure 1) and randomly assigned 419 to treatment: 210 to nivolumab and 209 to chemotherapy. All patients were included in the ITT population; 417 patients received at least one dose of the assigned treatment (figure 1). At the time of data cutoff on Nov 12, 2018, the median follow-up (ie, time from randomisation to last known date alive or death) for overall survival was 10·5 months (IQR 4·5–19·0) in the nivolumab group and 8·0 months (IQR 4·6–15·2) in the chemotherapy group. The primary reason for treatment discontinuation in both groups was progressive disease (figure 1).

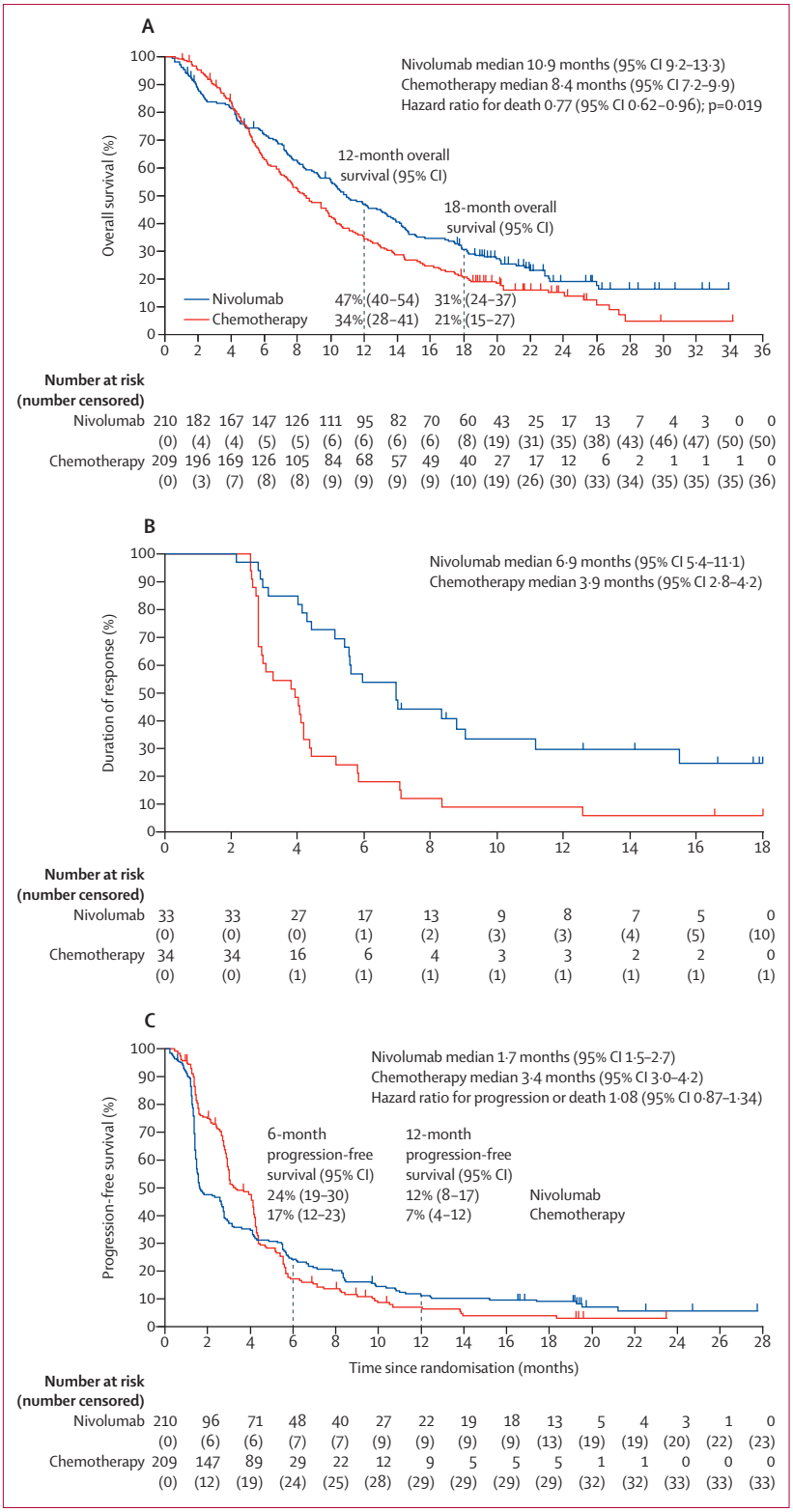

Figure 2: **(A) overall survival, (B) duration of response, and (C) progression-free survival**
Data shown per investigator assessment.

	Nivolumab group (n=171)*	Chemotherapy group (n=158)*
Objective response	33 (19%, 14–26)	34 (22%, 15–29)
Best overall response†		
Complete response	1 (1%)	2 (1%)
Partial response	32 (19%)	32 (20%)
Stable disease	31 (18%)	65 (41%)
Progressive disease	94 (55%)	51 (32%)
Not evaluable	13 (8%)	8 (5%)
Disease control	64 (37%, 30–45)	99 (63%, 55–70)
Median time to response, months (IQR)	2·6 (1·5–2·8)	1·5 (1·4–1·7)
Median duration of response, months (95% CI)	6·9 (5·4–11·1)	3·9 (2·8–4·2)
Patients with ongoing response (n/N [%])	7/33 (21%)‡	2/34 (6%)§

Data are n (%, 95% CI) or n (%), unless stated otherwise. *Randomly assigned patients who had target lesion measurements at baseline. †Percentages might not add up to 100% due to rounding. ‡One patient with a complete response and six patients with a partial response. §Two patients with a complete response.

Table 2: **Antitumour activity**

Baseline characteristics were generally similar across the treatment groups (table 1). All enrolled patients had oesophageal squamous cell carcinoma and 401 (96%) of 419 patients were Asian. All patients had received previous systemic anticancer therapy; 205 (49%) and 295 (70%) of 419 patients had previous surgery and radiotherapy, respectively. Nearly half of patients in each groups had tumours expressing at least 1% PD-L1 at baseline (table 1).

At a minimum follow-up (ie, time from random assignment of the last patient to data cutoff) of 17·6 months, overall survival was significantly improved in the nivolumab group compared with the chemotherapy group (median 10·9 months, 95% CI 9·2–13·3 *vs* 8·4 months, 7·2–9·9; HR for death 0·77, 95% CI 0·62–0·96, p=0·019; figure 2). Efficacy data for the individual chemotherapy regimens are in the appendix (p 6). 160 (76%) of 210 patients in the nivolumab group and 173 (83%) of 209 in the chemotherapy group had died by the time of data cutoff. The 12-month and 18-month overall survival estimates are shown in figure 2. Because the Kaplan-Meier curves for overall survival crossed and the interaction p value between treatment and time was 0·068 when testing the proportional hazards assumption using a stratified Cox model, a post-hoc analysis was done using the weighted log-rank test, accounting for the non-proportional hazards effect. This analysis showed a difference in overall survival between the two study groups (p=0·0019 in favour of nivolumab versus chemotherapy).

33 (19%, 95% CI 14–26) of 171 patients in the nivolumab group and 34 (22%, 15–29) of 158 patients in the chemotherapy group achieved an objective response (table 2). The median duration of response was substantially longer with nivolumab compared with chemotherapy (table 2, figure 2). Seven patients in the nivolumab group and two patients in the chemotherapy group had ongoing responses at data cutoff. The maximum change in target lesion size in the nivolumab and chemotherapy groups are in the appendix (p 14).

The HR for progression-free survival with nivolumab versus chemotherapy was 1·08 (0·87–1·34) (figure 2). 187 (89%) of 210 patients in the nivolumab group and 176 (84%) of 209 patients in the chemotherapy group had disease progression or died by the time of data cutoff. The 6-month and 12-month progression-free survival estimates are shown in figure 2. Median treatment duration was 2·6 months (IQR 1·0–6·1) with nivolumab and 2·6 months (1·2–4·2) with chemotherapy. Median relative treatment dose intensity was 100% (IQR 92–100) in the nivolumab group and 81% (68–96) in the chemotherapy group.

Treatment-related adverse events are summarised in table 3. The most common treatment-related adverse events were rash, diarrhoea, and decreased appetite in the nivolumab group; and alopecia, decreased neutrophil count, and decreased white blood cell count in the chemotherapy group (table 3). Serious treatment-related adverse events were reported in 33 (16%) of 209 patients treated with nivolumab (grade 3–4, 20 patients [10%], no grade 5 events), and in 47 (23%) of 208 patients treated with chemotherapy (grade 3–4, 39 patients [19%], two grade 5 events). The most common serious treatment-related adverse events of any grade with nivolumab were pyrexia (five [2%] of 209 patients) and interstitial lung disease (four [2%]) and with chemotherapy were febrile neutropenia (16 [8%] of 208 patients) and decreased appetite (six [3%]). The incidence of treatment-related adverse events leading to discontinuation was similar in both groups (table 3), the most common of which across both groups were interstitial lung disease and pneumonitis (appendix p 10). Dose delays due to treatment-related adverse events were more common with chemotherapy (any grade, 104 [50%]; grade 3–4, 81 [39%]) than with nivolumab (any grade, 34 [16%]; grade 3–4, 15 [7%]). In the chemotherapy group, 75 (36%) and 37 (18%) of 208 patients had any grade and grade 3–4 treatment-related adverse events that led to dose reductions, respectively. Deaths (from any cause) were reported for 11 (5%) of 209 patients in the nivolumab group and for nine (4%) of 208 patients in the chemotherapy group (appendix p 11). Five deaths were deemed to be treatment-related (table 3): two in the nivolumab group (one each of interstitial lung disease and pneumonitis) and three in the chemotherapy group (one each of pneumonia, spinal cord abscess, and interstitial lung disease).

Prespecified subanalyses for the risk of death across baseline demographic and disease characteristics are in figure 3 and the appendix (p 12). Median overall survival in patients with tumour PD-L1 expression of less than 1% was 10·9 months (95% CI 8·4–13·9) and of at least 1% was 10·9 months (8·0–14·2) with nivolumab, while with

	Nivolumab group (n=209)*				Chemotherapy group (n=208)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All events	99 (47%)	33 (16%)	5 (2%)	0	65 (31%)	85 (41%)	46 (22%)	2 (1%)
Serious events	13 (6%)	16 (8%)	4 (2%)†	0	6 (3%)	31 (15%)	8 (4%)	2 (1%)
Events leading to discontinuation	10 (5%)	8 (4%)	0	0	6 (3%)	9 (4%)	3 (1%)	1 (<1%)
Events leading to death‡	0	2 (1%)	0	0	0	1 (<1%)	0	2 (1%)
Events in 10% or more of treated patients in either group								
Rash	22 (11%)	1 (<1%)	0	0	29 (14%)	2 (1%)	0	0
Diarrhoea	20 (10%)	2 (1%)	0	0	18 (9%)	2 (1%)	0	0
Decreased appetite	14 (7%)	2 (1%)	0	0	46 (22%)	10 (5%)	0	0
Fatigue	14 (7%)	1 (<1%)	0	0	34 (16%)	9 (4%)	0	0
Malaise	9 (4%)	0	0	0	45 (22%)	0	0	0
Stomatitis	4 (2%)	1 (<1%)	0	0	24 (12%)	1 (<1%)	0	0
Nausea	4 (2%)	0	0	0	33 (16%)	1 (<1%)	0	0
Alopecia	3 (1%)	0	0	0	98 (47%)	0	0	0
Arthralgia	3 (1%)	0	0	0	20 (10%)	1 (<1%)	0	0
Neutrophil count decreased	2 (1%)	1 (<1%)	0	0	17 (8%)	29 (14%)	30 (14%)	0
Anaemia	1 (<1%)	4 (2%)	0	0	30 (14%)	19 (9%)	0	0
White blood cell count decreased	1 (<1%)	1 (<1%)	0	0	26 (13%)	32 (15%)	14 (7%)	0
Neutropenia	1 (<1%)	0	0	0	11 (5%)	18 (9%)	11 (5%)	0
Peripheral sensory neuropathy	1 (<1%)	0	0	0	46 (22%)	1 (<1%)	0	0
Febrile neutropenia	0	0	0	0	0	18 (9%)	4 (2%)	0
Neuropathy peripheral	0	0	0	0	21 (10%)	1 (<1%)	0	0

Data are n (%). *Patients who received at least one dose of the assigned treatment. †One case of grade 4 diabetic ketoacidosis was not reported before the data cutoff and therefore not captured here. ‡The deaths in the nivolumab group were due to interstitial lung disease and pneumonitis; the deaths in the chemotherapy group were due to pneumonia, spinal cord abscess, and interstitial lung disease. Some patients had adverse events lower than grade 5 that subsequently led to death.

Table 3: **Summary of treatment-related adverse events**

chemotherapy it was 9·3 months (7·2–12·0) and 8·1 months (6·0–9·9), respectively (appendix p 13). The prespecified interaction analysis indicated no significant interaction of treatment effect by PD-L1 status (appendix p 7).

The proportion of patients completing the EQ-5D-3L questionnaires exceeded 85% in both groups through week 42 (appendix p 8). There was an overall significant on-treatment improvement in quality of life for patients given nivolumab compared with those given chemotherapy (calculated for on-treatment data through week 42), in both EQ-5D-3L VAS (least squares mean 6·9, 95% CI 3·0–10·9; p=0·00069) and utility index (0·076, 0·011–0·142; p=0·023; appendix pp 15 and 16, respectively). The mean difference between groups favoured nivolumab at all timepoints and was clinically meaningful for the VAS at weeks 18 through 30 (appendix p 15) and for the utility index at weeks 24 through 42 (appendix p 16). Patients treated with nivolumab had a decreased risk of deterioration in quality of life compared with patients treated with chemotherapy for the VAS (HR 0·65, 95% CI 0·49–0·86, p=0·0030; median time to deterioration 4·3 months, 95% CI 2·8–8·2 *vs* 2·7 months, 1·7–2·9; appendix p 17) and the utility index (HR 0·73, 95% CI 0·55–0·97, p=0·032; median time to deterioration 4·2 months, 95% CI 2·8–7·0 *vs* 2·9 months, 1·8–3·1; appendix p 17).

119 (57%) of 210 patients in the nivolumab group and 115 (55%) of 209 patients in the chemotherapy group received subsequent therapy for advanced oesophageal cancer. The most common subsequent treatments in both nivolumab and chemotherapy groups, respectively, were taxanes (for 100 [48%] of 210 patients in the nivolumab group and 43 [21%] of 209 patients in the chemotherapy group), fluoropyrimidine-based chemotherapies (24 [11%] of 210 and 39 [19%] of 209), and platinum-based chemotherapies (20 [10%] of 210 and 22 [11%] of 209; appendix p 9).

Discussion

In this randomised, phase 3 trial, treatment with nivolumab was associated with significant improvement in overall survival and a favourable safety profile versus chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma. The survival benefit with nivolumab occurred regardless of patients' level of tumour PD-L1 expression.

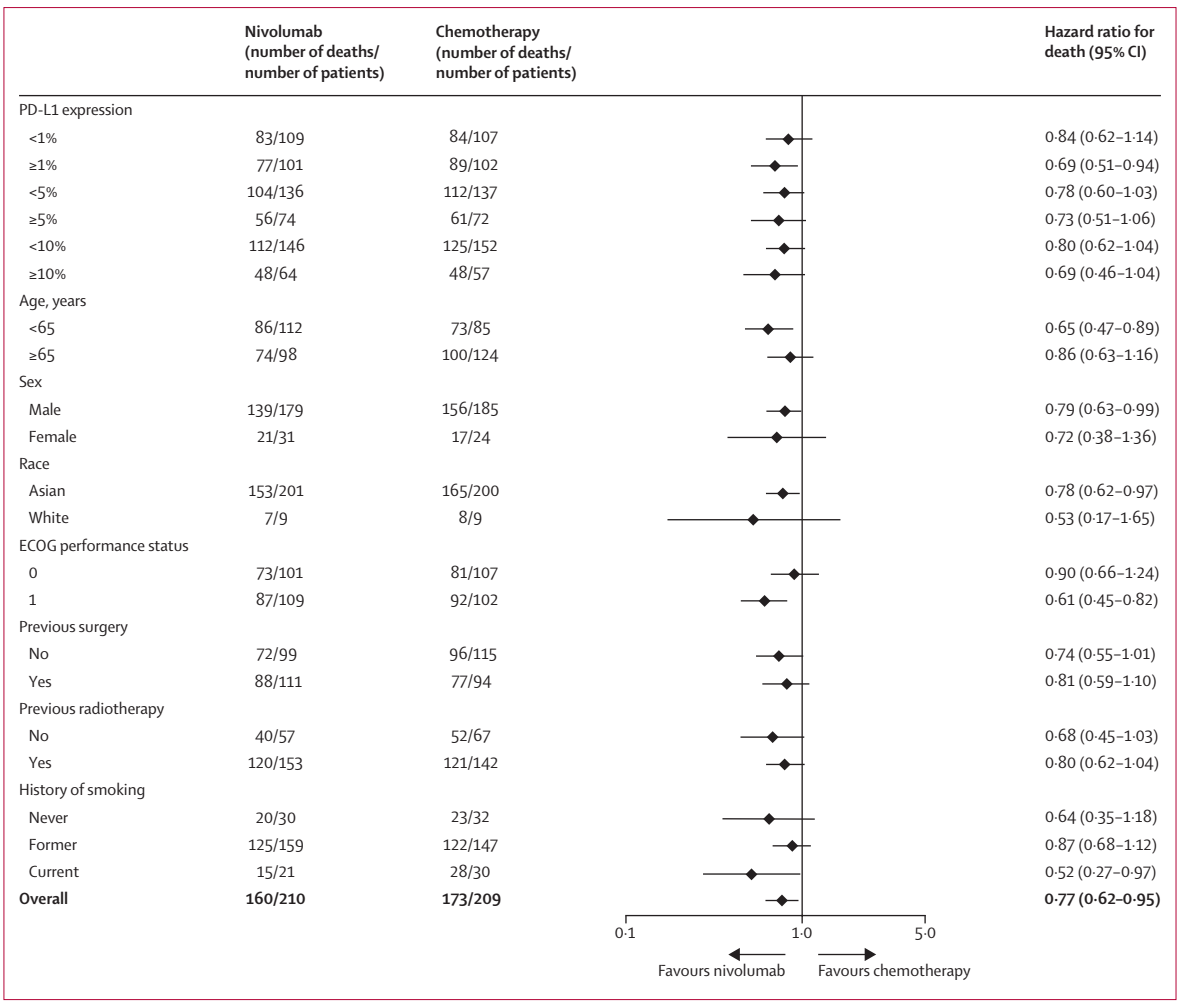

Figure 3: **Subgroup analysis of overall survival**
Hazard ratios and the corresponding 95% CIs for nivolumab relative to chemotherapy were calculated using the unstratified Cox proportional hazards model. ECOG=Eastern Cooperative Oncology Group.

The HR for the risk of death with nivolumab compared with chemotherapy was 0·77, and a 2·5-month difference in median overall survival was noted between the groups, both in favour of nivolumab. The proportion of patients alive at 12 and 18 months suggests durable overall survival benefit with nivolumab. The final analysis of another phase 3 trial of a PD-1 inhibitor, pembrolizumab (KEYNOTE-181), showed no significant difference in overall survival versus chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma.[27] In previously treated patients with unresectable advanced or recurrent oesophageal squamous cell carcinoma in the ATTRACTION-1 study,[28] clinical benefit occurred regardless of tumour PD-L1 expression. However, the numerically greater clinical benefit in patients with tumour PD-L1 expression of at least 1% versus those with less than 1% led to tumour PD-L1 expression being selected as a relevant biomarker and stratification factor for this study. Our results showed that survival benefit with nivolumab occurred regardless of tumour PD-L1 expression, although patients with PD-L1 expression of at least 1% had a 15% greater reduction in the risk of death than those with PD-L1 expression of less than 1%. The KEYNOTE-181 study,[27] which included patients with oesophageal adenocarcinoma as well as those with oesophageal squamous cell carcinoma, used a combined positive score for PD-L1 expression on tumours and immune cell infiltrates to assess the effect of PD-L1 expression on outcomes with pembrolizumab. However, in studies of patients with oesophageal squamous cell carcinoma, no comparative data have shown improved enrichment for efficacy with the combined positive score compared with tumour PD-L1 expression.

Overall survival assessed by additional prespecified baseline demographic and disease characteristics consistently favoured nivolumab versus chemotherapy in several subgroups, including age, sex, race, ECOG

performance status, sites of metastases, previous radiotherapy, and smoking history. A prespecified interaction analysis confirmed that tumour PD-L1 expression level was not a determinant of the overall survival benefit. Although significant interactions were observed for ECOG performance status, recurrent disease, and smoking history, the HRs were less than 1, suggesting there was no change in the direction of the treatment effect (these interactions were quantitative, not qualitative).

The proportion of patients with an objective response was similar between the nivolumab and chemotherapy groups. Data for objective response in the chemotherapy group was consistent with that reported with other taxane-based regimens in the second-line setting in Asian patients with oesophageal squamous cell carcinoma.[13,29,30] The median time to response was 1 month longer with nivolumab versus chemotherapy; however, responses were more durable with nivolumab. This finding is consistent with reports[31] that suggest that responses to immunotherapeutic agents might take more time to become apparent, but are more durable compared with chemotherapy. The higher proportion of patients with progressive disease in the nivolumab group compared with the chemotherapy group underlies the importance of identifying patients who are likely to respond to anti-PD-1 monotherapy. Exploratory post-hoc analyses are planned to assess atypical progression patterns. More than half the patients in the nivolumab group had received systemic anticancer therapy in a third-line setting, which suggests that nivolumab therapy does not preclude patients from receiving subsequent anticancer therapies. Additional biomarker research is underway to identify patient characteristics that might predict response to nivolumab.

Analyses of progression-free survival showed no significant difference (HR 1·08, 95% CI 0·87–1·34) between the nivolumab and chemotherapy groups. However, the progression-free survival curves crossed and ultimately showed sustained separation favouring nivolumab beyond 5 months. The overall survival curves also crossed and beyond 5 months diverged in favour of nivolumab. This finding has also occurred with the PD-1 inhibitor pembrolizumab versus chemotherapy[27] and with nivolumab in other solid tumours.[17,32,33] Crossing of the survival curves is indicative of non-proportionality; however, our post-hoc analysis using an alternative statistical method (weighted log-rank test) corroborated the improvement in overall survival with nivolumab versus chemotherapy.

Nivolumab was well tolerated with a numerically lower incidence of grade 3 or 4 treatment-related adverse events and adverse events leading to dose delay compared with chemotherapy; however, the difference was not statistically tested. The incidence of grade 3 or 4 treatment-related serious events was also numerically lower in patients treated with nivolumab. No new safety signals with nivolumab were identified, and the safety profile presented in this study is consistent with the profile previously established in patients with oesophageal squamous cell carcinoma and other solid tumours.[16,17,19,34]

Reduced quality of life is common in patients with advanced oesophageal cancer because of dysphagia, pain, and malnutrition brought about by oesophageal obstruction.[10] In accordance with the favourable efficacy and safety profile of nivolumab, significant, and at times clinically meaningful, improvements versus chemotherapy were noted in patient-reported health-related quality of life.

Our study had some limitations. First, despite enrolment of patients from different countries, most of the patients were from Asia. Although the small number of non-Asian patients in this study might limit the interpretation of the results in this population, analysis in Asian and non-Asian patients showed that overall survival favoured nivolumab versus chemotherapy in both subgroups. Second, ATTRACTION-3 had an open-label study design. The knowledge of the treatment might have potentially affected patient responses in the health-related quality of life questionnaires. However, in another study that assessed open-label trials with substantial imbalances in toxicities across groups, there were no differences in patient-reported outcomes, suggesting that any inherent biases do not meaningfully affect patient-reported outcomes.[35] Additionally, an open-label design was considered appropriate because of the differences in the dosing regimens and associated toxicities for each treatment group. The primary endpoint of overall survival is an objective measure, which would not be affected by the open-label nature of the study. Further, involvement of an independent data monitoring committee for safety assessments ensured anonymity of the treatment groups during data review.

In summary, nivolumab was associated with a significant improvement in overall survival versus chemotherapy and a favourable safety profile in previously treated patients with advanced oesophageal squamous cell carcinoma. Survival benefit occurred regardless of tumour PD-L1 expression. There were significant, and at times clinically meaningful, improvements in health-related quality of life with nivolumab versus chemotherapy. Nivolumab might represent a new standard second-line treatment option for patients with advanced oesophageal squamous cell carcinoma. A phase 3 study assessing nivolumab-based regimens versus chemotherapy in first-line treatment of patients with oesophageal squamous cell carcinoma is underway (NCT03143153).

Contributors

KK and YK conceived and designed the study in collaboration with ONO Pharmaceutical Company and Bristol-Myers Squibb. All authors gathered the data. IX and MK analysed and interpreted the data. All authors participated in developing, writing, reviewing, and approving the manuscript for submission. KK was responsible for the final decision to submit the manuscript for publication.

For the **Bristol-Myers Squibb policy on data sharing** see https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

Declaration of interests

KK reports serving as a consultant for ONO Pharmaceutical Company, Oncolys BioPharma, Merck Sharpe & Dohme (MSD) Oncology, and BeiGene; and receiving research funding from ONO Pharmaceutical Company, BeiGene, MSD Oncology, and Shionogi. B-CC reports receiving honoraria from ONO Pharmaceutical Company; stock ownership of TheraCanVac; holding patents for Champions Oncology; serving as a consultant for ONO Pharmaceutical Company, Bristol-Myers Squibb (BMS), AstraZeneca, Novartis, Janssen, Yuhan, MSD, Boehringer-Ingelheim, Roche, Pfizer, Eli Lilly, and Takeda; receiving research funding from Novartis, Bayer, AstraZeneca, Mogam Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, ONO Pharmaceutical Company, Dizal Pharma, and MSD; and receiving honoraria from AstraZeneca, Novartis, Bayer, Mogam Institute, Champions Oncology, Janssen, Yuhan, Dizal Pharma, and MSD. MT reports receiving research funding from ONO Pharmaceutical Company; and serving as a speaker for ONO Pharmaceutical Company, BMS, Daiichi Sankyo, and Taiho Pharmaceutical. MO reports serving as a speaker for Taiho Pharmaceutical, Chugai Pharma, Covidien, Johnson & Johnson, and Lilly; and receiving research funding from Taiho Pharmaceutical, Nippon Kayaku, Chugai Pharma, Covidien, Johnson & Johnson, Daiichi Sankyo, Yakult Honsha, Lilly Japan, Nihon Medi-Physics, Pfizer, Mochida Pharmaceutical, and Shionogi. SK reports receiving research funding from ONO Pharmaceutical Company, Lilly Japan, Taiho Pharmaceutical, and Boehringer Ingelheim, and BMS; and receiving personal fees from Chugai Pharma, Merck Serono, Bayer, Eisai, and Yakult Honsha. M-JA reports receiving honoraria from AstraZeneca, Lilly, MSD, and Takeda; serving as a consultant for Alpha Pharmaceuticals; and serving as an advisor with AstraZeneca, Roche, Lilly, MSD, and Takeda. YH reports receiving grants from ONO Pharmaceutical Company and BMS. YD reports receiving personal fees from ONO Pharmaceutical Company, Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Yakult Honsha, Takeda Pharmaceutical, Kaken Pharmaceutical, Abbott Japan, Eisai, Shionogi, Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Teijin Pharma, Sanofi, Astellas Pharma, Tsumura, AstraZeneca, Asahi Kasei Pharma, Medtronic, Johnson & Johnson, Olympus, and Intuitive Surgical; receiving grants from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Yakult Honsha, Takeda Pharmaceutical, Kaken Pharmaceutical, Abbott Japan, Eisai, Shionogi, Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Astellas Pharma, Tsumura, AstraZeneca, Johnson & Johnson, Nippon Kayaku, Novartis Pharma, Pfizer Japan, CSL Behring, and Nestle; and receiving conference fees from the Japanese Gastric Cancer Association, the Japan Esophageal Society, and the Japan Surgical Society. C-CY reports receiving research funding from ONO Pharmaceutical Company, Eisai, Effective Pharmaceuticals, and Deciphera Pharmaceuticals; receiving honoraria from Lilly, MSD, Amgen, and Eisai; and holding consulting roles with Lilly and MSD. S-BK reports receiving researching funding from Novartis, Genzyme, and Dongkook Pharma. C-HH reports receiving honoraria from ONO Pharmaceutical Company, MSD, and BMS; serving as a consultant for ONO Pharmaceutical Company; receiving research funding from ONO Pharmaceutical Company; serving in a consulting role for Novartis, Lilly, and MSD; and receiving research funding from MSD, AstraZeneca, and Genentech. IX reports employment with BMS and ownership of stock in BMS. MK reports employment with ONO Pharmaceutical Company and ownership of stock in ONO Pharmaceutical Company. YKi reports receiving honoraria from ONO Pharmaceutical Company, Ethicon, Olympus, Taiho Pharmaceutical, Chugai Pharma, Nippon Kayaku, and Asahi Kasei; and receiving research funding from Astellas Pharma, Otsuka, Kyowa Hakko Kirin, Kowa, CSL Behring, Kaken Pharmaceutical, Shionogi, Daiichi Sankyo, Taiho Pharmaceutical, Takeda, Chugai Pharma, Tsumura, Teijin Pharma, Medtronic, Boehringer Ingelheim, Merck Serono, Novartis, Asahi Kasei, Kureha, Sanofi, Sumitomo Dainippon Pharma, Taisho Toyama Pharma, Nippon Kayaku, Lilly, Pfizer, Yakult Honsha, GlaxoSmithKline, Medicon, EA Pharma, Otsuka, ONO Pharmaceutical Company, KCI Licensing, Nihon Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Eisai, Bayer Yakuhin, Abbot Japan, and Fujifilm Toyama Chemical. All other authors declare no competing interests.

Data sharing

See Bristol-Myers Squibb policy on data sharing.

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