# Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

*Jonathan D Spicer*, Marina C Garassino*, Heather Wakelee, Moishe Liberman, Terufumi Kato, Masahiro Tsuboi, Se-Hoon Lee, Ke-Neng Chen, Christophe Dooms, Margarita Majem, Ekkehard Eigendorff, Gastón L Martinengo, Olivier Bylicki, Delvys Rodríguez-Abreu, Jamie E Chaft, Silvia Novello, Jing Yang, Ashwini Arunachalam, Steven M Keller, Ayman Samkari, Shugeng Gao, on behalf of the KEYNOTE-671 Investigators†*

## Summary

**Background** At the first interim analysis of the KEYNOTE-671 trial, adding perioperative pembrolizumab to neoadjuvant chemotherapy significantly improved event-free survival in participants with early-stage non-small-cell lung cancer (NSCLC). We report overall survival and health-related quality of life outcomes from the second interim analysis.

**Methods** KEYNOTE-671 was a global phase 3 trial done at 189 medical centres. Eligible participants (aged ≥18 years) with resectable stage II, IIIA, or IIIB (N2) NSCLC were randomly assigned (1:1) to four cycles of neoadjuvant pembrolizumab (200 mg administered intravenously every 3 weeks) plus cisplatin-based chemotherapy followed by surgery and 13 cycles of adjuvant pembrolizumab (200 mg administered intravenously every 3 weeks) or to four cycles of neoadjuvant placebo (administered intravenously every 3 weeks) plus cisplatin-based chemotherapy followed by surgery and 13 cycles of adjuvant placebo (administered intravenously every 3 weeks). Randomisation was done centrally using an interactive response technology system and was stratified by disease stage, PD-L1 expression, histology, and geographical region in blocks of four. Participants, investigators, and sponsor personnel were masked to treatment assignments; local pharmacists were unmasked to support treatment preparation. The dual primary endpoints were overall survival and event-free survival evaluated in the intention-to-treat population. This study is registered at ClinicalTrials.gov, NCT03425643, and is ongoing but closed to enrolment.

**Findings** Between May 11, 2018, and Dec 15, 2021, 797 participants were randomly assigned to the pembrolizumab group (n=397) or the placebo group (n=400). Median study follow-up at the second interim analysis was 36·6 months (IQR 27·6–47·8). 36-month overall survival estimates were 71% (95% CI 66–76) in the pembrolizumab group and 64% (58–69) in the placebo group (hazard ratio 0·72 [95% CI 0·56–0·93]; one-sided p=0·0052; threshold, one-sided p=0·0054). Median event-free survival was 47·2 months (95% CI 32·9 to not reached) in the pembrolizumab group and 18·3 months (14·8–22·1) in the placebo group (hazard ratio 0·59 [95% CI 0·48–0·72]). In the as-treated population, grade 3–5 treatment-related adverse events occurred in 179 (45%) of 396 participants in the pembrolizumab group and in 151 (38%) of 399 participants in the placebo group. Treatment-related adverse events led to death in four (1%) participants in the pembrolizumab group and three (1%) participants in the placebo group.

**Interpretation** The significant overall survival benefit of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone coupled with a manageable safety profile support the use of perioperative pembrolizumab in patients with resectable, early-stage NSCLC.

**Funding** Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA.



Published **Online** September 14, 2024 https://doi.org/10.1016/S0140-6736(24)01756-2

See **Online/Comment** https://doi.org/10.1016/S0140-6736(24)01920-2

*Contributed equally

†The KEYNOTE-671 Investigators are listed in the appendix (pp 3–7)

**Department of Surgery, McGill University Health Centre, Montreal, QC, Canada** (J D Spicer MD); **Department of Medicine, University of Chicago Medicine and Biological Sciences, Chicago, IL, USA** (Prof M C Garassino MD); **Department of Medicine, Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA, USA** (Prof H Wakelee MD); **Division of Thoracic Surgery, Centre Hospitalier de l'Université de Montréal (CHUM), University of Montreal, Montreal, QC, Canada** (M Liberman MD); **Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan** (T Kato MD); **Department of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Japan** (Prof M Tsuboi MD); **Division of Hematology/Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea** (Prof S-H Lee MD); **Department of Thoracic Surgery, Beijing Cancer Hospital, Peking University, Beijing, China** (Prof K-N Chen MD); **Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium**

## Introduction

In 1994, two randomised clinical trials demonstrated a significant overall survival benefit for the addition of neoadjuvant[1] or perioperative[2] chemotherapy to surgery alone for resectable stage III non-small cell lung cancer (NSCLC). These results ushered in the era of multimodality therapy for locally advanced resectable NSCLC.[3] No neoadjuvant or perioperative treatment regimen has shown a significant overall survival benefit in the last 30 years.

An increasing array of therapeutic options are available for patients with resectable stage II or III

(C Dooms MD); **Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain** (M Majem MD); **Clinic for Internal Oncology and Hematology, Zentralklinik Bad Berka, Bad Berka, Germany** (E Eigendorff MD); **Department of Clinical Oncology, Sanatorio Parque, Rosario, Argentina** (G L Martinengo MD); **Department of Pneumology, HIA Sainte-Anne, Toulon, France** (Prof O Bylicki MD); **Department of Medical Oncology, Hospital Universitario Insular de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain** (D Rodríguez-Abreu MD); **Department of Oncology, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY, USA** (J E Chaft MD); **Department of Oncology, University of Turin, A.O.U. San Luigi Gonzaga di Orbassano, Turin, Italy** (Prof S Novello MD); **Biostatistics and Research Decision Sciences** (J Yang PhD), **Outcomes Research** (A Arunachalam MPH), **and Global Clinical Development** (S M Keller MD, A Samkari MD), **Merck & Co, Rahway, NJ, USA; Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China** (Prof S Gao MD)

Correspondence to: Dr Jonathan D Spicer, Department of Surgery, McGill University Health Centre, Montreal General Hospital, Montreal, QC H4G 1A4, Canada **jonathan.spicer@mcgill.ca**

See Online for appendix

## Research in context

### Evidence before this study

We searched PubMed on June 6, 2024, for English-language publications of randomised controlled trials published since database inception using combinations of the terms "PD-1 inhibitor", "PD-L1 inhibitor", "checkpoint inhibitor", "tyrosine kinase inhibitor", "chemotherapy", "neoadjuvant therapy", "adjuvant therapy", "perioperative therapy", "early stage non-small cell lung cancer" (or NSCLC), and "resectable non-small cell lung cancer" (or NSCLC). We also searched abstracts published in the past 3 years from the American Association for Cancer Research Annual Meeting, American Society of Clinical Oncology (ASCO) Annual Meeting, ASCO Monthly Plenary Series, European Lung Cancer Congress, European Society of Medical Oncology (ESMO) Congress, ESMO Virtual Plenaries, and World Conference on Lung Cancer using the same search terms. We identified randomised controlled trials that showed a significant event-free survival and pathological complete response benefit for nivolumab given as neoadjuvant therapy for molecularly unselected disease; a significant recurrence-free survival benefit for atezolizumab and pembrolizumab given as adjuvant therapy for molecularly unselected disease; a significant disease-free survival benefit for alectinib given as adjuvant therapy for *ALK*-translocated disease; a significant disease-free survival and overall survival benefit for osimertinib given as adjuvant therapy for *EGFR*-mutated disease; and a significant event-free survival, pathological complete response, and major pathological response benefit for durvalumab, nivolumab, pembrolizumab, tislelizumab, and toripalimab given as perioperative therapy for molecularly unselected disease. For all studies, the adverse event profile was considered to be as expected based on the known profiles of the individual therapies. Adjuvant alectinib, adjuvant osimertinib, neoadjuvant nivolumab, and perioperative nivolumab were shown to have no detrimental impact on health-related quality of life.

### Added value of this study

KEYNOTE-671 is the first randomised controlled trial to show that perioperative therapy significantly improves overall survival in addition to event-free survival, pathological complete response, and major pathological response in patients with molecularly unselected, resectable non-small-cell lung cancer (NSCLC). Pembrolizumab plus cisplatin-based chemotherapy in the neoadjuvant phase followed by surgery and pembrolizumab in the adjuvant phase significantly improved event-free survival and overall survival compared with placebo plus cisplatin-based chemotherapy in the neoadjuvant phase followed by surgery and placebo in the adjuvant phase in participants with resectable stage II, IIIA, or IIIB (N2) NSCLC. Health-related quality of life was not decreased with perioperative pembrolizumab compared with neoadjuvant chemotherapy alone and remained stable in both treatment groups during the adjuvant phase despite no active treatment in the control group. The adverse event profile of neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab was as expected, with blood count-related abnormalities, nausea, and fatigue—adverse events commonly associated with chemotherapy—the most frequently occurring treatment-related adverse events.

### Implications of all the available evidence

Perioperative PD-1 or PD-L1 inhibition added to neoadjuvant chemotherapy provides statistically significant, clinically meaningful improvements in efficacy compared with neoadjuvant chemotherapy alone in patients with molecularly unselected, resectable stage II, IIIA, or IIIB (N2) NSCLC. The significant improvements in overall survival, event-free survival, and pathological response, the absence of a long-term decrease in health-related quality of life, and the absence of new safety signals that we observed in KEYNOTE-671 support the addition of perioperative pembrolizumab to neoadjuvant platinum-based chemotherapy as a standard treatment option for patients with resectable NSCLC.

NSCLC assessed according to the American Joint Committee on Cancer staging system, 8th edition (AJCC 8).[4] Phase 3 trials have shown an overall survival benefit for adjuvant osimertinib in resected, *EGFR*-mutated NSCLC[5] and a disease-free survival benefit for adjuvant alectinib in resected, *ALK*-translocated NSCLC.[6] For patients without these molecular alterations, neoadjuvant, perioperative, and adjuvant PD-1 and PD-L1 inhibitor-based regimens have shown meaningful event-free and disease-free survival benefits in early-stage NSCLC.[7–15] The ultimate objective for patients with resectable NSCLC is to prolong survival without compromising health-related quality of life. Despite representing important advances, none of the PD-1-based or PD-L1-based regimens have demonstrated an overall survival benefit in the intention-to-treat population,[7–15] and limited health-related quality of life data have been published.[16,17]

The KEYNOTE-671 trial is evaluating a perioperative approach of neoadjuvant pembrolizumab plus cisplatin-based chemotherapy followed by surgical resection and adjuvant pembrolizumab for patients with resectable stage II or III NSCLC. At the first interim analysis, perioperative pembrolizumab significantly improved event-free survival (hazard ratio [HR] 0·58 [95% CI 0·46–0·72]; one-sided p<0·0001; one-sided threshold p=0·0046), major pathological response (30% *vs* 11%; one-sided p<0·0001), and pathological complete response (18% *vs* 4%; one-sided p<0·0001) compared with neoadjuvant chemotherapy alone and

had a safety profile consistent with the known safety profiles of the individual medications; the overall survival benefit of perioperative pembrolizumab was not significant at the first interim analysis.[11] We report efficacy, safety, and health-related quality of life outcomes from the second interim analysis.

## Methods

### Study design and participants

KEYNOTE-671 is a randomised, double-blind, placebo-controlled, phase 3 study done at 189 medical centres globally (appendix pp 3–7). Complete eligibility criteria have been published[11] and are available in the protocol (appendix). In brief, eligible participants were aged 18 years or older; had previously untreated, pathologically confirmed stage II, IIIA, or IIIB (N2) NSCLC as assessed per AJCC 8[4] that was considered to be resectable after surgical consultation and investigator assessment; had an Eastern Cooperative Oncology Group performance status of 0–1 within 10 days before randomisation; and were able to provide a tumour sample for PD-L1 assessment. Baseline disease staging requirements are available in the appendix (p 8).

The trial protocol and all amendments, which included changes that affected trial design (summarised in the Document History section of the protocol [appendix]), were approved by the appropriate ethics body for each participating centre (appendix pp 8–10). All participants provided written, informed consent. An external, independent data and safety monitoring committee oversaw the trial by assessing safety regularly and efficacy at prespecified interim analyses. The trial was conducted in accordance with the protocol, the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki ethical principles, and all local regulations. Clinically important protocol deviations related to eligibility criteria or study drug administration occurred in three participants in the pembrolizumab group and six participants in the placebo group (additional details are available in the appendix [p 10]).

This study is registered with ClinicalTrials.gov, NCT03425643, and is ongoing but closed to enrolment.

### Randomisation and masking

Randomisation was done using an interactive response system (Almac Clinical Technologies, Souderton, PA, USA) and a participant randomisation list generated by the sponsor and was stratified by disease stage (II *vs* III), PD-L1 tumour proportion score (TPS; <50% *vs* ≥50%), tumour histology (squamous *vs* non-squamous), and geographical region (east Asia *vs* other). Participants were randomly assigned (1:1) in blocks of four per stratum to neoadjuvant pembrolizumab plus cisplatin-based chemotherapy followed by surgery and adjuvant pembrolizumab (pembrolizumab group) or to neoadjuvant placebo plus cisplatin-based chemotherapy followed by surgery and adjuvant placebo (placebo group). Participants, investigators, site staff, and sponsor personnel involved in study treatment administration or clinical evaluation were masked to treatment assignments. Local pharmacists not otherwise involved with the care of study participants were aware of assignments to support treatment preparation. Steps taken at the site level to ensure that treatment assignments remained masked to all but the local pharmacist include an identical appearance of pembrolizumab and placebo and the maintenance of a pharmacy binder that contains all unmasked study documentation. Designated sponsor personnel were unmasked to treatment assignments to support questions related to unmasked study activity and conduct site monitoring to ensure compliance with masking procedures.

### Procedures

The neoadjuvant phase comprised four cycles of pembrolizumab 200 mg or placebo (normal saline) given intravenously once every 3 weeks in combination with cisplatin 75 mg/m² given intravenously once every 3 weeks and either gemcitabine 1000 mg/m² given intravenously on days 1 and 8 of 3-week cycles for participants with squamous histology or pemetrexed 500 mg/m² given intravenously once every 3 weeks for those with non-squamous histology. Lobectomy, bilobectomy, pneumonectomy, sleeve lobectomy, or sleeve pneumonectomy, with or without chest wall resection, was to be performed per local standard-of-care no later than 20 weeks after the first dose of neoadjuvant therapy. Radiotherapy was administered in select circumstances as detailed in the appendix (p 10). The adjuvant phase was to be initiated between 4 weeks and 12 weeks after surgery and comprised pembrolizumab 200 mg or saline placebo given intravenously once every 3 weeks for up to 13 additional cycles. Pembrolizumab, placebo, chemotherapy, and, if administered, radiotherapy, were continued until the maximum number of administrations was reached, occurrence of disease progression or recurrence, occurrence of unacceptable toxic effects, investigator decision to stop treatment, withdrawal of consent, or other reasons (appendix pp 10–11), whichever occurred first. Full details regarding treatment decisions, including treatment interruptions, dose reductions (not permitted for pembrolizumab or placebo), and treatment discontinuation are in the protocol (appendix). Participants continued to be followed per the study protocol following treatment completion or discontinuation unless they withdrew consent for study participation. All subsequent anticancer treatments were administered at the discretion of the investigator and recorded in the study database.

During screening and where permitted by law, participants self-reported their sex as female, male, undifferentiated, or unknown, their race as one or more of American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or

Other Pacific Islander, or White, and their ethnicity as Hispanic or Latino, Not Hispanic or Latino, or Unknown. PD-L1 expression in tumour tissue was assessed at a central laboratory during screening (Covance, Indianapolis, IN, USA) using PD-L1 IHC 22C3 pharmDx (Agilent Technologies; Carpinteria, CA, USA). CT or MRI of the chest and abdomen was performed during screening, throughout all treatment phases, and during follow-up according to the schedule summarised in the appendix (p 11). All other imaging assessments, including MRI of the brain and [$^{18}$F]fluorodeoxyglucose-PET with or without CT, were performed at the discretion of the investigator. The type of imaging used to establish the disease stage during screening was not collected in the database. Participants were contacted by telephone approximately every 12 weeks during the survival follow-up phase to determine survival status.

Adverse events and laboratory abnormalities that occurred from randomisation to 30 days after treatment discontinuation (up to 90 days for serious events in the absence of new anticancer therapy) were recorded by the investigator at all trial visits. Adverse events were documented according to the Medical Dictionary for Regulatory Affairs, version 25.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to treatment by the investigator.

Participants completed the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and the supplemental lung cancer-specific module (QLQ-LC13) in the local language using an electronic tablet device before any other study procedures at baseline, at the last scheduled study visit before the planned surgery, on day 1 of adjuvant cycles 1–4, 7, 10, and 13, at treatment discontinuation, at the 30-day safety follow-up visit, and at each post-treatment visit. The QLQ-C30 is a 30-item standardised oncology instrument for measuring patient-reported physical, psychological, and social functions, cancer symptoms, and global health status/quality of life (GHS/QoL).[18] The QLC-LC13 is a 13-item standardised instrument that captures lung cancer-specific symptoms and toxic effects of conventional chemotherapy and radiotherapy.[19]

### Outcomes

The dual primary endpoints were event-free survival, defined as the time from randomisation to the first occurrence of local progression that precluded the planned surgery, unresectable tumour at the time of surgery, progression or recurrence per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 by the investigator's assessment, or death from any cause, and overall survival, defined as the time from randomisation to death from any cause. The secondary endpoints were major pathological response and pathological complete response as assessed per blinded, central examination by a pathologist (reported previously[11]), change from baseline in the neoadjuvant phase and in the adjuvant phase in GHS/QoL (based on items 29 and 30 of the EORTC QLQ-C30[18]), and safety. Prespecified exploratory endpoints included the proportion of participants with improved, stable, or deteriorated GHS/QoL and change from baseline in the neoadjuvant phase and in the adjuvant phase in physical functioning (based on items 1–5 of the EORTC QLQ-C30[18]), role functioning (based on items 6 and 7 of the QLQ-C30[18]), dyspnoea (based on item 8 of the QLQ-C30[18]), cough (based on item 31 of the EORTC QLQ-LC13[19]), and chest pain (based on item 40 of the QLQ-LC13[19]). Improvement of GHS/QoL was defined as an increase from baseline of 10 points or more at any time during the study (excluding week 11 of the neoadjuvant phase) that was confirmed at the next consecutive visit. Stability of GHS/QoL was defined as an increase from baseline of 10 points or more at any time during the study (excluding week 11 of the neoadjuvant phase) that was not confirmed at the next consecutive visit, a change from baseline of less than 10 points at consecutive visits (excluding week 11 of the neoadjuvant phase), or a change from baseline of less than 10 points that was followed by an improvement at the next consecutive visit (excluding week 11 of the neoadjuvant phase). Deterioration of GHS/QoL was defined as a decrease from baseline of 10 points or more at any time during the study (excluding week 11 of the neoadjuvant phase) when the criteria for improvement or stability were not met. A 10-point threshold is the historical standard for assessing clinically meaningful improvement and deterioration in EORTC QLQ-C30 scores.[20] For QLQ-C30 GHS/QoL and functional scales, higher scores indicate greater level of function. For QLQ-C30 and QLQ-LC13 symptoms, higher scores indicate greater severity of symptoms.

### Statistical analysis

As previously reported,[11] the familywise type I error rate of 0·025 (one-sided) was strictly controlled across the event-free survival, overall survival, major pathological response, and pathological complete response hypotheses and among the interim and final analyses using the graphical method of Maurer and Bretz.[21] The initial one-sided alpha allocation for each hypothesis was 0·01 for event-free survival, 0·0148 for overall survival, 0·0001 for major pathological response, and 0·0001 for pathological complete response. Per the multiplicity strategy, the full alpha of 0·025 would be allocated to test overall survival if the null hypotheses for event-free survival, major pathological response, and pathological complete response were rejected. The Lan–DeMets O'Brien–Fleming spending function was used to control the type I

error for the analyses of event-free survival and overall survival at the interim and final analyses. The hypotheses tested at each analysis are available in the appendix (p 27). The study would be considered positive if there was a significant improvement in either event-free survival or overall survival in the pembrolizumab group at an interim or final analysis.

The study was to enrol approximately 786 participants. With the occurrence of 416 event-free survival events and two analyses, the study has 90·1% power to detect a difference in event-free survival of HR=0·7 at one-sided alpha=0·01. With the occurrence of 386 deaths and four interim analyses and a final analysis, the study has 90% power to detect a difference in overall survival of HR=0·7 at one-sided alpha=0·0148. The sample size and power calculations assume that event-free survival follows an exponential distribution with a median of 21 months for the placebo group and 30 months for the pembrolizumab group, that overall survival follows an exponential distribution with a median of 34 months for the placebo group and 48·6 months for the pembrolizumab group, that the enrolment period is 36 months with a ramp-up period of 6 months, and that the monthly drop-out rate for both event-free survival and overall survival is 1%.

Event-free survival and overall survival were estimated from the time of randomisation (prespecified) and from the time of surgery (exploratory) using the Kaplan–Meier method; 36 months was a timepoint of interest. For analysis of overall survival, participants were censored at the time the participant was last known to be alive in the absence of a death date. For analysis of event-free survival, participants were censored at the time of the last disease assessment in the absence of local progression that precluded the planned surgery, an unresectable tumour at the time of surgery, progression or recurrence per RECIST version 1.1 by the investigator's assessment, or a death date. A constrained longitudinal data analysis model was used to estimate least-squares mean changes in patient-reported outcome scores from baseline to week 11 of the neoadjuvant phase and week 10 of the adjuvant phase (see appendix pp 11–12 for more details).

The magnitude of the treatment difference (ie, HR and 95% CI) in overall survival and event-free survival in the overall population was calculated using a stratified Cox regression model with trial group as a covariate and Efron's tie-handling method. If the proportional hazards assumption was violated, the restricted mean survival time method was performed as a sensitivity analysis. Between-group differences in overall survival in the overall population were assessed using the stratified log-rank test; because statistical significance for event-free survival was achieved previously,[11] formal statistical testing for event-free survival was not performed at this analysis. Between-group differences in the change from baseline in patient-reported outcomes scores were estimated using a constrained longitudinal data analysis model in which missing data were considered as missing at random (appendix pp 11–12). Between-group differences in the percentage of participants with improved and improved or stable GHS/QoL compared with baseline were assessed using the stratified Miettinen and Nurminen method; participants with missing data were considered as not achieving improvement or stability. The randomisation stratification factors were applied to all stratified analyses. The consistency of the treatment effect for overall survival and event-free survival in the overall population was assessed in protocol-specified subgroups based on age, sex, race, geographical region, disease stage (II *vs* III), PD-L1 TPS, tumour histology, smoking status, *EGFR* mutation status, and *ALK* translocation status and post-hoc subgroups based on disease stage (IIA *vs* IIB *vs* IIIA *vs* IIIB), nodal stage, and combined disease and nodal stage (IIIA N2 *vs* IIIA non-N2). Post-hoc landmark analyses of the treatment effect for event-free survival from the time of surgery were done in subgroups based on pathological complete response, major pathological response, and receipt of adjuvant therapy. Post-hoc analysis of the treatment effect for overall survival from the time of surgery was assessed in subgroups based on receipt of adjuvant therapy. The magnitude of the treatment difference in all subgroups was calculated using an unstratified Cox regression model with trial group as a covariate. The subgroup analyses of overall survival and event-free survival and the analyses of health-related quality of life were not adjusted for multiple comparisons.

The full statistical analysis plan is available in the protocol (appendix). Efficacy was assessed in the intention-to-treat population (ie, all participants randomly assigned to a treatment group); the exploratory landmark analyses included only those participants who underwent planned surgery. Safety and treatment exposure were assessed in the as-treated population (ie, all participants who received at least one administration of allocated study treatment). Health-related quality of life was assessed in the patient-reported outcomes population (ie, all participants who received at least one administration of allocated study treatment and completed at least one patient-reported outcomes assessment). An independent data and safety monitoring committee oversaw the study and assessed efficacy and safety at prespecified interim analyses. As previously reported,[11] the committee reported that the superiority threshold for major pathological response, pathological complete response, and event-free survival, but not overall survival, had been met after reviewing the results of the first interim analysis and recommended that the study continue as planned so that statistical significance of the difference in overall survival could be assessed in accordance with the analysis plan. The second interim analysis, results of which are reported here, was to occur when approximately 416 participants had disease progression or recurrence or died and was based on a

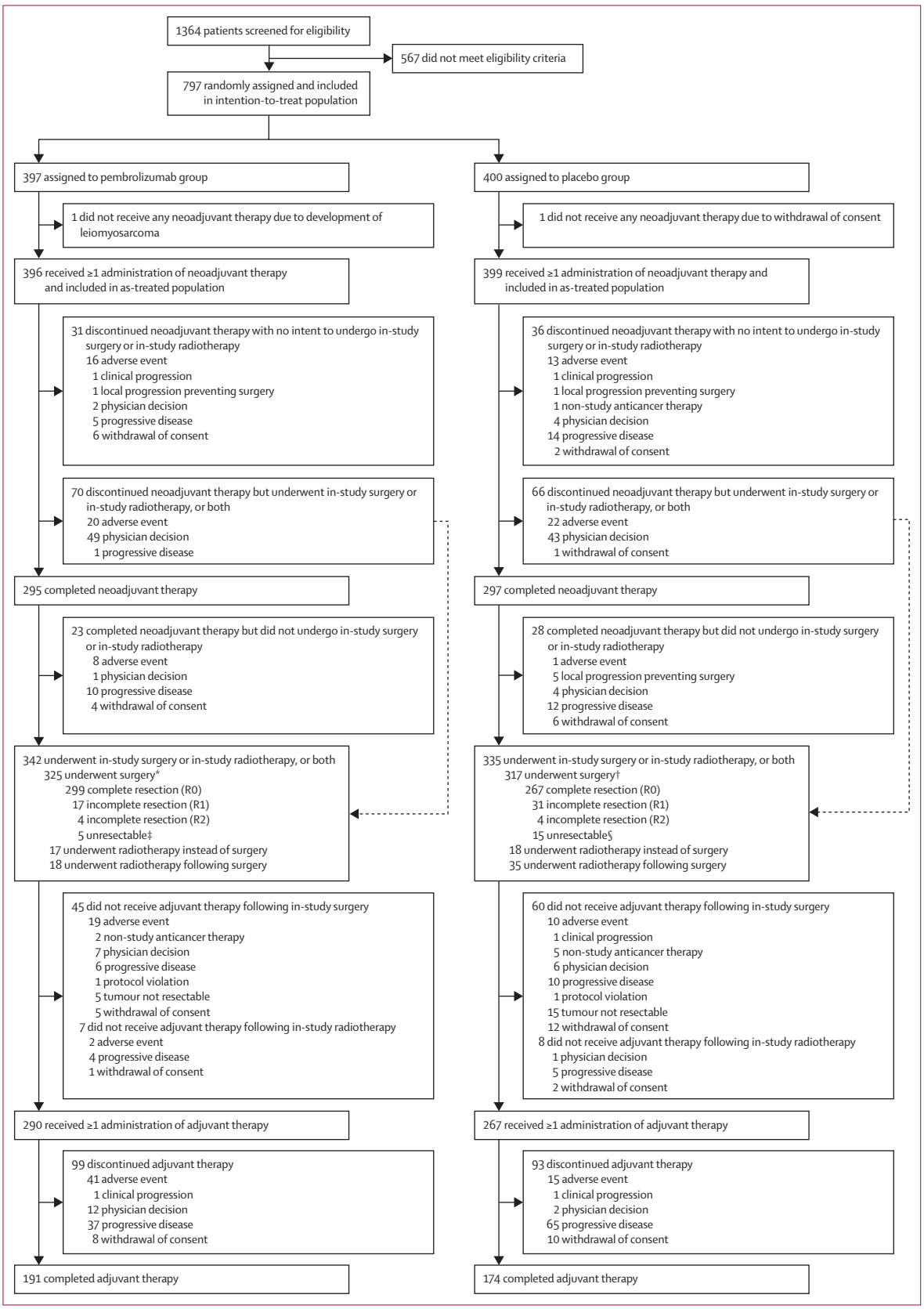



***Figure 1:*** **Trial profile**
The pembrolizumab group included neoadjuvant therapy with pembrolizumab plus platinum-based chemotherapy followed by surgery or radiotherapy (or both) and adjuvant pembrolizumab. The placebo group included neoadjuvant therapy with placebo plus platinum-based chemotherapy followed by surgery or radiotherapy (or both) and adjuvant placebo. *In the pembrolizumab group, 307 participants underwent in-study surgery alone and 18 participants underwent both in-study surgery and in-study radiotherapy; an additional 8 participants underwent off-study surgery. †In the placebo group, 282 participants underwent in-study surgery alone and 35 participants underwent both in-study surgery and in-study radiotherapy; an additional 7 participants underwent off-study surgery. ‡Includes 4 participants who underwent exploratory thoracotomy and 1 participant who underwent lobectomy but was found to have metastatic disease at the time of surgery. §Includes 13 participants who underwent exploratory thoracotomy and 2 participants who underwent lobectomy but were found to have metastatic disease at the time of surgery.

| | Pembrolizumab group (n=397) | Placebo group (n=400) |
|---|---|---|
| Age, years | 63 (58–69) | 64 (58–70) |
| <65 | 221 (56%) | 214 (54%) |
| ≥65 | 176 (44%) | 186 (47%) |
| Sex | | |
| Female | 118 (30%) | 116 (29%) |
| Male | 279 (70%) | 284 (71%) |
| Race | | |
| American Indian or Alaska Native | 1 (<1%) | 0 |
| Asian | 124 (31%) | 125 (31%) |
| Black or African American | 6 (2%) | 10 (3%) |
| Multiple | 3 (1%) | 10 (3%) |
| White | 250 (63%) | 239 (60%) |
| Missing | 13 (3%) | 16 (4%) |
| Geographical region | | |
| East Asia | 123 (31%) | 121 (30%) |
| Not east Asia | 274 (69%) | 279 (70%) |
| ECOG performance status | | |
| 0 | 253 (64%) | 246 (62%) |
| 1 | 144 (36%) | 154 (39%) |
| Smoking status | | |
| Current | 96 (24%) | 103 (26%) |
| Former | 247 (62%) | 250 (63%) |
| Never | 54 (14%) | 47 (12%) |
| Clinical disease stage | | |
| II | 118 (30%) | 121 (30%) |
| IIA | 22 (6%) | 19 (5%) |
| IIB | 96 (24%) | 102 (26%) |
| III | 279 (70%) | 279 (70%) |
| IIIA | 217 (55%) | 224 (56%) |
| IIIB | 62 (16%) | 55 (14%) |
| Tumour stage | | |
| T1 | 55 (14%) | 61 (15%) |
| T2 | 106 (27%) | 126 (32%) |
| T3 | 121 (30%) | 109 (27%) |
| T4 | 115 (29%) | 104 (26%) |
| Clinical node stage | | |
| N0 | 148 (37%) | 142 (36%) |
| N1 | 81 (20%) | 71 (18%) |
| N2 | 168 (42%) | 187 (47%) |
| Histological features | | |
| Non-squamous | 226 (57%) | 227 (57%) |
| Squamous | 171 (43%) | 173 (43%) |
| PD-L1 tumour proportion score | | |
| ≥50% | 132 (33%) | 134 (34%) |
| <50% | 265 (67%) | 266 (67%) |
| 1–49% | 127 (32%) | 115 (29%) |
| <1% | 138 (35%) | 151 (38%) |
| *EGFR* mutation status | | |
| No | 111 (28%) | 124 (31%) |
| Yes | 14 (4%) | 19 (5%) |
| Unknown | 272 (69%) | 257 (64%) |
| *ALK* translocation status | | |
| No | 104 (26%) | 132 (33%) |
| Yes | 12 (3%) | 9 (2%) |
| Unknown | 281 (71%) | 259 (65%) |

(Table 1 continues in next column)

(Continued from previous column)

Data are median (IQR) or n (%). Some proportions might not total 100% due to rounding. ECOG=Eastern Cooperative Oncology Group.

***Table 1:*** **Baseline demographic and disease characteristics in the intention-to-treat population**

data cutoff of July 10, 2023. Based on the observed number of deaths, the multiplicity-adjusted superiority threshold for overall survival at the second interim analysis was one-sided p=0·0054. Given that superiority for the pembrolizumab group was demonstrated for all primary and secondary hypotheses as of the second interim analysis, the remaining protocol-specified analyses will be descriptive only to assess the long-term treatment effect. Sample size and power calculations were done using R (version 4.3.2) with the gsDesign package. Statistical analyses were done using SAS (version 9.4).

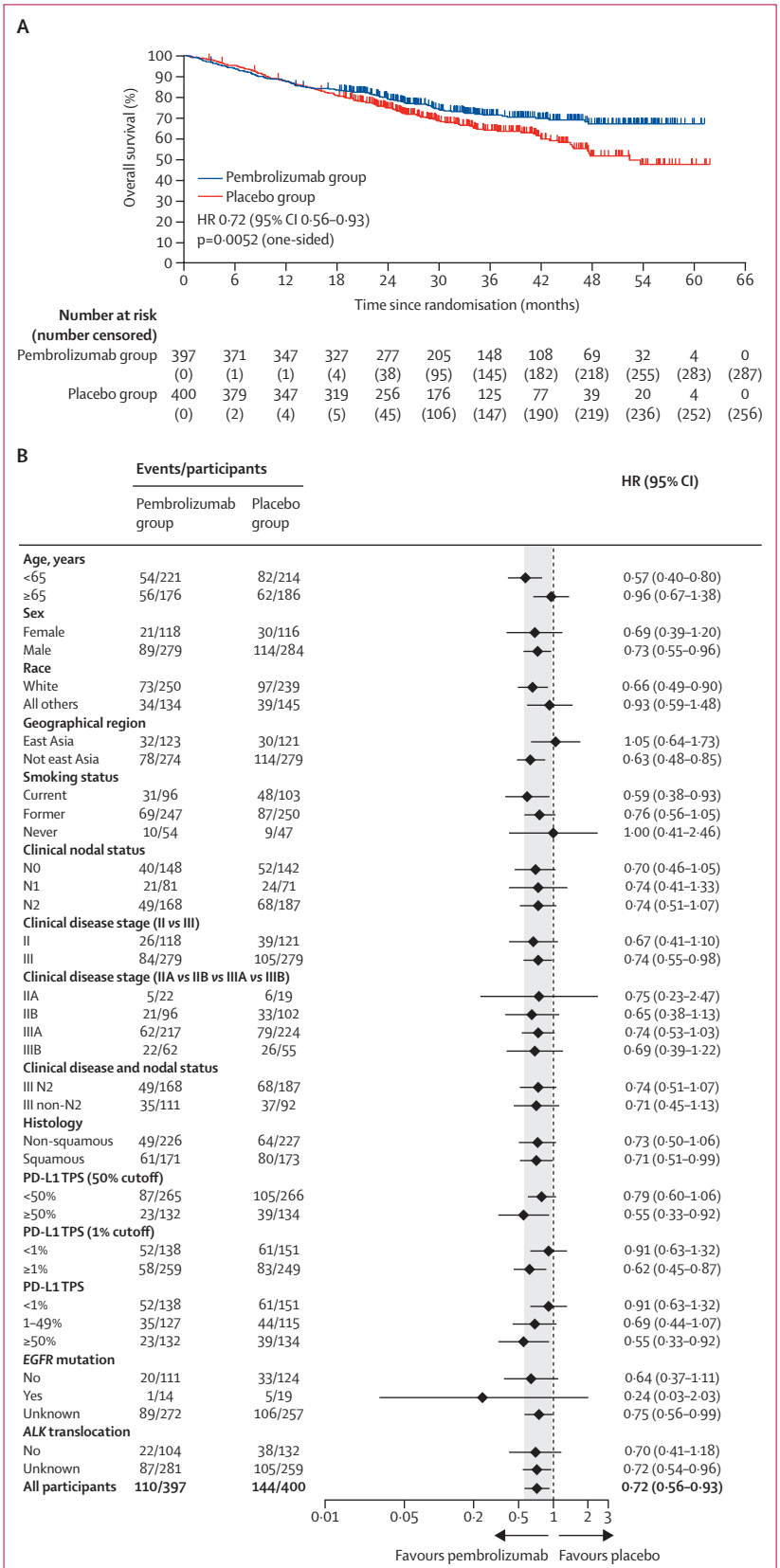
### Role of the funding source

Authors employed by the study funder contributed to study design and participated in data collection, data analysis, data interpretation, and writing of the report. The funder maintained the study database and ensured data were collected according to the protocol.

## Results

Of the 1364 patients who were screened for eligibility, 797 were randomly assigned between May 11, 2018, and Dec 15, 2021, to receive neoadjuvant pembrolizumab plus chemotherapy and adjuvant pembrolizumab (pembrolizumab group; n=397) or neoadjuvant placebo plus chemotherapy and adjuvant placebo (placebo group; n=400) and included in the intention-to-treat population (figure 1). As previously reported,[11] baseline demographic and disease characteristics were balanced between the two groups (table 1). 435 (55%) of 797 participants were younger than 65 years, 563 (71%) were male, 244 (31%) enrolled in east Asia, 696 (87%) were current or former smokers, 344 (43%) had squamous histology, 558 (70%) had stage III disease, and 355 (45%) had N2 nodal status.

The median time from randomisation to data cutoff was 36·6 months (IQR 27·6–47·8). Among the 396 participants who received at least one administration of neoadjuvant pembrolizumab plus chemotherapy, 295 (74%) received all four administrations of neoadjuvant pembrolizumab, 325 (82%) underwent in-study surgery, 290 (73%) received at least one administration of adjuvant pembrolizumab, and 191 (48%) completed the regimen (ie, received at least one administration of neoadjuvant




pembrolizumab plus chemotherapy and 13 administrations of adjuvant pembrolizumab; figure 1). Among the 399 participants who received at least one administration of neoadjuvant placebo plus chemotherapy, 297 (74%) received all four administrations of neoadjuvant placebo, 317 (79%) underwent in-study surgery, 267 (67%) received at least one administration of adjuvant placebo, and 174 (44%) completed the regimen. Across phases, the median number of pembrolizumab and placebo administrations was 15 (IQR 4–17) and 12 (4–17), respectively (appendix p 28). In the intention-to-treat population, 118 (30%) of 397 participants in the pembrolizumab group and 208 (52%) of 400 in the placebo group received subsequent therapy, including 30 (8%) and 114 (29%), respectively, who received a subsequent PD-1 or PD-L1 inhibitor. Among participants who experienced disease progression or recurrence, 99 (80%) of 124 in the pembrolizumab group and 178 (86%) of 208 in the placebo group received at least one subsequent anticancer therapy, including 26 (21%) and 104 (50%), respectively, who received a subsequent PD-1 or PD-L1 inhibitor (appendix p 29).

110 (28%) of 397 participants in the pembrolizumab group and 144 (36%) of 400 participants in the placebo group died. The Kaplan–Meier survival curves began to diverge in favour of the pembrolizumab group at month 16. Baseline demographic and disease characteristics for the participants who died within the first 16 months are available in the appendix (p 30). Kaplan–Meier estimates of 36-month overall survival were 71% (95% CI 66–76) in the pembrolizumab group and 64% (58–69) in the placebo group (HR 0·72 [95% CI 0·56–0·93]; one-sided p=0·0052; figure 2A). Median overall survival and the boundaries of the 95% CI were not reached in the pembrolizumab group. Median overall survival was 52·4 months (95% CI 45·7 to not reached) in the placebo group. In a prespecified sensitivity analysis, the restricted mean survival time at 60 months was 46·6 months in the pembrolizumab group and 42·5 months in the placebo group (difference 4·2 months [95% CI 1·1–7·3]). Overall survival in prespecified subgroups is shown in figure 2B. Kaplan–Meier curves for the prespecified histology, disease stage (II *vs* III), and PD-L1 TPS subgroups, the

***Figure 2*: Overall survival in the intention-to-treat population**
(A) Kaplan–Meier estimates of overall survival in the overall population; tick marks indicate censored data. (B) Overall survival in subgroups of the overall population, with the vertical grey shaded band indicating the 95% CI for the overall population. All subgroups were prespecified except for the subgroups of clinical nodal status, clinical disease stage (IIA *vs* IIB *vs* IIIA *vs* IIIB), and clinical disease and nodal status, which were post hoc. Per protocol, the subgroup of participants with *ALK* translocation is not shown because it included <30 participants. The analysis of the overall population was stratified by the randomisation stratification factors, whereas the analyses of the subgroups were not stratified in accordance with the protocol. HR=hazard ratio. TPS=tumour proportion score.

post-hoc nodal status, disease stage (IIA *vs* IIB *vs* IIIA *vs* IIIB), combined disease stage and nodal status (III N2 *vs* III non-N2) subgroups, and post-hoc landmark analyses from the time of in-study surgery based on receipt of adjuvant therapy are available in the appendix (pp 13–18).

174 (44%) of 397 participants in the pembrolizumab group and 248 (62%) of 400 participants in the placebo group had an event-free survival event, most commonly disease progression or recurrence (appendix p 31). Median event-free survival was 47·2 months (95% CI 32·9 to not reached) in the pembrolizumab group and 18·3 months (14·8–22·1) in the placebo group (HR 0·59 [95% CI 0·48–0·72]; figure 3A). Kaplan–Meier estimates of 36-month event-free survival were 54% (95% CI 49–59) in the pembrolizumab group and 35% (30–41) in the placebo group. Event-free survival in prespecified and post hoc subgroups is shown in figure 3B, with select Kaplan–Meier curves available in the appendix (pp 19–23). Post-hoc landmark analyses of event-free survival from the time of in-study surgery in subgroups based on receipt of adjuvant therapy and attainment of pathological complete response or major pathological response are also available in the appendix (pp 24–25).

In the health-related quality of life population, 388 (98%) of 395 participants in the pembrolizumab group and 391 (98%) of 398 participants in the placebo group completed the EORTC QLQ-C30 at baseline; 271 (69%) and 247 (62%), respectively, completed the questionnaire at week 10 of the adjuvant phase (appendix pp 32–33). Among participants expected to complete the questionnaire at adjuvant week 10, compliance was 271 (92%) of 294 participants in the pembrolizumab group and 247 (93%) of 266 participants in the placebo group (appendix pp 32–33). Mean GHS/QoL scores at baseline were 73·5 points (SD 19·1) in the pembrolizumab group and 72·8 points (19·8) in the placebo group. Least-squares mean changes from baseline in the GHS/QoL score were –9·3 points (95% CI –11·7 to –6·9) in the pembrolizumab group and –10·7 points (–13·1 to –8·4) in the placebo group at week 11 of the neoadjuvant phase (difference 1·4 points [–1·6 to 4·5]; appendix p 34) and –1·5 points (–3·7 to 0·6) and –3·7 points (–6·0 to –1·5),

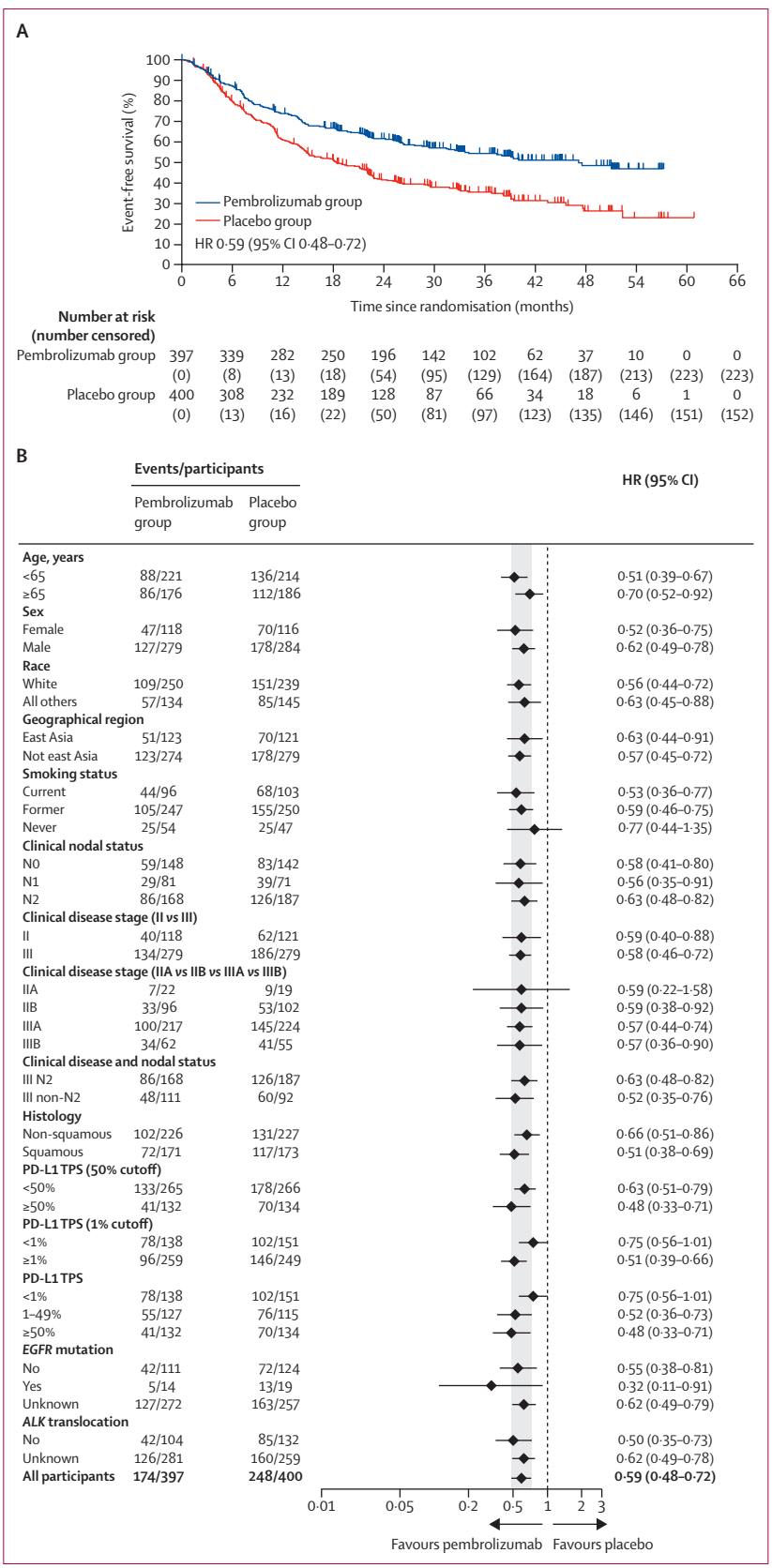



***Figure 3:*** **Event-free survival in the intention-to-treat population**
(A) Kaplan–Meier estimates of event-free survival in the overall population; tick marks indicate censored data. (B) Event-free survival in subgroups of the overall population, with the vertical grey shaded band indicating the 95% CI for the overall population. All subgroups were prespecified except for the subgroups of clinical nodal status, clinical disease stage (IIA *vs* IIB *vs* IIIA *vs* IIIB), and clinical disease and nodal status, which were exploratory. Per protocol, the subgroup of participants with *ALK* translocation is not shown because it included <30 participants. The analysis of the overall population was stratified by the randomisation stratification factors, whereas the analyses of the subgroups were not stratified in accordance with the protocol. HR=hazard ratio. TPS=tumour proportion score.

respectively, at week 10 of the adjuvant phase (difference 2·2 points [–0·6 to 5·0]; appendix p 35). The empirical mean change from baseline in GHS/QoL scores over time is shown in figure 4. Outcomes for physical functioning, role functioning, dyspnoea, cough, and chest pain are shown in the appendix (pp 26, 34–35). The proportion of participants with improved or stable GHS/QoL scores was 232 of 395 participants in the pembrolizumab group (59% [95% CI 54–64]) and 206 of 398 participants in the placebo group (52% [47–57]; difference 7 percentage points [<1–14]; appendix p 36).

Across all treatment phases in the as-treated population, treatment-related adverse events occurred in 383 (97%) of 396 participants in the pembrolizumab group and 381 (95%) of 399 participants in the placebo group. Treatment-related adverse events of grade 3 or higher occurred in 179 (45%) participants in the pembrolizumab group and 151 (38%) participants in the placebo group; serious treatment-related adverse events occurred in 73 (18%) and 58 (15%) participants, respectively. Treatment-related adverse events led to death in four (1%) participants in the pembrolizumab group (one participant each from atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death) and three (1%) participants in the placebo group (one participant each from acute coronary syndrome, pneumonia, and pulmonary haemorrhage). Treatment-related adverse events led to discontinuation of all treatment in 54 (14%) participants in the pembrolizumab group and 21 (5%) participants in the placebo group. Treatment-related adverse events of any grade that occurred in at least 30% of participants were nausea (216 [55%] in the pembrolizumab group *vs* 205 [51%] in the placebo group), decreased neutrophil count (169 [43%] *vs* 168 [42%]), and anaemia (143 [36%] *vs* 135 [34%]; table 2). Treatment-related adverse events of grade 3 or higher that occurred in at least 5% of participants were decreased neutrophil count (83 [21%] *vs* 79 [20%]), anaemia (29 [7%] *vs* 23 [6%]), decreased platelet count (21 [5%] *vs* 24 [6%]), and decreased white-cell count (21 [5%] *vs* 22 [6%]; table 2). Adverse events are summarised by treatment phase in the appendix (pp 37–41). Immune-mediated adverse events and infusion reactions occurred in 103 (26%) of 396 participants in the pembrolizumab group and in 36 (9%) of 399 participants in the placebo group (appendix p 40). These events were of grade 3 or higher in 26 (7%) participants in the pembrolizumab group and six (2%) participants in the placebo group. One (<1%) participant in the pembrolizumab group died from pneumonitis (recorded as the aforementioned immune-mediated lung disease).

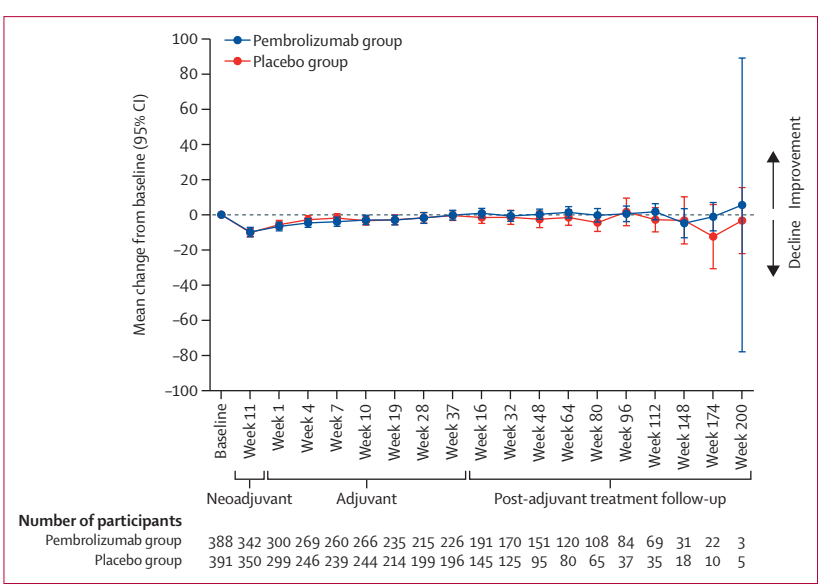



***Figure 4:*** **Empirical mean change from baseline in the EORTC Core Quality of Life Questionnaire global health status/quality of life score over time in the patient-reported outcomes population**
All values are accompanied by their associated 95% CI. Per protocol, week 37 was considered the end of the adjuvant therapy phase for health-related quality of life analyses. EORTC=European Organisation for Research and Treatment of Cancer.

## Discussion

With a median follow-up of 3 years, neoadjuvant pembrolizumab plus cisplatin-based chemotherapy followed by adjuvant pembrolizumab significantly improved overall survival compared with neoadjuvant chemotherapy alone in participants with molecularly unselected, resectable stage II, IIIA, or IIIB (N2) NSCLC in this placebo-controlled phase 3 trial, with an HR of 0·72 (95% CI 0·56–0·93; one-sided p=0·0052). The overall survival curves began to diverge in favour of pembrolizumab at approximately month 16 and remained separated, with survival estimates favouring the pembrolizumab group by 7 percentage points at month 36. The event-free survival benefit of pembrolizumab observed at the first interim analysis was maintained,[11] and event-free survival estimates favoured the pembrolizumab group by 19 percentage points at month 36. The type of subsequent therapy in the placebo group was as expected and reflects global standards of care for locoregional recurrence and distant metastasis.

An event-free survival benefit for perioperative pembrolizumab was observed across all prespecified and exploratory subgroups assessed. An overall survival benefit was observed regardless of sex, clinical disease and nodal stages, histology, *EGFR* mutation status, and *ALK* translocation status. Notably, the relative benefit of pembrolizumab for overall survival was similar in participants with stage II (HR 0·67 [95% CI 0·41–1·10]) and stage III N2 (0·74 [0·51–1·07]) disease. Based on HR point estimates, the relative benefit of pembrolizumab for overall survival appeared to be less clear in the subgroups of age 65 years and older, non-White race, geographical region of east Asia, never smoker, and PD-L1 TPS less than 1%. The overall survival data remain immature at this analysis, which might explain the

different results for event-free and overall survival in subgroups. The primary purpose of subgroup analyses is to explore the consistency of the treatment effect, and for all overall and event-free survival subgroups in KEYNOTE-671, the 95% CIs overlapped those of the overall population. The results of subgroup analyses are descriptive only and should be interpreted with caution because they are not adjusted for multiple comparisons and the trial is not powered to compare outcomes in subgroups.

In exploratory landmark analyses, perioperative pembrolizumab improved event-free survival from the time of in-study surgery regardless of whether participants received adjuvant therapy, experienced pathological complete response, or experienced major pathological response. Participants who received adjuvant therapy also had improved overall survival from the time of surgery with perioperative pembrolizumab, whereas those without adjuvant therapy did not experience a clear overall survival benefit with pembrolizumab. In both treatment groups, participants who received adjuvant therapy had longer event-free and overall survival than those who did not receive adjuvant therapy. These results, which are based on exploratory analysis of a post-randomisation factor and must be interpreted with caution, do not eliminate the possibility that both the neoadjuvant and adjuvant treatment phases contribute to the overall benefit of the perioperative regimen. Conclusive determination of the relative contributions of the individual treatment phases would require a different study design than that of KEYNOTE-671.

In the past year, results of five phase 3 clinical trials—KEYNOTE-671,[11] AEGEAN,[12] CheckMate 77T,[15] Neotorch,[14] and RATIONALE-315[13]—have shown that perioperative regimens of PD-1 and PD-L1 inhibitors significantly improve major pathological response, pathological complete response, and event-free survival in resectable early-stage NSCLC. Allowing for differences in follow-up duration, use of subsequent therapy, including subsequent PD-1 or PD-L1 inhibitors, was similar among these studies. Despite differences in the enrolled populations and design, a generally consistent benefit for perioperative immune checkpoint inhibition was observed across these trials, supporting the validity of this treatment approach. To the best of our knowledge, KEYNOTE-671 is the first of these trials to show a statistically significant overall survival benefit.

With one additional year of follow-up compared with the first interim analysis[11] and all participants either completing or discontinuing treatment, no new safety signals or additional treatment-related deaths were identified for the perioperative pembrolizumab regimen. During the combined neoadjuvant and surgery phases, the proportion of participants who experienced treatment-related adverse events, including those of grade 3 or higher, was similar between the treatment groups, with the most common adverse events reported being those associated with chemotherapy. The inclusion of pembrolizumab in the neoadjuvant phase was not associated with additional adverse events during the surgical treatment phase. As expected given the lack of active therapy in the placebo group, more participants in the pembrolizumab group experienced treatment-related adverse events during the adjuvant phase, including events of grade 3 or higher (34 [12%] of 290 in the pembrolizumab group and 16 [6%] of 267 in the placebo group) and that were serious (19 [7%] and eight [3%], respectively). Importantly, only one participant in the pembrolizumab group died due to a treatment-related adverse event (atrial fibrillation) during the adjuvant phase. Overall, the safety profile of the perioperative pembrolizumab regimen is consistent with the safety profile of pembrolizumab plus chemotherapy in the setting of metastatic disease[22,23] and is manageable with careful monitoring and appropriate supportive therapy.

Health-related quality of life is another important consideration in the treatment of early-stage cancer, particularly when many patients are free from symptoms of active disease following resection. As assessed using validated instruments,[18,19] there were no between-group differences in the least-squares mean change from baseline in the neoadjuvant or adjuvant phase for patient-reported GHS/QoL, physical functioning, role functioning, dyspnoea, cough, or chest pain. Based on a 10-point threshold and in both groups, most health-related quality-of-life scores decreased during the neoadjuvant phase before returning to approximately baseline levels during the adjuvant phase. A decrease in health-related quality of life during the neoadjuvant phase and a return to

| | Pembrolizumab group (n=396) | | Placebo group (n=399) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| Nausea | 216 (55%) | 8 (2%) | 205 (51%) | 6 (2%) |
| Neutrophil count decreased | 169 (43%) | 83 (21%) | 168 (42%) | 79 (20%) |
| Anaemia | 143 (36%) | 29 (7%) | 135 (34%) | 23 (6%) |
| White blood cell count decreased | 111 (28%) | 21 (5%) | 98 (25%) | 22 (6%) |
| Fatigue | 108 (27%) | 6 (2%) | 95 (24%) | 3 (1%) |
| Constipation | 107 (27%) | 3 (1%) | 101 (25%) | 0 |
| Decreased appetite | 92 (23%) | 7 (2%) | 89 (22%) | 0 |
| Vomiting | 76 (19%) | 4 (1%) | 58 (15%) | 1 (<1%) |
| Platelet count decreased | 74 (19%) | 21 (5%) | 75 (19%) | 24 (6%) |
| Blood creatinine increased | 57 (14%) | 3 (1%) | 48 (12%) | 0 |
| Diarrhoea | 53 (13%) | 7 (2%) | 56 (14%) | 3 (1%) |
| Alanine aminotransferase increased | 51 (13%) | 7 (2%) | 33 (8%) | 4 (1%) |
| Rash | 47 (12%) | 2 (1%) | 26 (7%) | 0 |
| Asthenia | 45 (11%) | 4 (1%) | 57 (14%) | 2 (1%) |
| Alopecia | 41 (10%) | 0 | 41 (10%) | 1 (<1%) |

Data are n (%). Treatment-related adverse events were adverse events considered to be related to pembrolizumab or placebo by the investigator.

***Table 2:*** **Treatment-related adverse events that occurred in ≥10% of participants in either treatment group of the as-treated population**

approximately baseline levels thereafter was also observed for perioperative nivolumab in the CheckMate 77T trial.[17] The return to approximately baseline levels is notable given participants in the placebo group received no active therapy during the adjuvant phase, suggesting that although adverse events are more common with adjuvant checkpoint inhibitors, health-related quality of life is not negatively impacted. The decrease in quality of life during the neoadjuvant phase likely reflects the adverse impact of chemotherapy and tumour-related symptom burden. The return to baseline during the adjuvant phase likely reflects the lack of chemotherapy and decreased, or even resolved, tumour-related symptom burden following resection. Recovery in health-related quality of life post-surgery is also reflected in findings from the VIOLET trial of video-assisted thoracoscopic or open lobectomy for lung cancer; in this study, physical functioning scores initially declined following surgery before returning to approximately baseline levels.[24]

Limitations of the KEYNOTE-671 trial, as well as the other trials of perioperative immune checkpoint inhibition for resectable NSCLC,[12–15] include a design that does not permit direct analysis of the relative contributions of the neoadjuvant and adjuvant components of the treatment regimen, a follow-up duration that remains relatively short for a trial of participants with early-stage disease, and the potential lack of generalisability of the results due to differences in the study population versus the general population of participants with resectable NSCLC (eg, enrolment of younger participants and under-representation of Black participants). We note that while Black participants were under-represented in the overall population (16 [2%] of 797), they represented a larger proportion of participants enrolled in the USA (eight [10%] of 78). Neoadjuvant chemotherapy in KEYNOTE-671 was limited to cisplatin-based regimens based on the totality of data available at the time the study was designed. Based on evidence for pembrolizumab plus chemotherapy in the metastatic setting,[22] the results of KEYNOTE-671 are expected to be generalisable to carboplatin-based regimens. This is reflected in the global regulatory approvals for the perioperative pembrolizumab regimen.[25,26] A limitation of the health-related quality of life analysis is the use of a lung cancer-specific instrument developed for participants with unresectable disease treated with chemotherapy or radiotherapy.[19]

In conclusion, the addition of perioperative pembrolizumab to neoadjuvant chemotherapy resulted in a significant improvement in overall survival consistent with the previously demonstrated improvements in event-free survival, major pathological response, and pathological complete response compared with neoadjuvant chemotherapy alone. The efficacy benefits of perioperative pembrolizumab did not incur a long-term decrease in health-related quality of life, and no new safety signals emerged with additional follow-up. These findings support perioperative pembrolizumab as a standard-of-care treatment option for patients with resectable stage II to IIIB (N2) NSCLC.

#### Contributors

MCG, HW, JY, SMK, and AS participated in the conception, design, and planning of the study. JDS, MCG, HW, ML, TK, MT, S-HL, K-NC, CD, MM, EE, GLM, OB, DR-A, JEC, SN, and SG enrolled and treated participants and acquired data. JY performed the statistical analysis. JDS, MCG, AA, JY, SMK, and AS analysed and interpreted the study data. JDS, HW, JY, SMK, and AS accessed and verified the study data. All authors had full access to all the data in the study, provided critical review of the manuscript, and approved the submitted draft. All authors vouch for data accuracy and completeness, fidelity of the study to the protocol and its amendments, and study conduct in accordance with Good Clinical Practice guidelines. All authors had responsibility for the final decision to submit for publication.

#### Declaration of interests

JDS, MCG, HW, ML, TK, MT, S-HL, K-NC, CD, MM, EE, GLM, OB, DR-A, JEC, SN, and SG report funding to their institution from Merck Sharp & Dohme (MSD), a subsidiary of Merck & Co, Rahway, NJ, USA to support conduct of this study. JDS, MCG, HW, ML, TK, MT, S-HL, K-NC, CD, MM, EE, GLM, OB, DR-A, JEC, SN, JY, AA, SMK, AS, and SG received medical writing and editorial support for the preparation of this manuscript from MSD. JDS additionally reports receiving grants to the institution from AstraZeneca, MSD, Roche, BMS, CLS Therapeutics, Protalix Biotherapeutics, Pfizer, and Regeneron; receiving consulting fees from AstraZeneca, Merck, Roche, BMS, Novartis, Chemocentryx, Amgen, Protalix Biotherapeutics, Xenetic Biosciences, Regeneron, Eisai, and Pfizer; receiving payment for a speaking role from Peerview, OncLive, and Medscape; receiving support for attending meetings or travel from AstraZeneca, Merck, and BMS; participating on a clinical trial safety monitoring board for AstraZeneca; and receiving equipment, materials, drugs, gifts, or other services via grant to the institution from Roche, MSD, BMS, and AstraZeneca. MCG additionally reports receiving consulting fees from AstraZeneca, Abion, MSD International, Bayer, BMS, Boehringer Ingelheim Italia, Celgene, Eli Lilly, Incyte, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati, Daiichi-Sankyo, Regeneron, Merck & Co, Blueprint, Janssen, Sanofi, AbbVie, BeiGene, Oncohost, Medscape, Gilead, Io Biotech, and Revolution Medicines; receiving payment or honoraria for lectures, presentations, speakers' bureaus, or educational events from AstraZeneca, Merck & Co, Daiichi Sankyo, Gilead, Eli Lilly, and Regeneron; and receiving support for attending meetings or travel from AstraZeneca. HW additionally reports research funding to the institution from Bayer, AstraZeneca, BMS, Genentech/Roche, MSD, Helsinn, SeaGen, and Xcovery; serving as a compensated advisory board member for Mirati, IOBiotech, OncoC4, and BeiGene; serving as an uncompensated advisory board member for MSD, Genentech/Roche, BMS, and AstraZeneca; serving as a past president of the International Association for the Study of Lung Cancer (IASLC); and serving on the executive committee of ECOG-ACRIN. TK additionally reports research grants to the institution from AbbVie, Amgen, Arrivent, AstraZeneca, Bayer, BeiGene, BluePrint, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Haihe, Janssen, Merck KGaA, MSD, Novartis, Pfizer, Regeneron, and Takeda; receiving honoraria for lectures, presentations, speakers' bureaus, or educational events from Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Janssen, Merck KGaA, MSD, Novartis, Ono, Pfizer, Taiho, and Takeda; receiving honoraria for participation on a data safety monitoring board or advisory board from AstraZeneca, BeiGene, Chugai, Daiichi-Sankyo, Janssen, Merck KGaA, MSD, Novartis, and Pfizer; and having a spouse who is an employee of Eli Lilly. MT additionally reports research grants to the institution from MSD, AstraZeneca KK, Bristol-Myers Squibb KK, Ono Pharmaceutical Co, Eli Lilly Japan, Novartis, MiRXES, and Johnson & Johnson Japan; receiving honoraria for lectures from Amgen KK, Johnson & Johnson Japan, Medtronic Japan, AstraZeneca KK, Eli Lilly Japan, Chugai Pharmaceutical Co, Taiho Pharma, Bristol-Myers Squibb KK, Ono Pharmaceutical Co, Novartis, MSD, and Daiichi-Sankyo; serving as a participant on an advisory board for Bristol-Myers Squibb KK, AstraZeneca KK, MSD, Novartis, and MiRXES; and serving as a

participant on a data safety monitoring board for Chugai Pharmaceutical Co. S-HL additionally reports research grants to the institution from MSD and receiving honoraria for a lecture from MSD. MM additionally reports receiving honoraria for lectures, presentations, speakers' bureaus, or educational events from MSD, Lilly, Pfizer, AstraZeneca, Roche, Sanofi, Regeneron, BeiGene, Immedica, Novartis, and BMS; and receiving support to attend meetings or travel from MSD, Pfizer, AstraZeneca, and Roche. EE additionally reports receiving payment for expert testimony from MSD. OB additionally reports support for attending meetings or travel from MSD for ASCO 2023 and from AstraZeneca for ESMO 2023 and ASCO 2024; and participating as a compensated advisory board member for BMS, Roche, Takeda, MSD, AstraZeneca, Janssen, and MSD. DR-A additionally reports receiving honoraria for lectures from MSD, Roche, BMS, Novartis, Takeda, Lilly, and AstraZeneca; receiving support for attending meetings or travel from Roche, MSD, Novartis, and Sanofi; and participation on an advisory board from MSD, Regeneron, BMS, GSK, and Lilly. JEC additionally reports receiving research grants to the institution from AstraZeneca, BMS, Novartis, Genentech, Merck & Co, and BeiGene; and receiving consulting fees from AstraZeneca, Boehringer Ingelheim, BMS, Lilly, Genentech, Merck & Co, Regeneron-Sanofi, Janssen, Guardant Health, Flame Biosciences, and Roche. SN additionally reports receiving honoraria for lectures, presentations, speakers' bureaus, or educational events from AstraZeneca, Amgen, BeiGene, Pfizer, MSD, Sanofi, Takeda, Thermo Fisher, Janssen, Novartis, and Roche; and participating on a data safety monitoring board or advisory board from AstraZeneca, Amgen, BeiGene, Pfizer, MSD, Sanofi, Takeda, Janssen, and Roche. JY additionally reports receiving salary for full-time employment from MSD. AA, SMK, and AS additionally report receiving salary for full-time employment from MSD and holding stock in Merck & Co, Rahway, NJ, USA.

### Data sharing

Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an SAS portal so that the requestor can perform the proposed analyses.

### Acknowledgments

This study was funded by Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA. JDS's time was additionally supported by a clinician-scientist grant from the *Fonds de Recherche du Quebec – Santé* (Junior 2 #297821). JEC's time was additionally supported by a grant from the National Institutes of Health (P30 CA008748). We thank the patients and their families and caregivers for participating in the study; the investigators and site personnel; the independent data and safety monitoring committee; and the following employees of Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA: Geri Lyn Ferraro, Ann Marie Mantz, and Andrea Rybak-Feiglin for study support; Gregory M Lubiniecki for input into study design and study oversight; M Catherine Pietanza for input into study design and study oversight; Xuan Deng, Erin H Jensen, and Jin Zhang for statistical support; Josephine M Norquist for input into the patient-reported outcomes analysis; and Melanie A Leiby for medical writing and editorial assistance.

### References

1 Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994; **330:** 153–58.

2 Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 1994; **86:** 673–80.

3 Conroy MR, Dennehy C, Forde PM. Neoadjuvant immune checkpoint inhibitor therapy in resectable non-small cell lung cancer. *Lung Cancer* 2023; **183:** 107314.

4 Brierly JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors, 8th edn. Oxford: John Wiley & Sons, 2016.

5 Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected *EGFR*-mutated NSCLC. *N Engl J Med* 2023; **389:** 137–47.

6 Wu YL, Dziadziuszko R, Ahn JS, et al. Alectinib in resected *ALK*-positive non-small-cell lung cancer. *N Engl J Med* 2024; **390:** 1265–76.

7 Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet* 2021; **398:** 1344–57.

8 Felip E, Altorki N, Zhou C, et al. Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial. *Ann Oncol* 2023; **34:** 907–19.

9 O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 2022; **23:** 1274–86.

10 Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 2022; **386:** 1973–85.

11 Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 2023; **389:** 491–503.

12 Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med* 2023; **389:** 1672–84.

13 Yue D, Wang W, Liu H, et al. VP1-2024: RATIONALE-315: Event-free survival (EFS) and overall survival (OS) of neoadjuvant tislelizumab (TIS) plus chemotherapy (CT) with adjuvant TIS in resectable non-small cell lung cancer (NSCLC). *Ann Oncol* 2024; **35:** 332–33.

14 Lu S, Zhang W, Wu L, et al. Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: the Neotorch randomized clinical trial. *JAMA* 2024; **331:** 201–11.

15 Cascone T, Awad MM, Spicer JD, et al. Perioperative nivolumab in resectable lung cancer. *N Engl J Med* 2024; **390:** 1756–69.

16 Felip E, Wang C, Ciuleanu TE, et al. Nivolumab (NIVO) plus platinum-doublet chemotherapy (chemo) versus chemo as neoadjuvant treatment for resectable non-small cell lung cancer (NSCLC): health-related quality of life (HRQoL) outcomes from CheckMate 816. *Ann Oncol* 2022; **33:** S973–4.

17 Spicer J, Provencio Pulla M, Awad M, et al. Health-related quality of life (HRQoL) outcomes from CheckMate 77T: neoadjuvant nivolumab (nivo) plus chemotherapy (chemo) followed by adjuvant nivo in resectable NSCLC. *ESMO Open* 2024; **9:** 121P (abstr).

18 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

19 Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. *Eur J Cancer* 1994; **30A:** 635–42.

20 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16:** 139–44.

21 Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. *Stat Biopharm Res* 2013; **5:** 311–20.

22 Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 2078–92.

23 Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018; **379:** 2040–51.

24 Lim E, Batchelor TJP, Dunning J, et al. Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer. *NEJM Evid* 2022; **1**: EVIDoa2100016.

25 US Food & Drug Administration. FDA approves neoadjuvant/adjuvant pembrolizumab for resectable non-small cell lung cancer. 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-adjuvant-pembrolizumab-resectable-non-small-cell-lung-cancer#:~:text=On%20October%2016%2C%202023%2C%20the,non%2Dsmall%20cell%20lung%20cancer (accessed Aug 9, 2024).

26 European Medicines Agency. Keytruda—opinion on variation to marketing authorisation. 2024. https://www.ema.europa.eu/en/medicines/human/variation/keytruda-1 (accessed Aug 9, 2024).